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(54) **COMPOUNDS, PREPARATION METHODS AND USES THEREOF**

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A61K 31/444	(2006.01)
A61K 31/453	(2006.01)
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C07D 405/04	(2006.01)
C07D 405/12	(2006.01)
C07D 405/14	(2006.01)
C07D 413/04	(2006.01)
C07D 413/14	(2006.01)
C07D 417/14	(2006.01)
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C07D 471/08	(2006.01)
C07D 473/34	(2006.01)
C07D 487/04	(2006.01)
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(57) **ABSTRACT**

Provided herein are novel compounds, for example, compounds having a Formula A, B, C, D, E, or F, or a pharmaceutically acceptable salt thereof. Also provided herein are methods of preparing the compounds and methods of using the compounds, for example, in inhibiting PI3K in a cell, and/or in treating various diseases such as cancer.

Fig. 1

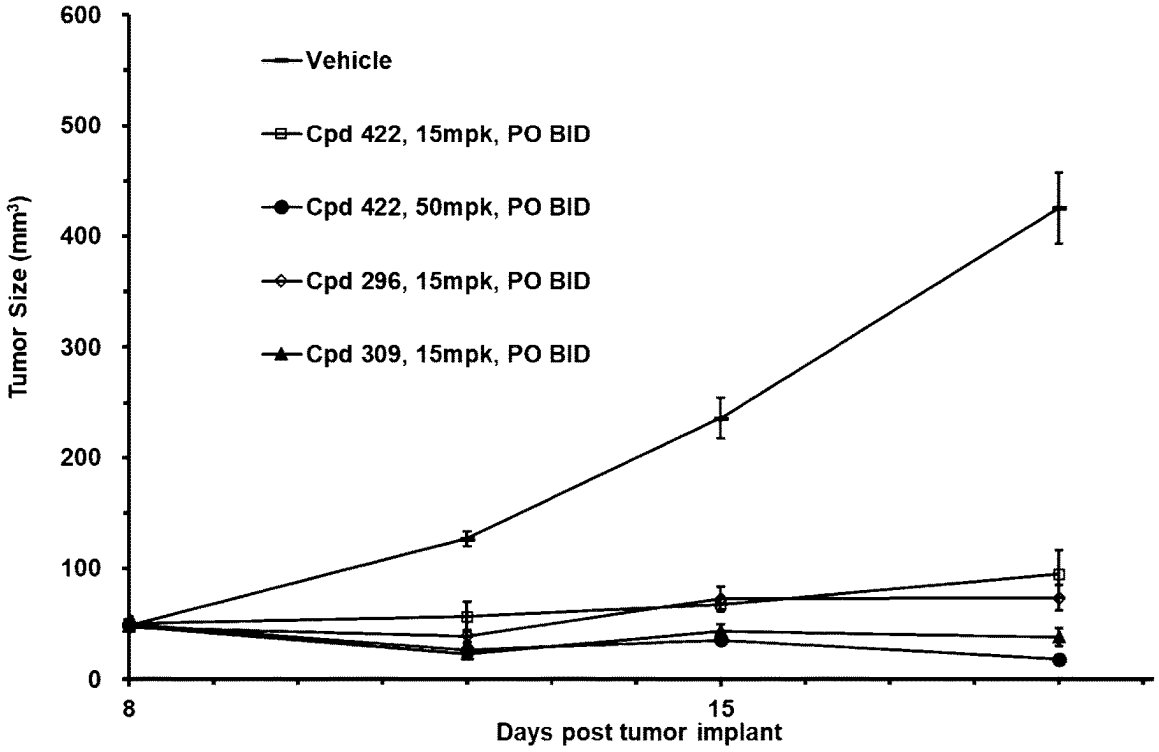
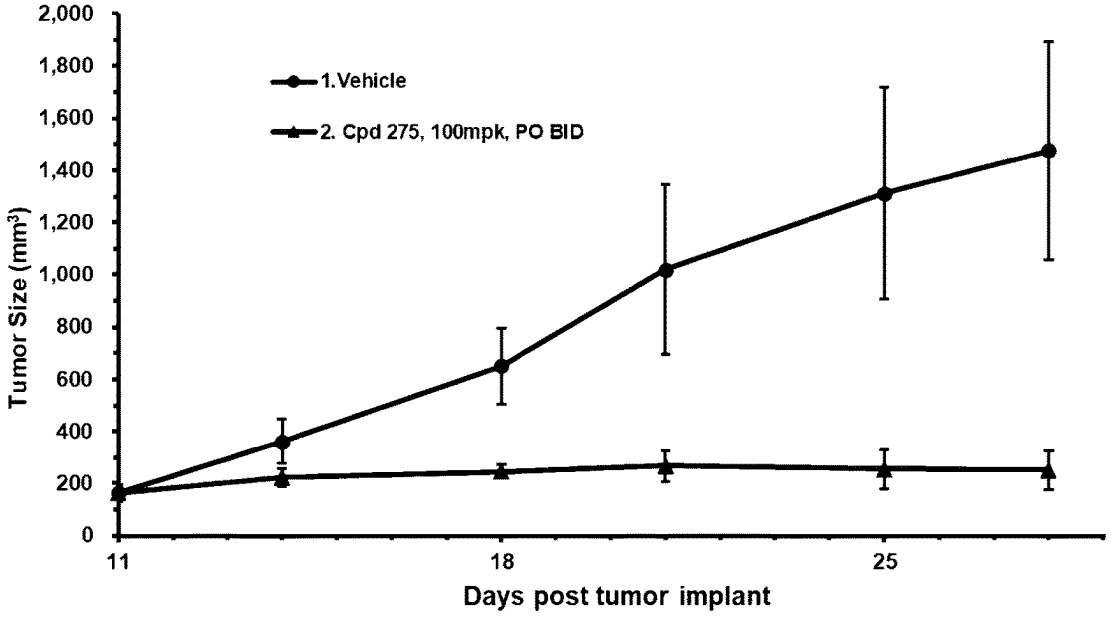

600
500
400
300
200
100
0
Tumor Size (mm³)
Vehicle
Cpd 422, 15mpk, PO BID
Cpd 422, 50mpk, PO BID
Cpd 296, 15mpk, PO BID
Cpd 309, 15mpk, PO BID
8
15
Days post tumor implant

Fig.2


2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
Tumor Size (mm³)
1.Vehicle
2. Cpd 275, 100mpk, PO BID
11
18
25
Days post tumor implant

COMPOUNDS, PREPARATION METHODS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to International Application Nos. PCT/CN2022/088724, filed on Apr. 24, 2022; PCT/CN2022/118054, filed on Sep. 9, 2022; PCT/CN2022/139776, filed on Dec. 16, 2022; and PCT/CN2023/076413, filed on Feb. 16, 2023, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

Field of the Disclosure

[0002] In various embodiments, the present disclosure generally relates to novel compounds, compositions comprising the same, methods of preparing and methods of using the same, e.g., for inhibiting PI3Ks and/or for treating a number of diseases or disorders, such as cancer.

Background

[0003] The phosphoinositide 3-kinases (PI3Ks) are members of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises more than a dozen kinases with distinct substrate specificities, expression patterns, and modes of regulation. PI3K-alpha (PI3Ka) is a heterodimeric protein complex composed of the catalytic subunit p110α (coded by the PIK3CA gene) and the regulatory subunit p85α (coded by the PIK3R1 gene) (Vasan N. et al. *Annals of Oncology,* 30(10):x3-x11 (2019). p110α binds to p85α and catalyzes the phosphorylation of the lipid phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3).

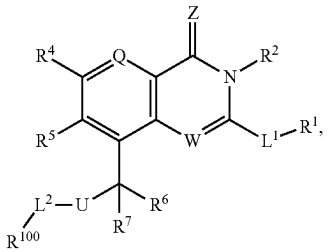
[0004] PI3Ks signaling pathway has been associated with a number of diseases, in particular cancers. Genetic alterations in genes in PI3K signaling are believed to be involved in a range of diseases, including in cancers such as breast, endometrial, gastric, colorectal, ovarian, cervical, head-and-neck, liver, lung, and prostate cancers. A number of cancer-associated PIK3CA mutations have been identified, such as PI3KCA-H1047R mutation. These mutations can lead to activation of the PI3K pathway resulting in increased cell growth and tumorigenesis.

BRIEF SUMMARY

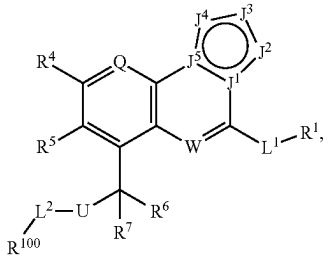
[0005] The present disclosure is based in part on Applicant's discovery of compounds that can act as inhibitors of PI3K, in particular, inhibitors of PI3K-alpha ("PI3Ka"), such as those having H1047R mutations. In various embodiments, the present disclosure provides novel compounds, pharmaceutical compositions, methods of preparing and using the same. The compounds and compositions herein are useful for treating various diseases or disorders, such as a cancer described herein.

[0006] In some embodiments, the present disclosure provides a compound of Formula A, B, C, D, E, or F, or a pharmaceutically acceptable salt thereof, as defined herein:

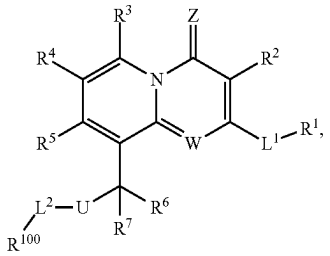
Formula A



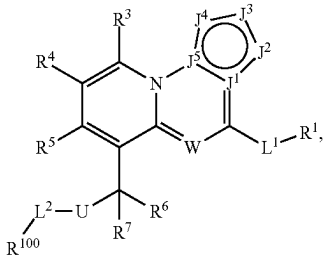
Formula B



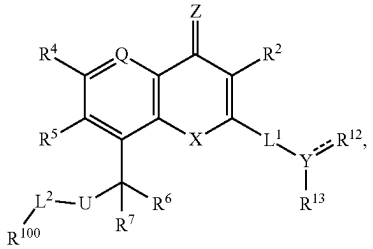
Formula C



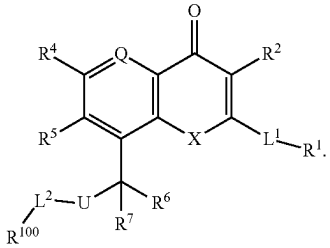
Formula D



Formula E



Formula F



[0007] In some embodiments, the compound of Formula A can be characterized as having a structure according to a subformula selected from Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5. In some embodiments, the compound of Formula B can be characterized as having a structure according to a subformula selected from Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b. In some embodiments, the compound of Formula C can be characterized as having a structure according to a subformula selected from Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5. In some embodiments, the compound of Formula D can be characterized as having a structure according to a subformula of Formula IV. In some embodiments, the compound of Formula E can also be characterized as having a structure according to a subformula selected from Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI. In some embodiments, the compound of Formula F can also be characterized as having a structure according to a subformula selected from Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b. In some embodiments, the present disclosure also provides a compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure also provides a compound selected from the compounds shown in Examples section herein, or a pharmaceutically acceptable salt thereof.

[0008] Certain embodiments of the present disclosure are directed to a pharmaceutical composition comprising one or more of the compounds of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof) and optionally a pharmaceutically acceptable excipient. The pharmaceutical composition described herein can be formulated for various routes of administration, such as oral administration, parenteral administration, or inhalation etc.

[0009] Certain embodiments are directed to a method of treating a disease or disorder associated with the activity of PI3K. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof) or a therapeutically effective amount of a pharmaceutical composition described herein. Diseases or disorders associated with PI3K suitable to be treated with the method include any of the cancers described herein. In some embodiments, diseases or disorders associated with PI3K suitable to be treated with the method include CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3CA-related overgrowth syndrome (PROS).

[0010] In some embodiments, a method of treating cancer is provided. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof) or a therapeutically effective amount of a pharmaceutical composition described herein. In various embodiments, the cancer can be endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

[0011] The administering in the methods herein is not limited to any particular route of administration. For example, in some embodiments, the administering can be orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally, or parenterally.

[0012] The compounds of the present disclosure can be used as a monotherapy or in a combination therapy. In some embodiments, the combination therapy includes treating the subject with a targeted therapeutic agent, chemotherapeutic agent, therapeutic antibody, radiation, cell therapy, and/or immunotherapy.

[0013] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention herein.

BRIEF DESCRIPTION OF THE FIGURES

[0014] FIG. **1** shows vivo efficacy studies in human lung cancer tumor xenograft model NCI-H1048 of some exemplary compounds.

[0015] FIG. **2** shows vivo efficacy studies in human tumor xenograft model CAL33 of some exemplary compounds.

DETAILED DESCRIPTION

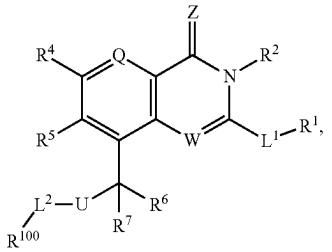
[0016] In a broad aspect, the present disclosure provides compounds and compositions that are useful for inhibiting PI3Ks, such as PI3Ka with a H1047R mutation, and/or treating or preventing various diseases or disorders described herein, e.g., cancer.

Compounds

Formula A

[0017] In some embodiments, the present disclosure provides a compound of Formula A, or a pharmaceutically acceptable salt thereof:

Formula A



[0018] wherein:

[0019] W is CR^{10} or N, wherein R^{10} is hydrogen, deuterium, halogen, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or C_{1-4} alkoxy optionally substituted with 1-3 fluorine;

[0020] Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy;

[0021] Q is N or CR^3, wherein R^3 is hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0022] U is null, O, S, S(O), SO_2, or NR^8, wherein R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0023] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0024] R^1 is hydrogen or a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0025] R^2, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1, preferably, R^2 is not halogen, CN, OH, or OG^1,

[0026] R^6 and R^7 are each independently hydrogen, deuterium, halogen, CN, G^2, or OG^2,

[0027] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0028] R^{100} is —R^{102}-R^{103}, wherein R^{102} is null, O, NH, C_{1-4} alkylene or C_{1-4} heteroalkylene having 1 or 2 heteroatoms, and R^{103} is hydrogen, COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, $SO_2NG^3G^3$, or a 5- or 6-membered ring having a hydrogen bond donor, e.g., a tetrazolyl;

[0029] wherein:

[0030] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

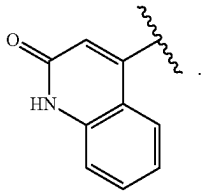
[0031] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0032] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

[0033] In some embodiments, U in Formula A is NR^8.

[0034] In some embodiments, U in Formula A is O.

[0035] In some embodiments, U in Formula A is null. In such embodiments, R^{100} in some cases can be hydrogen. For example, in some embodiments, U-L^2-R^{100} can be represented by

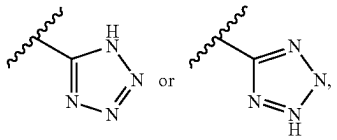


[0036] In some embodiments, U in Formula A is S, S(O), or SO_2.

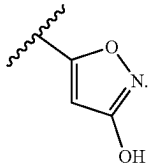
[0037] In some embodiments, R^{100} in Formula A is R^{103}, i.e., R^{102} is null.

[0038] In some embodiments, R^{103} is COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, or $SO_2NG^3G^3$.

[0039] In some embodiments, R^{103} is a 5- or 6-membered ring having a hydrogen bond donor, typically a heterocyclic ring or a heteroaryl, more preferably, a carboxylic acid bioisostere, e.g., a tetrazolyl. The hydrogen bond donor can be derived from a ring atom, such as

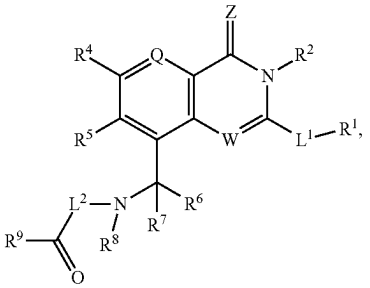


or a non-ring atom, for example,



[0040] In some embodiments, the compound of Formula A can be characterized as having a structure according to Formula I:

Formula I



[0041] wherein:

[0042] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

[0043] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0044] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$,

[0045] wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure,

[0046] wherein W, Q, Z, L^1, L^2, R^1, R^2, R^4, and R^5 are defined herein.

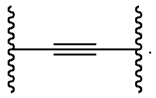
[0047] In some embodiments, Q in Formula A (e.g., Formula I) is N.

[0048] In some embodiments, Q in Formula A (e.g., Formula I) is CR^3, wherein R^3 is defined herein. For example, in some embodiments, R^3 is hydrogen. In some embodiments, R^3 is deuterium. In some embodiments, R^3 is halogen (such as F, Cl). In some embodiments, R^3 is CN. In some embodiments, R^3 is OH, or OG^1, wherein G^1 is defined herein. In some embodiments, R^3 is G^1, wherein G^1 is defined herein. In some embodiments, R^3 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0049] In some preferred embodiments, Z in Formula A (e.g., Formula I) is O.

[0050] In some embodiments, Z in Formula A (e.g., Formula I) is NR^{11}, wherein R^{11} is defined herein. For example, in some embodiments, R^{11} can be a C_{1-4} alkoxy, such as methoxy. When Z is NR^{11}, the compound may have geometric isomers due to the double bond in the $C{=}NR^{11}$ moiety. Unless otherwise specified or contradictory from context, the compounds herein having a $C{=}NR^{11}$ moiety should be understood as encompassing either geometric isomer or any mixture thereof.

[0051] In some embodiments, L^1 in Formula A (e.g., Formula I) is O, C(O), S, S(O), SO_2, or NR^{101}. In some embodiments, L^1 in Formula A (e.g., Formula I) is an optionally substituted C_{1-6} alkylene, such as CH_2. In some embodiments, L^1 in Formula A (e.g., Formula I) is optionally substituted C_{2-6} alkynylene, such as

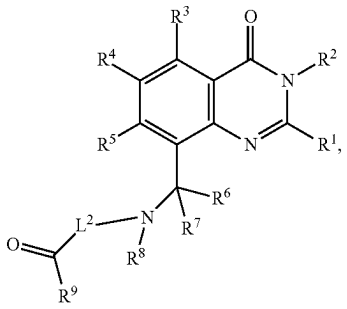


In some embodiments, L^1 in Formula A (e.g., Formula I) is an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms.

[0052] In some preferred embodiments, L^1 in Formula A (e.g., Formula I) is null.

[0053] For example, in some embodiments, the compound of Formula I can be characterized as having a structure according to Formula I-1:

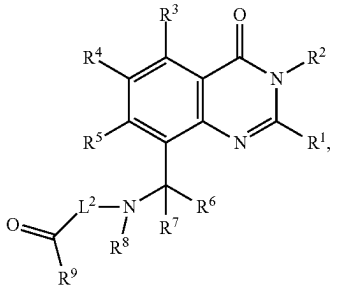
Formula I-1



[0054] wherein W, L^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

[0055] In some preferred embodiments, W in Formula A (e.g., Formula I or I-1) is N. For example, in some embodiments, the compound of Formula I-1 has a structure of Formula I-1-a:

Formula I-1-a

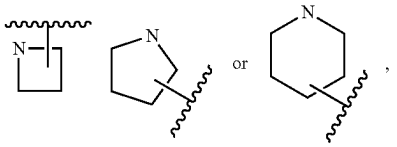


wherein L^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

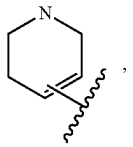
[0056] In some embodiments, W in Formula A (e.g., Formula I or I-1) is CR^{10}, wherein R^{10} is defined herein. For example, in some embodiments, R^{10} is hydrogen.

[0057] R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is typically an optionally substituted 4-12 (e.g., 4, 5, 6, 7, 8, 9, or 10) membered heterocyclyl having 1 or 2 ring heteroatoms each independently selected from O, N, or S. When substituted, the 4-12 membered heterocyclyl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, oxo, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. In some embodiments, the 3-12 membered ring for G^4 is a 3-7 membered ring.

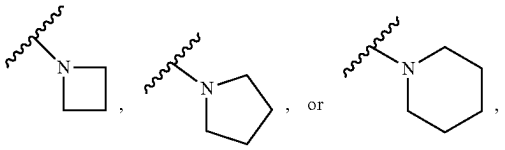
[0058] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is an optionally substituted 4-7 membered monocyclic heterocyclyl having 1 or 2 ring heteroatoms each independently selected from O, N, or S. For example, in some embodiments, R^1 can be an optionally substituted 4-7 membered monocyclic heterocyclyl having 1 ring heteroatom, preferably, 1 ring nitrogen atom. In some embodiments, the monocyclic heterocyclyl is a fully saturated heterocyclyl ring, such as



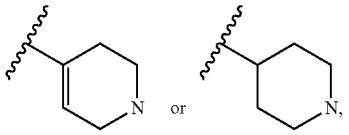
which is optionally substituted. In some embodiments, the monocyclic heterocyclyl contains 1 or more carbon-carbon or carbon-nitrogen double bonds in the ring, such as



which is optionally substituted. The monocyclic heterocyclyl can be attached to the remainder of Formula A through a carbon or N ring atom. For example, in some embodiments, R^1 can be attached to the remainder of Formula A through a ring nitrogen atom, such as



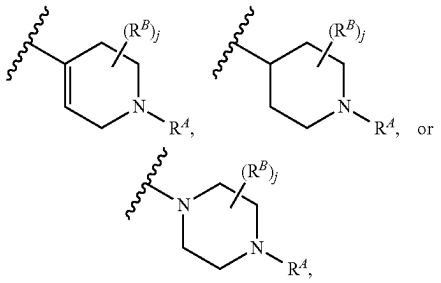
which is optionally substituted. In some embodiments, R^1 can be attached to the remainder of Formula A through a ring carbon atom, such as



which is optionally substituted. When substituted, the 4-7 membered monocyclic heterocyclyl can be substituted any available positions as valence permits, including at ring carbon and/or nitrogen atom(s). When substituted, the 4-7 membered monocyclic heterocyclyl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, oxo, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,

5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

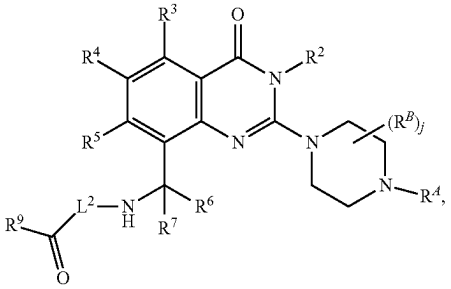
[0059] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



wherein R^A is G^{4A}, $C(O)G^4$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1} wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; wherein R^B at each occurrence is independently F, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and j is 0, 1, or 2. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-7 membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-7 membered ring is a C_{3-7} cycloalkyl. In some embodiments, the 3-7 membered ring is a 4-7 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-7 membered ring is phenyl. In some embodiments, the 3-7 membered ring is a 5-membered heteroaryl having 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-7 membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-7 membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, or phenyl. In some embodiments, j is 0. In some embodiments, j is 1 or 2, and R^B is defined herein, for example, in some embodiments, R^B is methyl. In some embodiments, R^A can also have the definition described herein below for the variable R^C or R^D.

[0060] For example, in some embodiments, the compound of Formula A can have a structure according to Formula I-1-b:

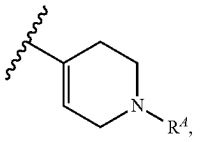
Formula I-1-b



wherein the variables j, L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^A and R^B are defined herein.

[0061] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-1:

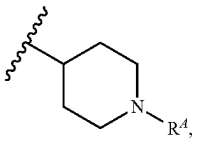
(M-1)



wherein R^A is defined herein.

[0062] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-2:

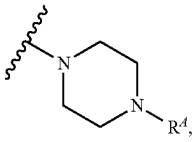
(M-2)



wherein R^A is defined herein.

[0063] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-3:

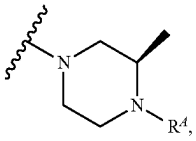
(M-3)



wherein R^A is defined herein.

[0064] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-4:

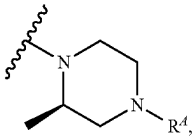
(M-4)



wherein R^A is defined herein.

[0065] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-5:

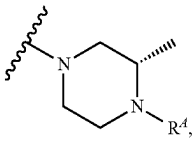
(M-5)



wherein R^A is defined herein.

[0066] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-6:

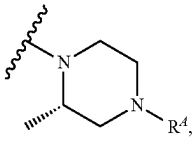
(M-6)



wherein R^A is defined herein.

[0067] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-7:

(M-7)

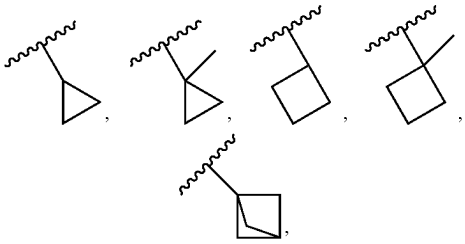


wherein R^A is defined herein.

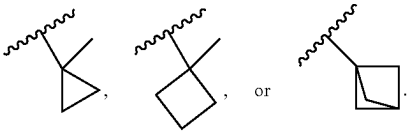
[0068] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-7) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)NHG^{5A}$, $C(O)NG^{5A}G^{5A}$, SO_2G^{5A}, SO_2NHG^{5A}, or $SO_2NG^{5A}G^{5A}$, wherein G^{5A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl; (ii) 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1}, wherein G^{B1} at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or cyclopropyl.

[0069] For example, in some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-7 above, and M-8 to M-15 as described hereinbelow) can be G^{5A}, $C(O)G^{5A}$ $C(010G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl. In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-7) can be C_{1-4} alkyl optionally substituted with 1-3 F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl.

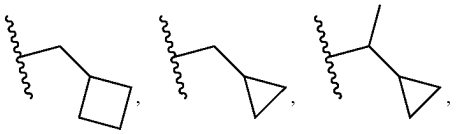
[0070] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)N(CH_3)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



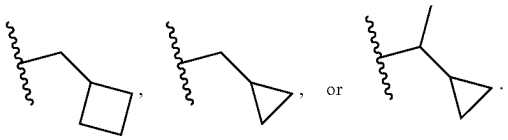
etc. In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



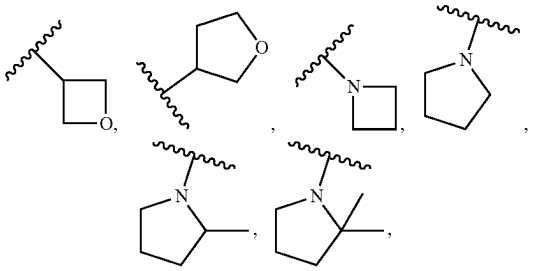
[0071] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)N(CH_3)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



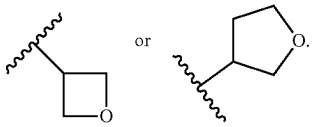
etc. In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be $C(O)G^{5A}$ or $C(O)OG^{5A}$, wherein G^{5A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



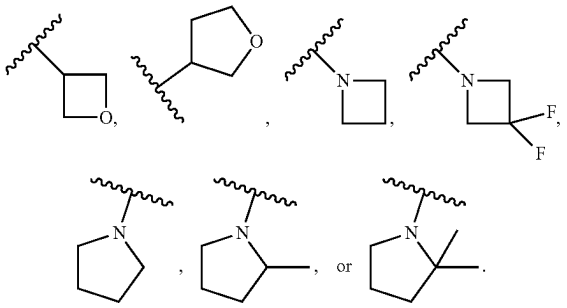
[0072] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)N(CH_3)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



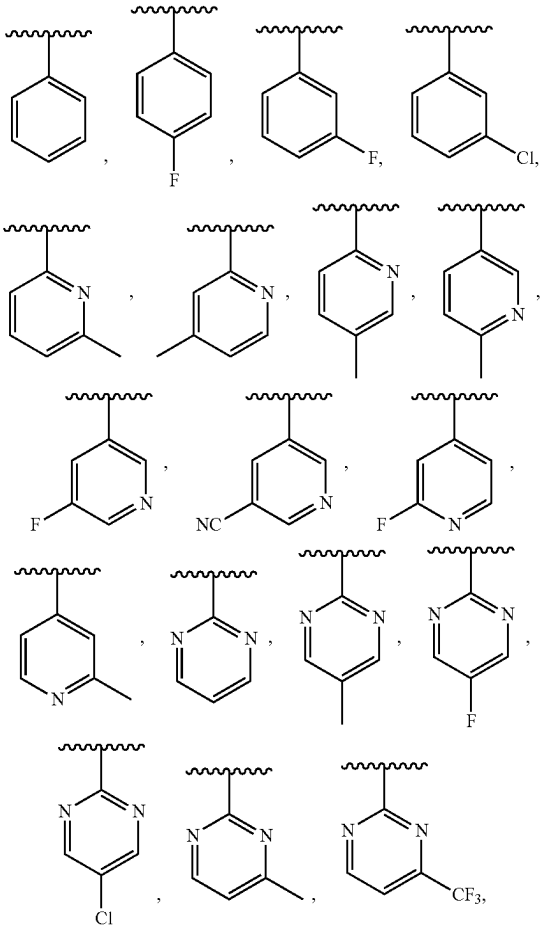
etc. Preferably, the 4-6 membered heterocyclic does not connect to a heteroatom through a ring heteroatom. For example, in some embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be G^{5A} which can be



In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be $C(O)G^{5A}$, wherein G^{5A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



[0073] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be G^{5A}, $C(O)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is phenyl or 5-10 membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



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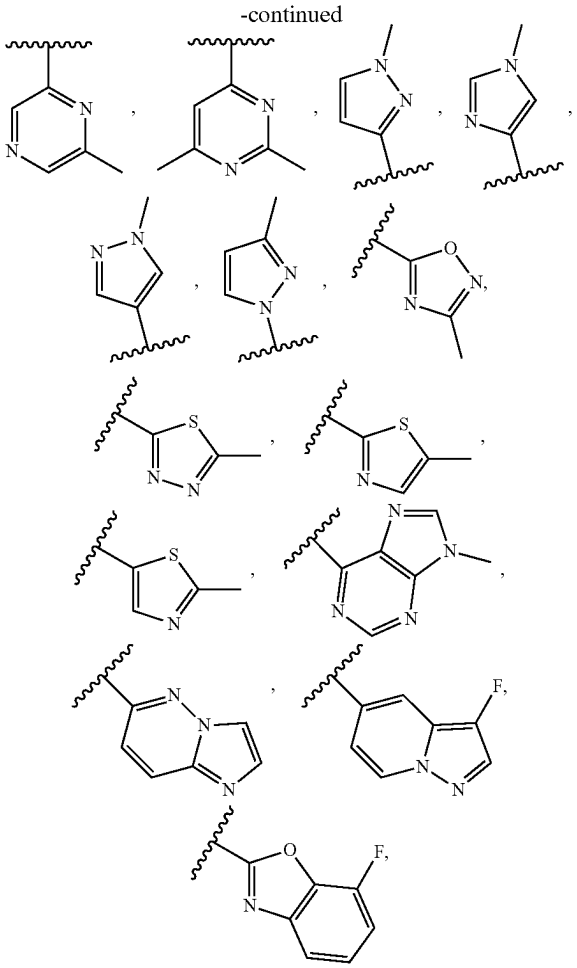
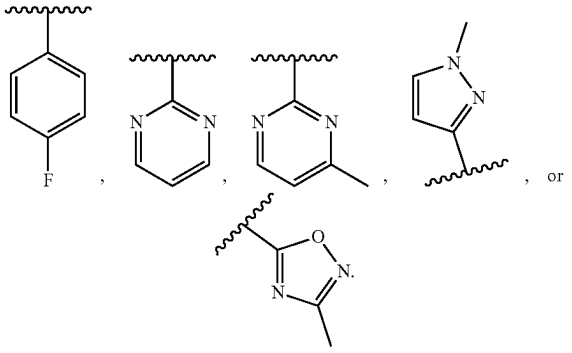


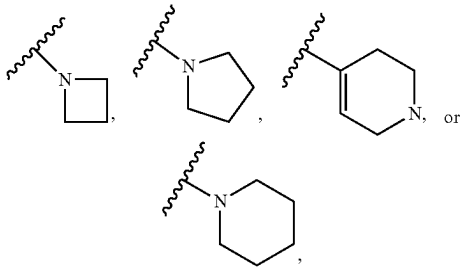
etc. In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be G^{5A} or $C(O)G^{5A}$, wherein G^{5A} is phenyl or 5- or 6-membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



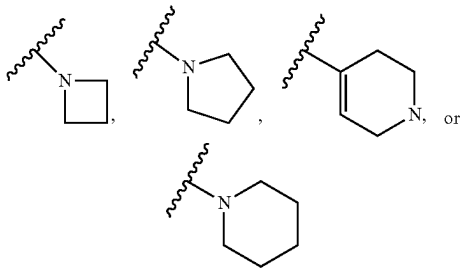
[0074] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be $C(O)NHG^{5A}$ wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). For example, R^A can be CONH(isopropyl).

[0075] In some preferred embodiments, R^A in the structures herein (e.g., M-1 to M-15) can be $C(O)NG^{5A}G^{5A}$, wherein one instance of G^5 is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. For example, R^A can be $CON(CH_3)_2$.

[0076] In some more specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



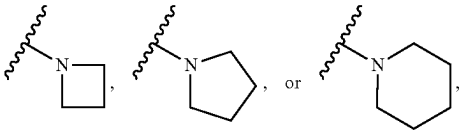
which is optionally substituted. Typically, when substituted, the



can be substituted with 1-3 (e.g., 1 or 2) substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, NH—$C(O)G^5$, or $C(O)G^5$, wherein G^5 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is indepen-

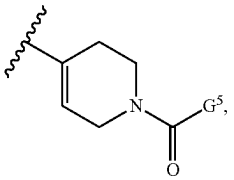
dently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0077] For example, in some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



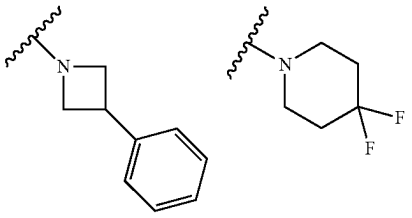
each of which is optionally substituted with 1-3 (e.g., 1 or 2) substituents independently selected from deuterium, F, G^5, or NH—C(O)G^5, wherein G^5 is defined herein. For example, in some embodiments, G^5 is a C_{1-4} alkyl optionally substituted with 1-3F. In some embodiments, G^5 is a 3-12, such as 3-7 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl), pyrimidinyl, phenyl, etc.), such as phenyl, which is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B is defined herein.

[0078] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



wherein G^5 is defined herein. For example, in some embodiments, G^5 is a C_{1-4} alkyl optionally substituted with 1-3F. In some embodiments, G^5 is a 3-12, such as 3-7 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), which is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B is defined herein.

[0079] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be selected from:



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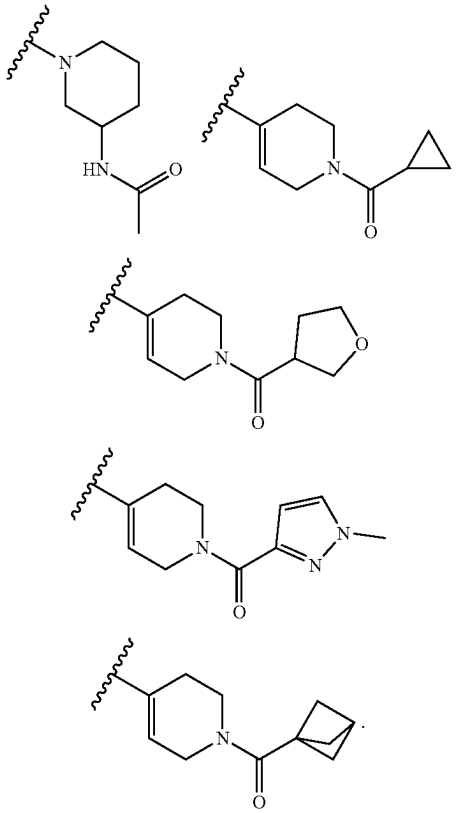
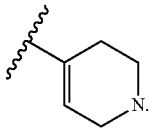
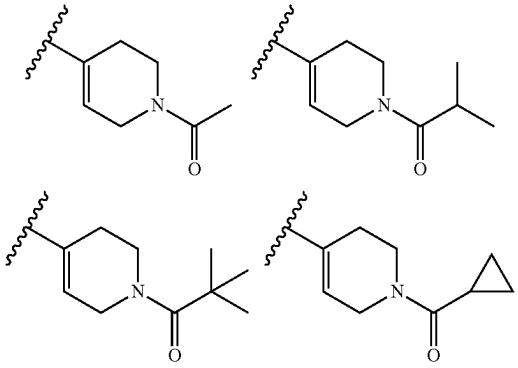


[0080] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted



For example, R^1 can be selected from:



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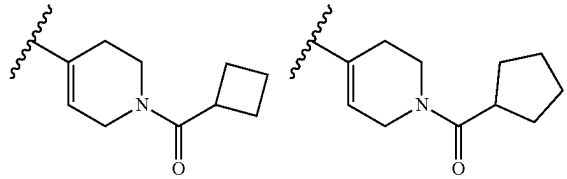

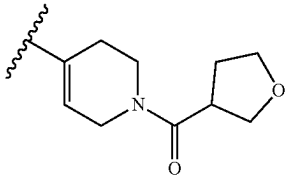

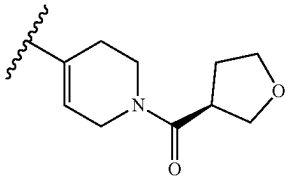

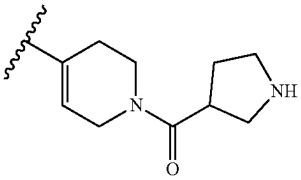

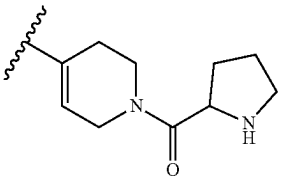

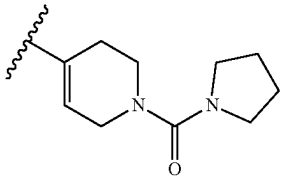

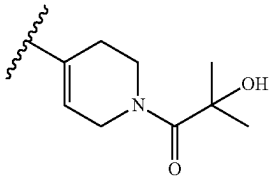

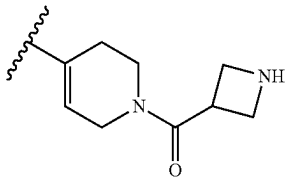

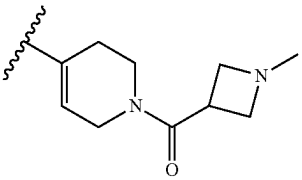

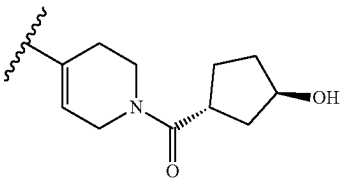

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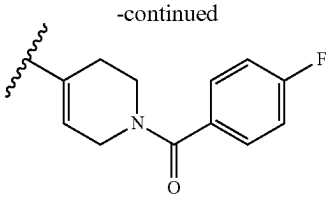

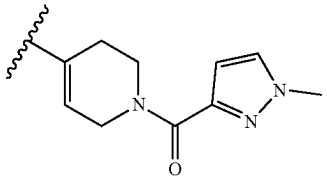

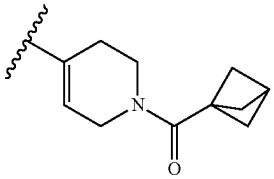

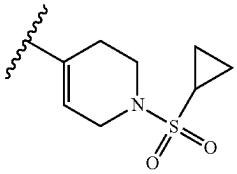

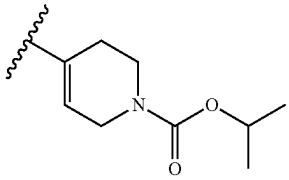

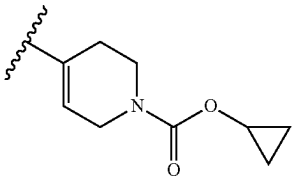

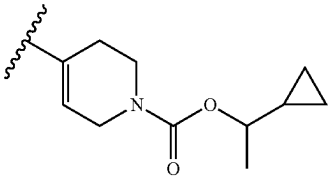

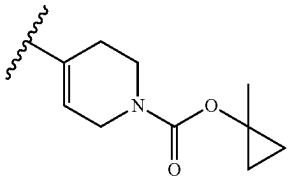

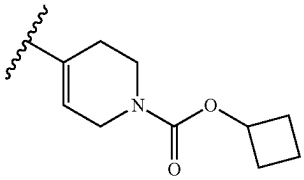

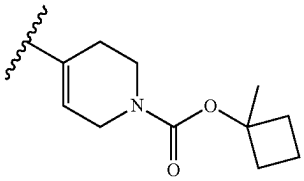

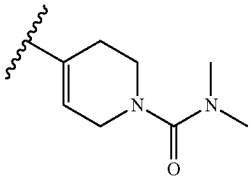

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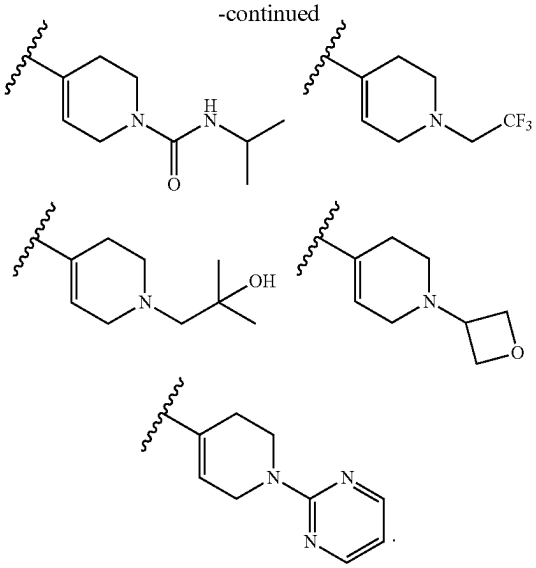
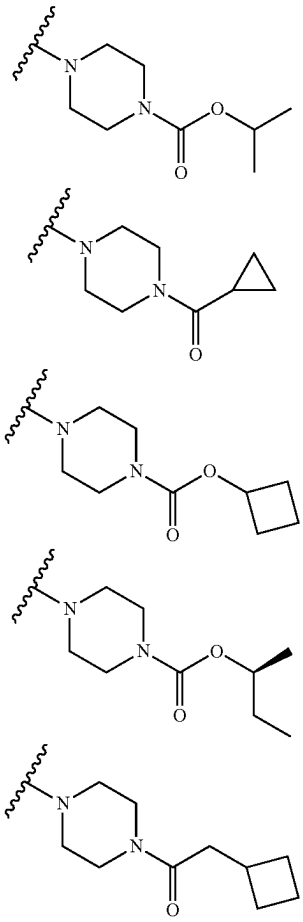


[0081] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted piperazine, for example, R^1 can be selected from:



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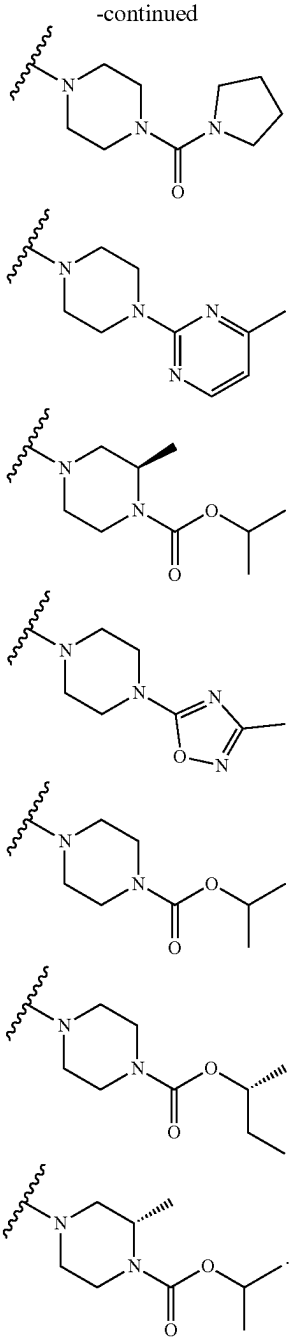
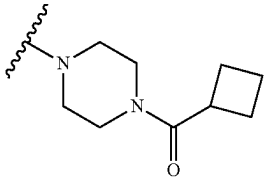


[0082] For example, in some embodiments, R^1 can be selected from:



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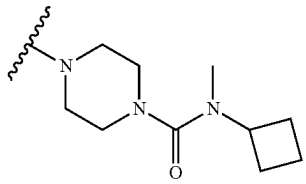

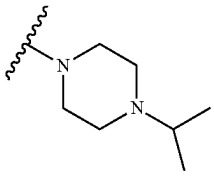

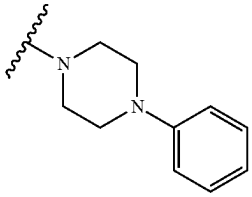

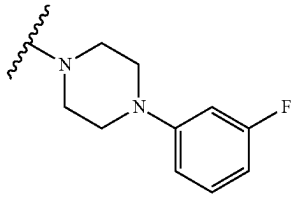

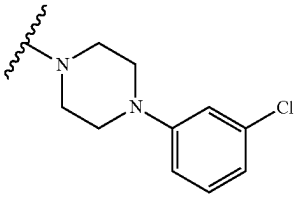

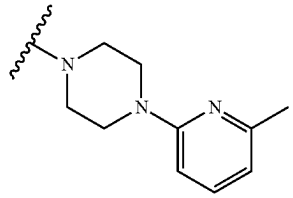

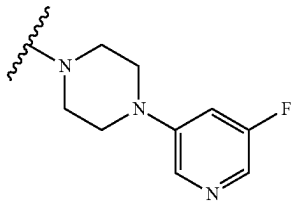

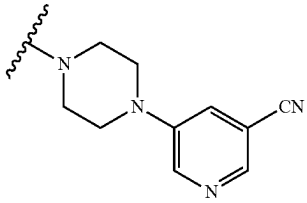

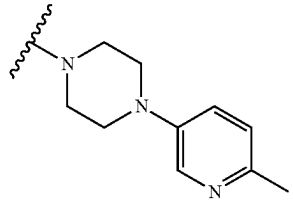

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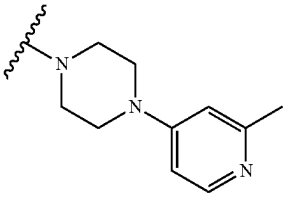

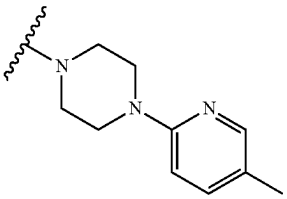

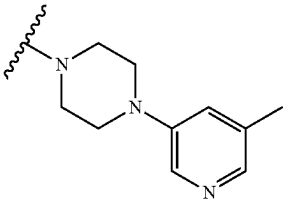

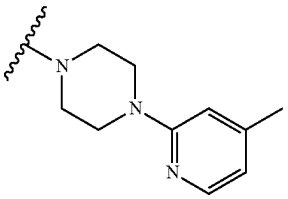

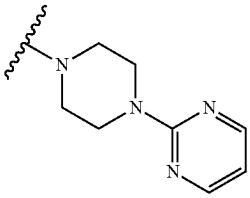

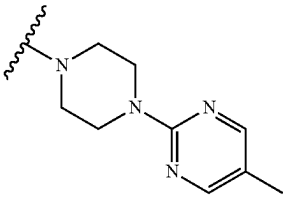

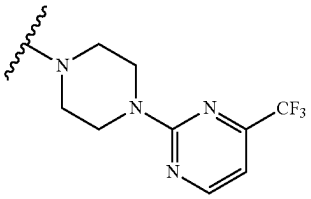

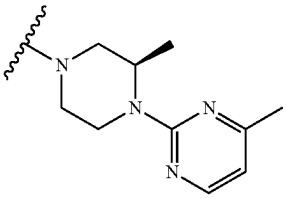

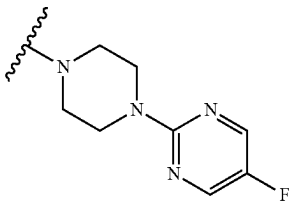

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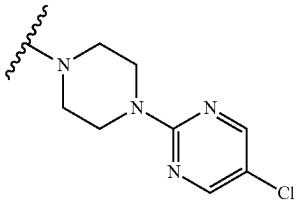

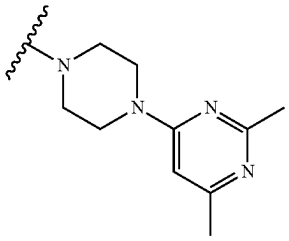

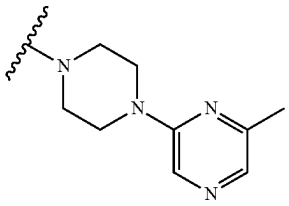

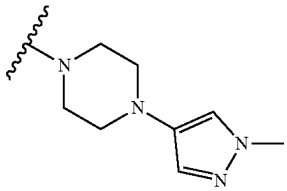

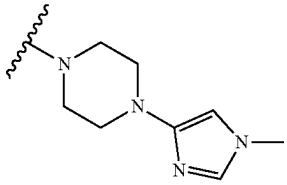

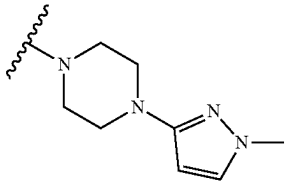

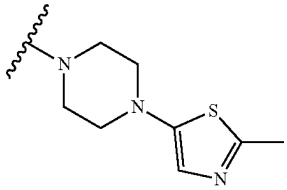

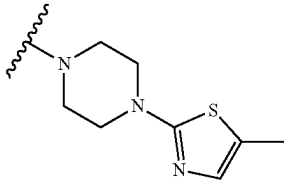

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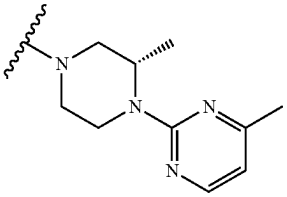

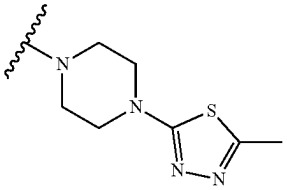

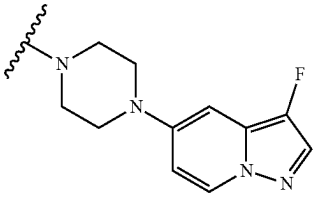

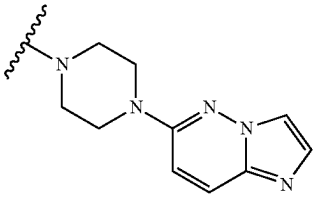

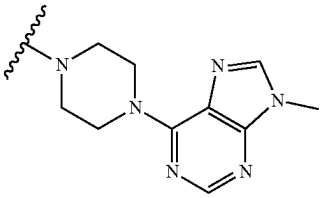

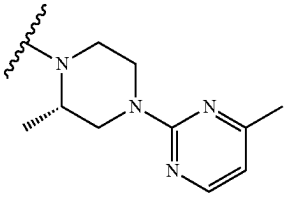

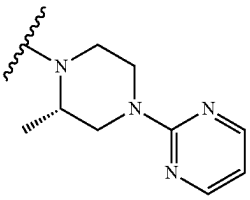

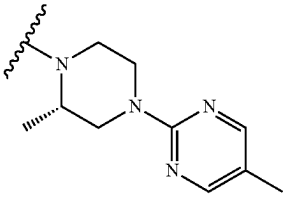

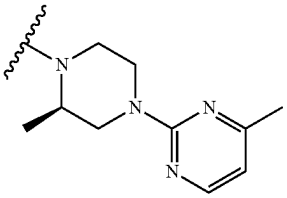

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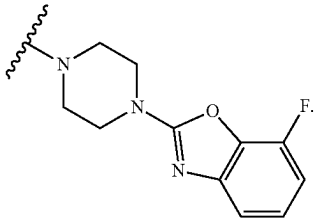
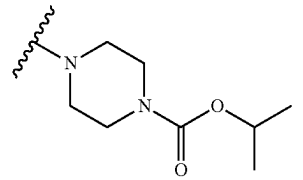
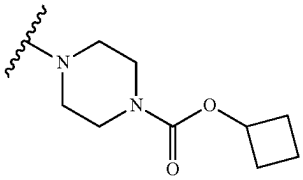
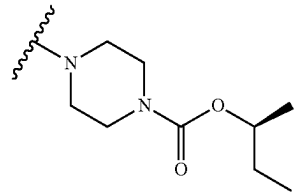
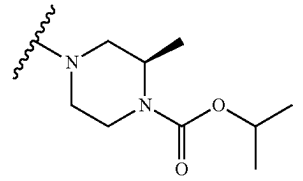


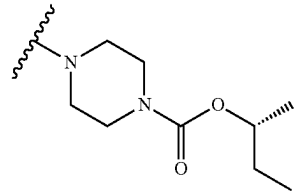
[0083] In some embodiments, R^1 can be selected from:

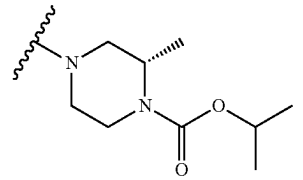


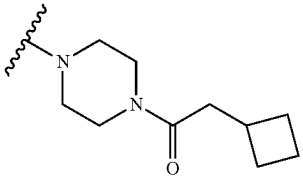












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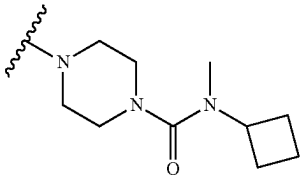

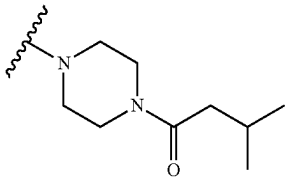

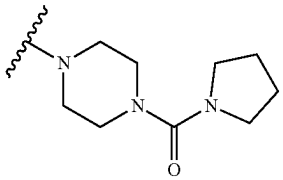

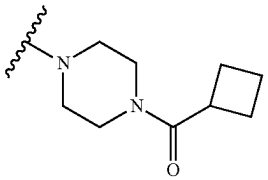

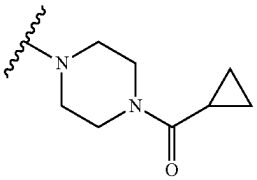

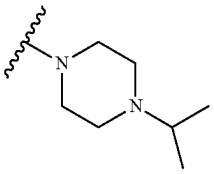

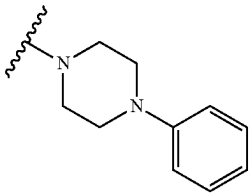

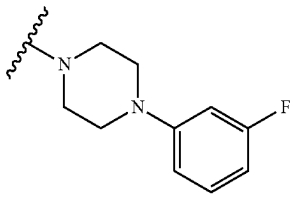

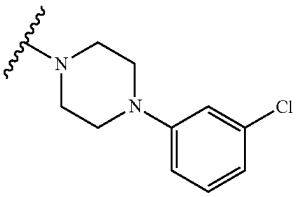

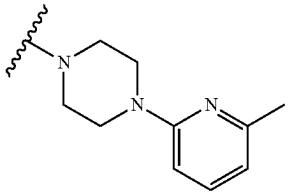

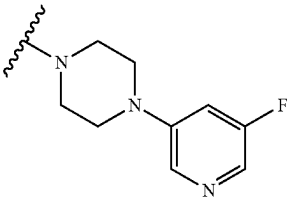

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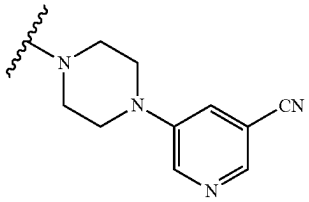

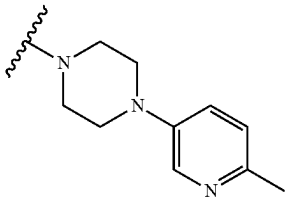

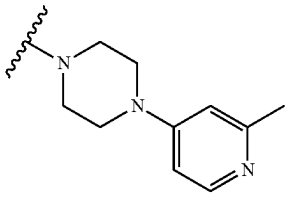

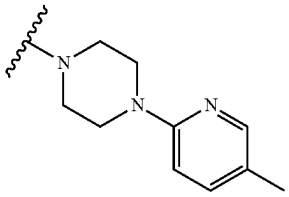

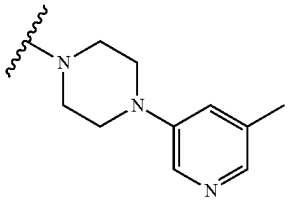

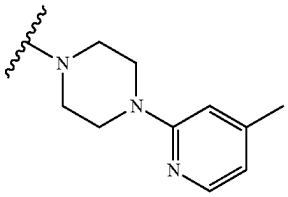

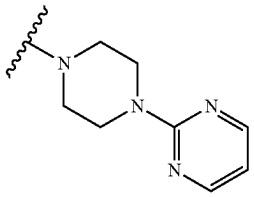

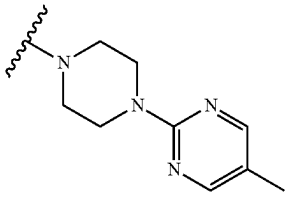

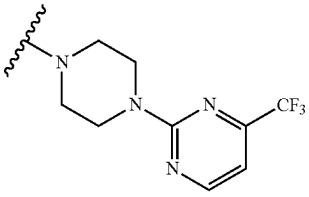

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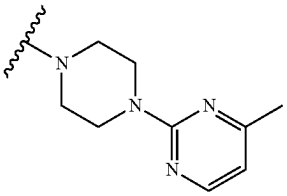

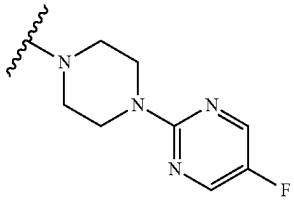

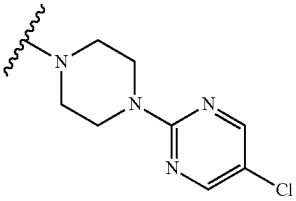

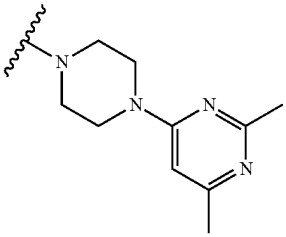

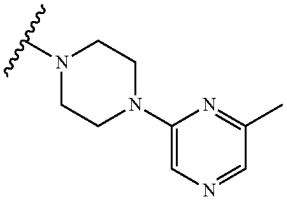

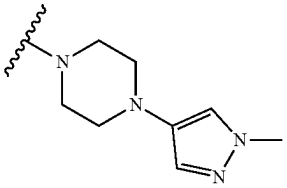

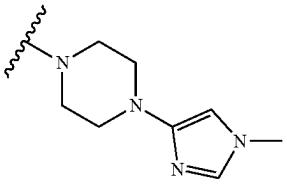

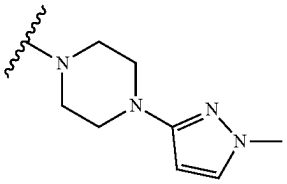

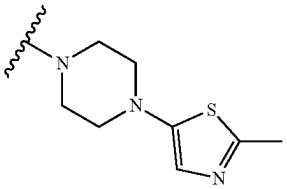

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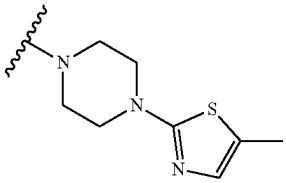

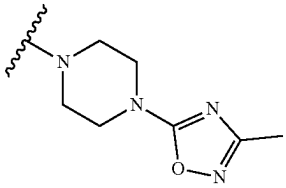

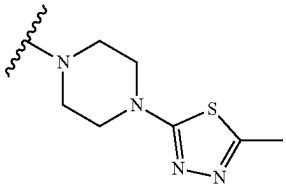

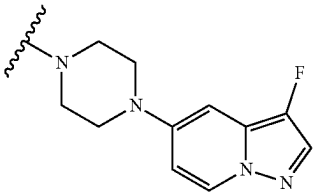

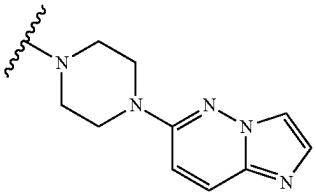

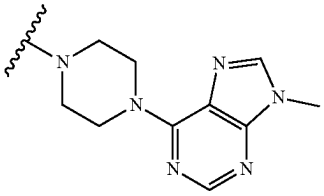

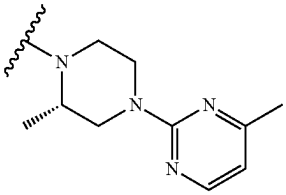

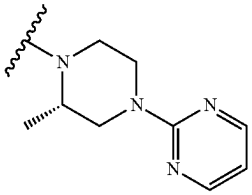

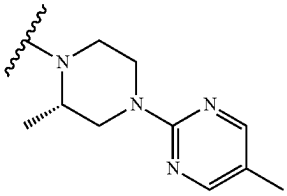

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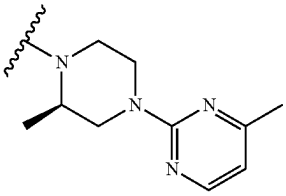
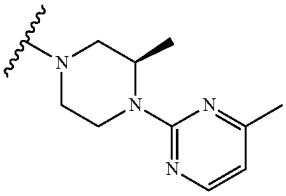
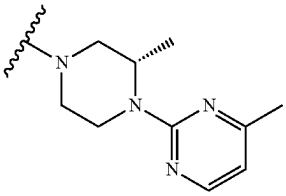
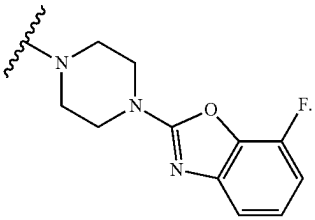
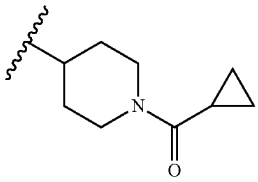


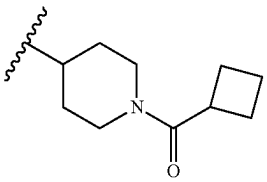


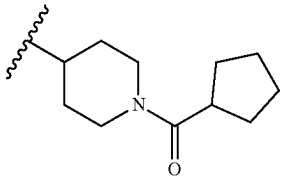


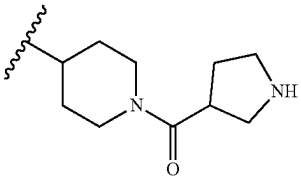


[0084] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted piperidine, for example, R^1 can be selected from:









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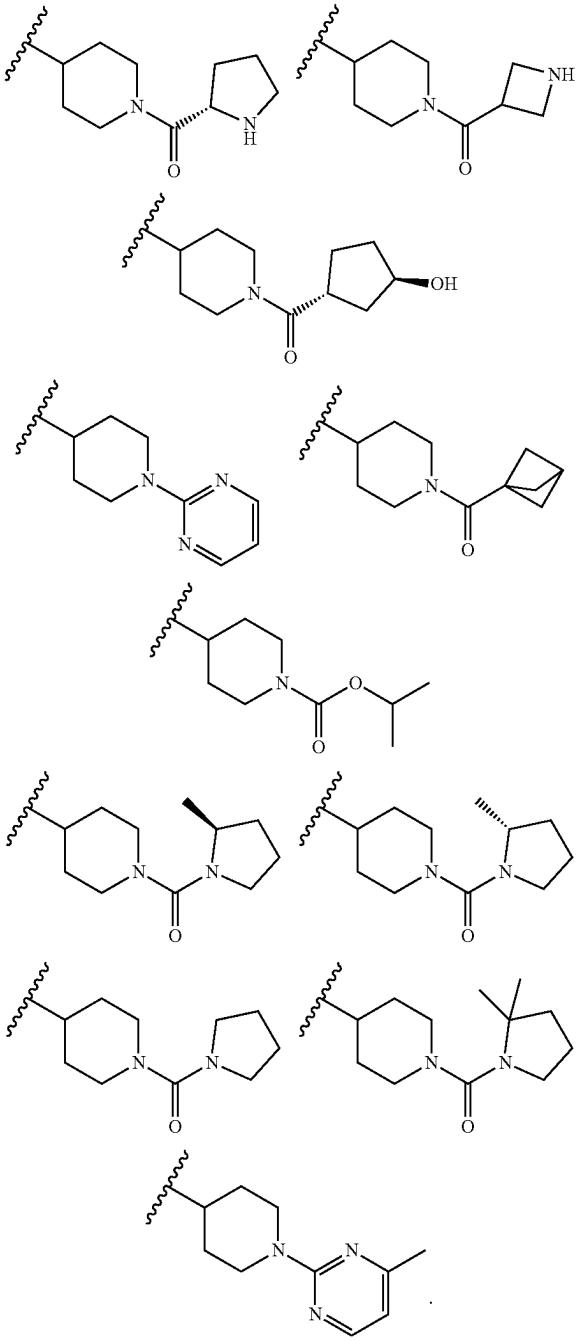

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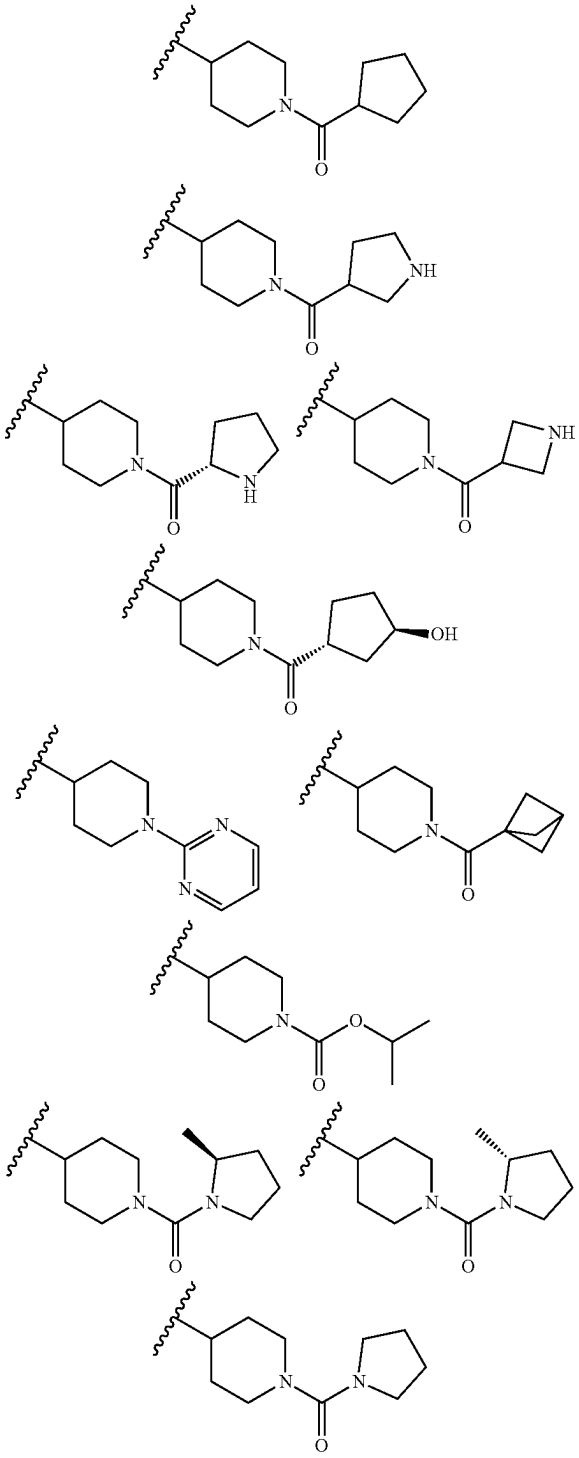
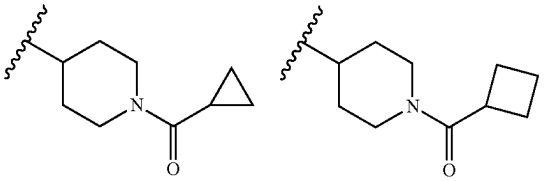
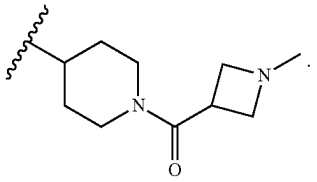


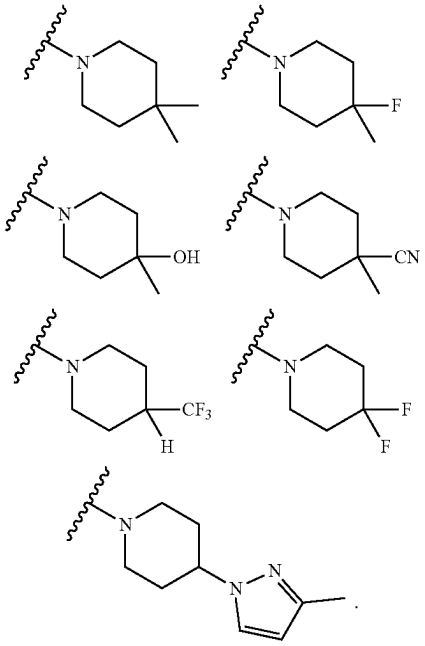
[0085] In some embodiments, R^1 can be selected from:



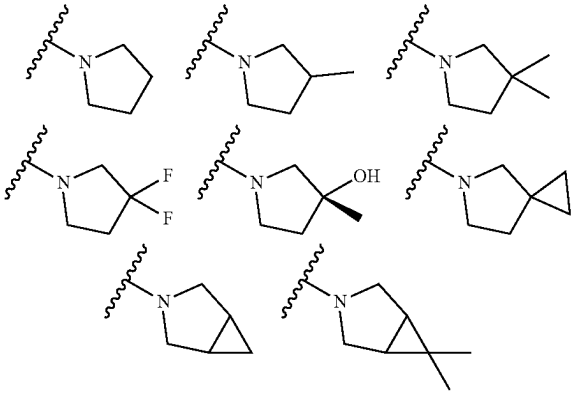
[0086] In some embodiments, R^1 can be selected from:



[0087] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted piperidine, which attaches to the remainder of the molecule through the ring nitrogen, for example, in some embodiments, R^1 can be selected from:



[0088] In some embodiments, R^1 can be selected from:



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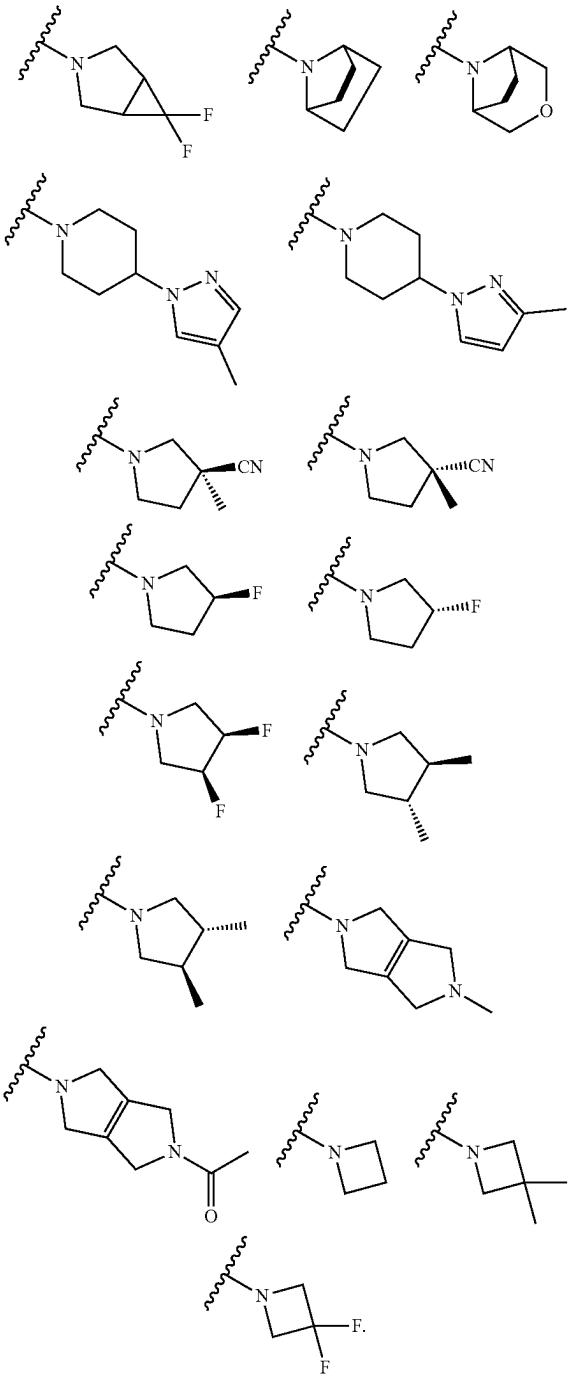
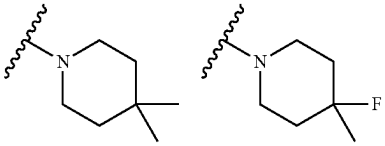


[0089] In some embodiments, R^1 can be selected from:



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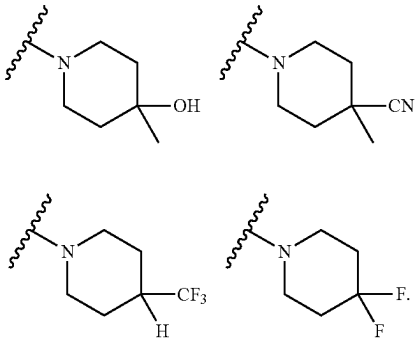
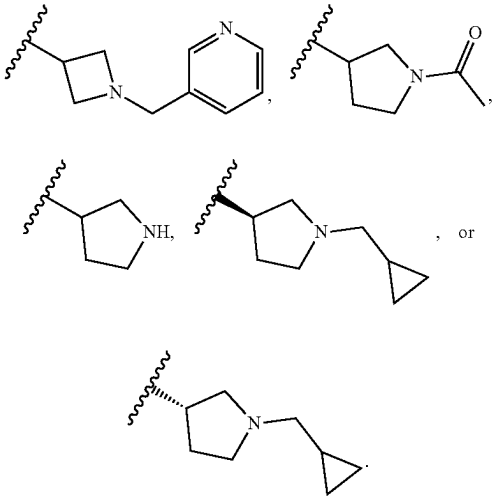
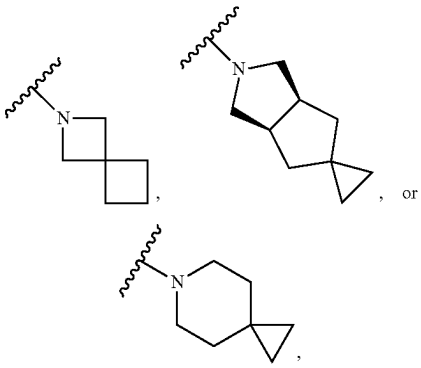


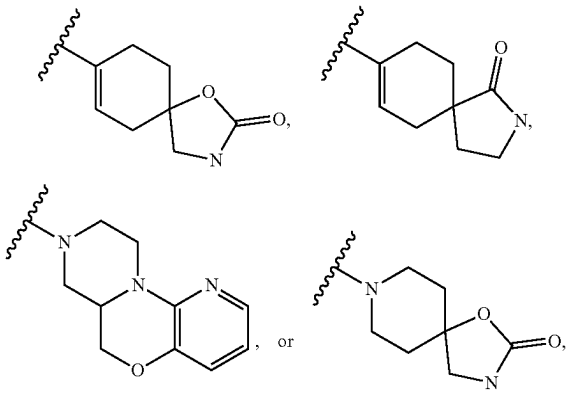
[0090] In some specific embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be selected from:



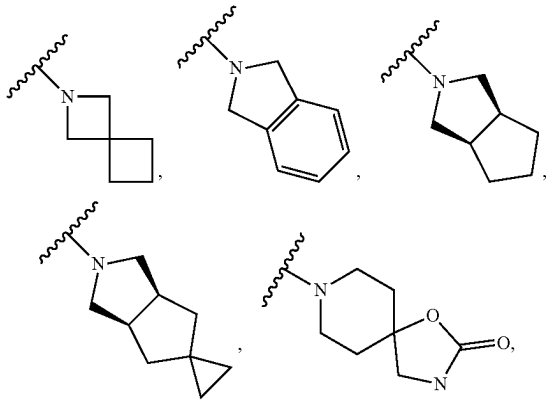
[0091] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is an optionally substituted 6-12 (preferably 7-11 membered, such as 8, 9, or 10-membered) polycyclic heterocyclyl (such as spiro, fused, or bridged bicyclic heterocyclyl) having 1-3 ring heteroatoms each independently selected from O, N, or S. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is an optionally substituted 6-12 membered polycyclic heterocyclyl (such as spiro, fused, or bridged bicyclic heterocyclyl) having 1 or 2 ring heteroatoms each independently selected from O, N, or S. For example, in some embodiments, the 6-12 membered polycyclic heterocyclyl contains 1 ring heteroatom, preferably, ring nitrogen, which can be present in any of the rings of the heterocyclyl. In some embodiments, the 6-12 membered polycyclic heterocyclyl contains 2 ring heteroatoms, such as two ring nitrogens or one ring nitrogen and one ring oxygen, wherein the heteroatoms can be in any one or more of the rings of the heterocyclyl. In some embodiments, the polycyclic heterocyclyl is a fully saturated heterocyclyl ring, such as



which is optionally substituted. In some embodiments, the polycyclic heterocyclyl contains 1 or more carbon-carbon or carbon-nitrogen double bonds in the ring and/or a carbonyl group, such as



which is optionally substituted. The polycyclic heterocyclyl can be attached to the remainder of Formula A through a carbon or N ring atom. For example, in some embodiments, R^1 can be attached to the remainder of Formula A through a ring nitrogen atom, such as



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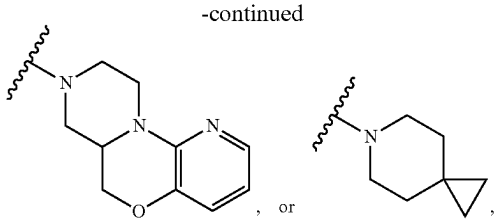
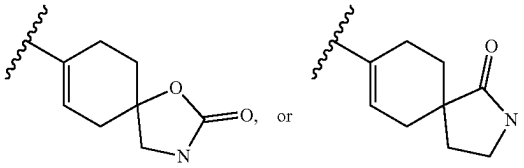
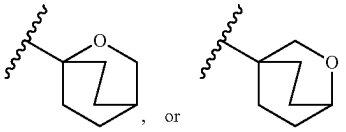


each of which is optionally substituted.

[0092] In some embodiments, R^1 can be attached to the remainder of Formula A through a ring carbon atom, such as



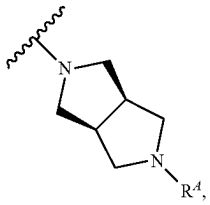
which is optionally substituted. In some embodiments, the polycyclic heterocyclyl is a bridged heterocyclyl ring, such as



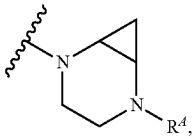
which is optionally substituted. Each ring of the 6-12 membered polycyclic heterocyclyl can be independently optionally substituted at any available positions as valence permits, including at ring carbon and/or nitrogen atom(s). When substituted, the 6-12 membered polycyclic heterocyclyl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, oxo, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. For example, in some embodiments, the substituents for the 6-12 membered polycyclic heterocyclyl can be independently selected from F, CN, methyl, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, or $C(O)NG^4G^4$, wherein G^4 is defined above.

[0093] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can have a structure according to:

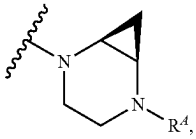
(M-8)



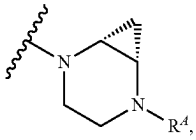
(M-9)



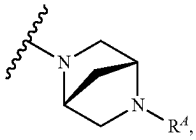
(M-10)



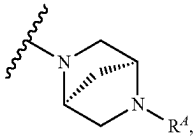
(M-11)



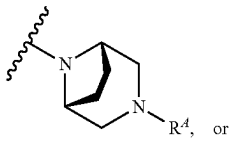
(M-12)



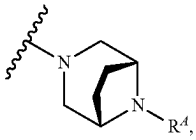
(M-13)



(M-14)



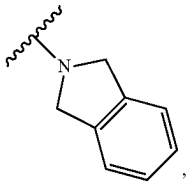
(M-15)



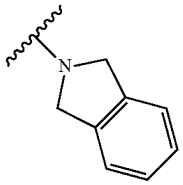
wherein R^A is G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}SO_2G^{4A}$, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl,

e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-12 (e.g., 3-7) membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-12 (e.g., 3-7) membered ring is a C_{3-7} cycloalkyl. In some embodiments, the 3-12 (e.g., 3-7) membered ring is a 4-7 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 (e.g., 3-7) membered ring is phenyl. In some embodiments, the 3-12 (e.g., 3-7) membered ring is a 5-membered heteroaryl having 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 (e.g., 3-7) membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 (e.g., 3-7) membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, or phenyl. In some embodiments, R^A in M-8 to M-15 can be any of those R^A described herein.

[0094] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is

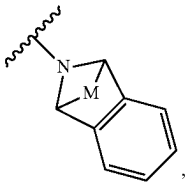


wherein each of the two rings can be independently optionally substituted. When one or both rings are substituted, the

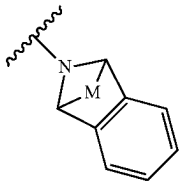


can be typically substituted with one or more substituents, such as with a total of 1-3 (e.g., 1 or 2) substituents, each independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—C(O)G^5, or C(O)G^5, wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0095] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is



wherein M is —CH_2—, or —CH_2CH_2—, wherein each of the rings can be independently optionally substituted. When at least one of the rings are substituted, the

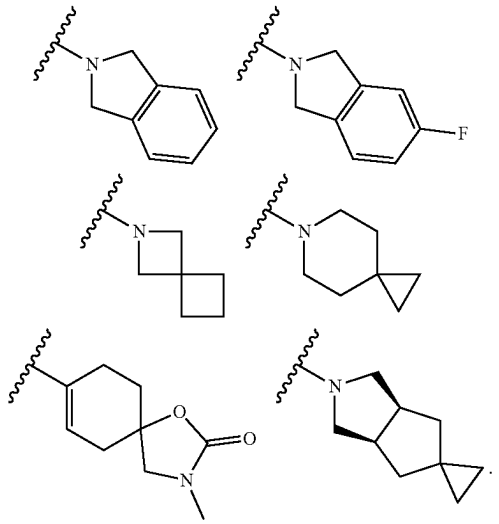


can be typically with one or more substituents, such as with a total of 1-3 (e.g., 1 or 2) substituents, each independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—C(O)G^5, or C(O)G^5,

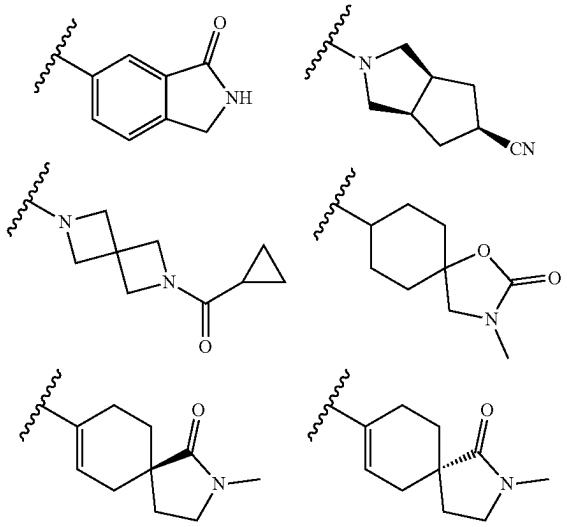
[0096] wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxa-

zolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0097] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is selected from:



[0098] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is selected from:



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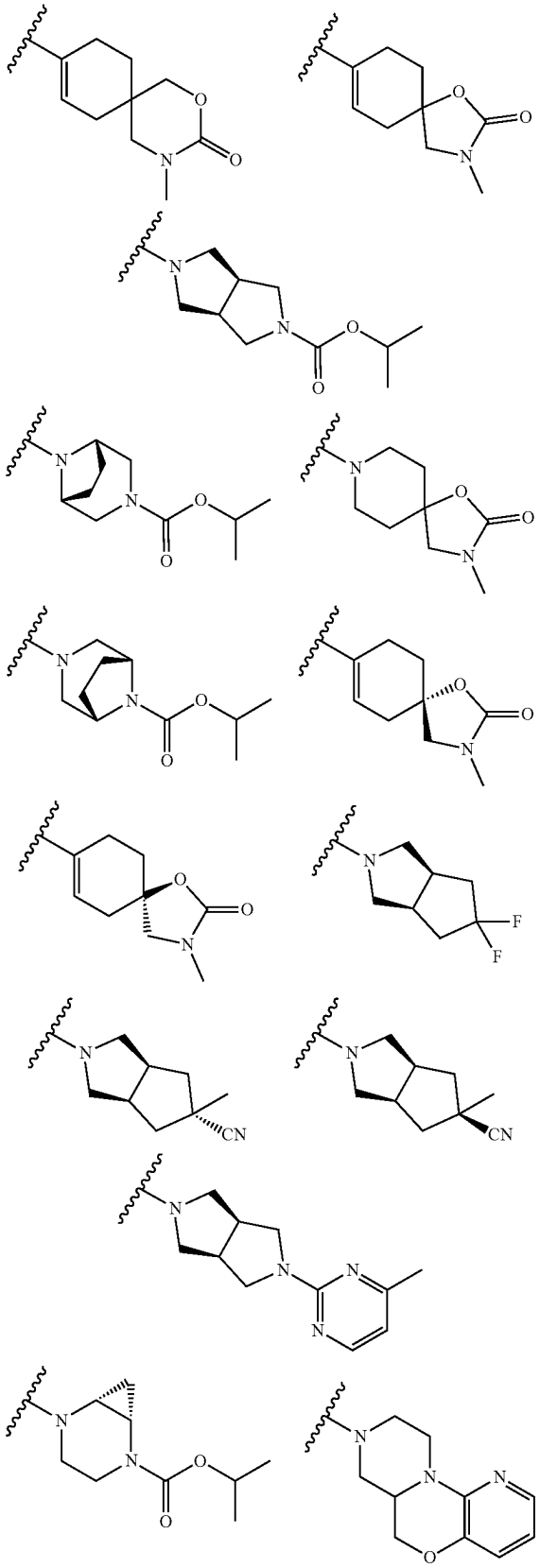

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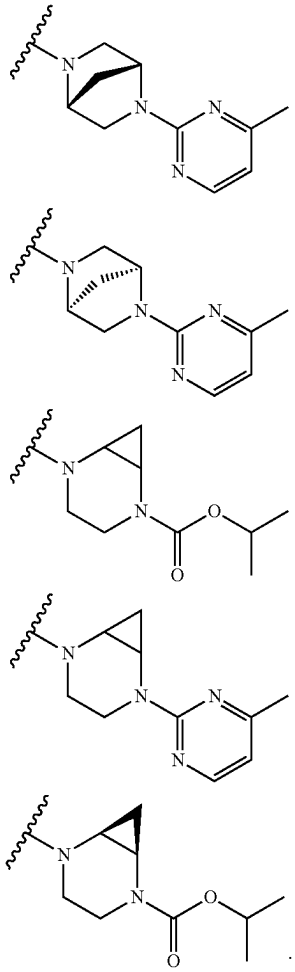
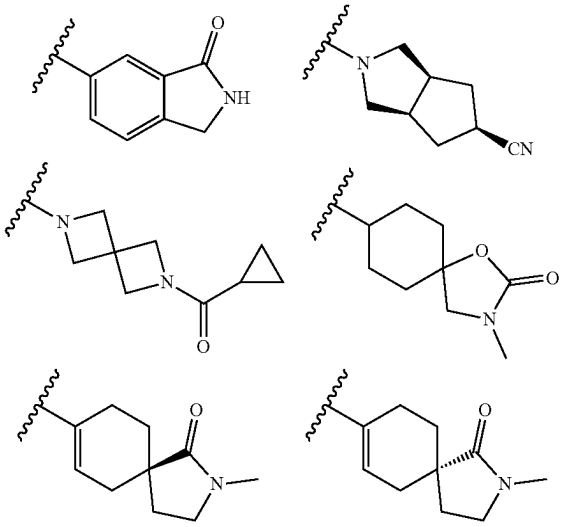


[0099] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) is selected from:



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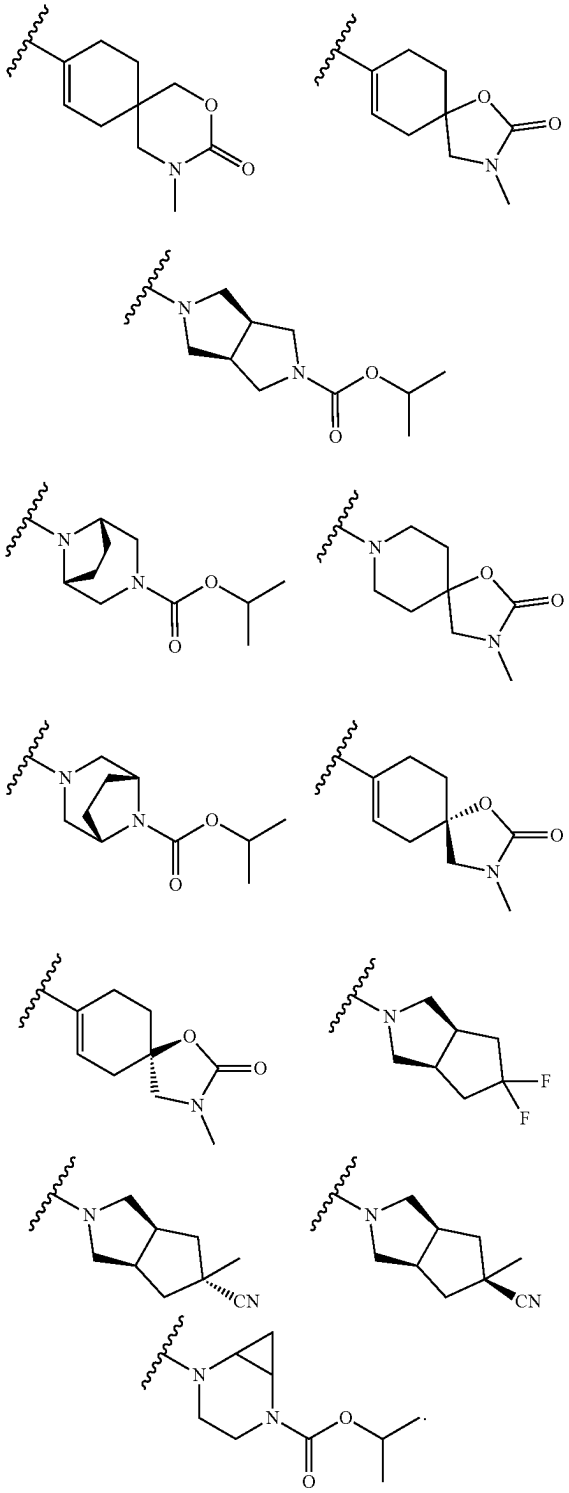
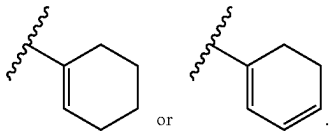
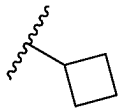


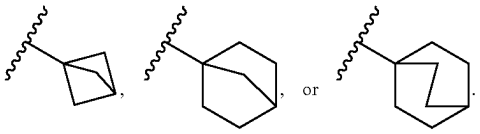
[0100] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be a 4-10, such as a 4-7 membered carbocyclyl, which is optionally substituted. The 4-10 membered carbocyclyl can be monocyclic or polycyclic. In some embodiments, the 4-10 membered carbocyclyl has one or two carbon-carbon double bonds, such as



In some embodiments, the 4-10 membered carbocyclyl can also be fully saturated, such as

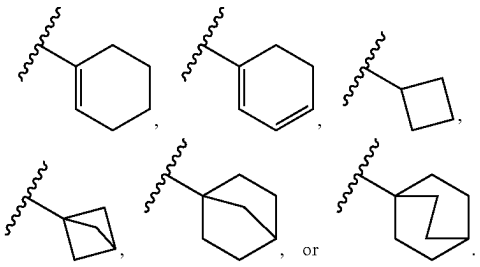


or cyclohexyl. In some embodiments, the 4-10 membered carbocyclyl can be a bridged ring, such as

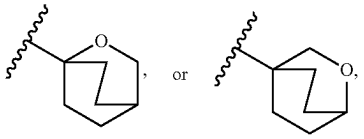


When substituted, the 4-10 membered carbocyclyl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, $NH—C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0101] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be

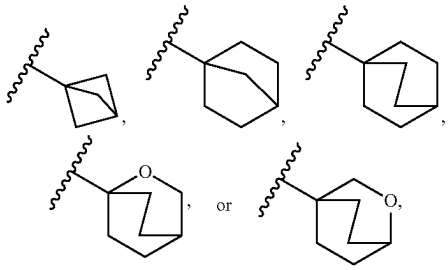


or can be



each of which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, $NH—C(O)G^5$, or $C(O)G^5$, wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

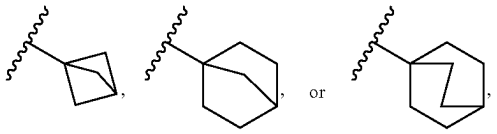
[0102] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be a bridged 5-12 membered ring structure, which is optionally substituted, wherein the bridged ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S. As used herein, a bridged ring structure refers to any ring structure that contains at least one bridge. Non-limiting bridged bicyclic ring structures include



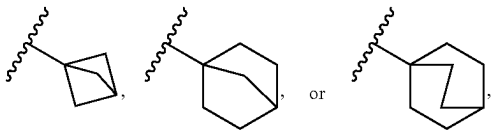
etc. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be a 5-12 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted. For example, in some embodiments, R^1 is a 5-8 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be a 5-12 membered (preferably, 7-10 membered, e.g., 7 or 8 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one ring heteroatom which is a ring oxygen. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be a 5-12 membered (preferably, 8-10 membered) bridged bicyclic heterocyclic ring structure, which is option-

ally substituted, wherein the bridged bicyclic heterocyclic ring structure has one or two ring heteroatoms independently selected from S, O, and N.

[0103] For example, in some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



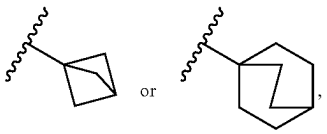
each of which is optionally substituted. When substituted, each of



can be typically substituted with 1-3 substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$,

[0104] wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

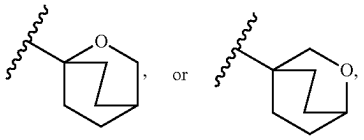
[0105] In some preferred embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



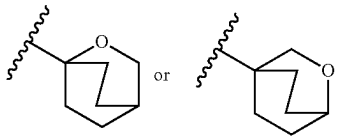
each of which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—$C(O)G^5$, or $C(O)G^5$,

[0106] wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

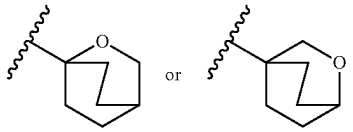
[0107] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



each of which is optionally substituted. When substituted, each of



can typically be substituted with 1-3 substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. In some preferred embodiments, each of

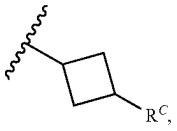


can be optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—C(O)G^5, or C(O)G^5,

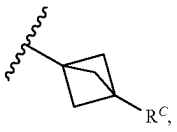
[0108] wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0109] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be a structure of

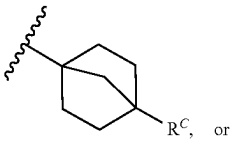
(M-16)



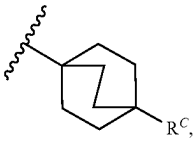
(M-17)



(M-18)

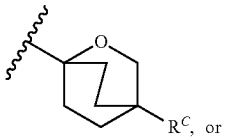


(M-19)

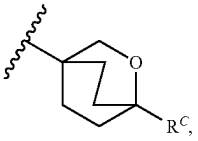


or can be a structure of

(M-19′)



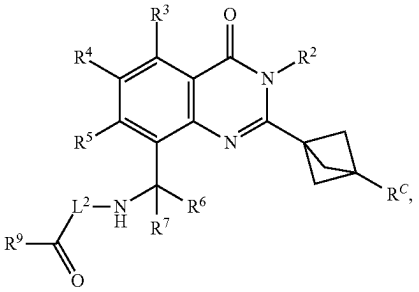
(M-19″)



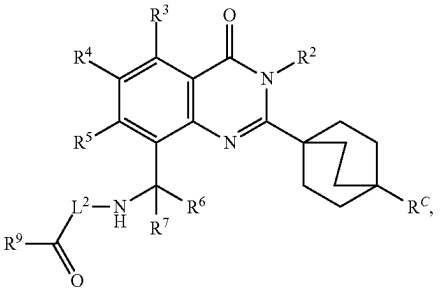
wherein R^C is hydrogen, halogen (e.g., F), CN, COOH, $CONH_2$, G^{4A}, OG^{4A}, C(O)G^{4A}, C(O)OG^{4A}, C(O)NHG^{4A}, C(O)N$G^{4A}G^{4A}$, NHC(O)G^{4A}, NHC(O)OG^{4A}, NHC(O)NHG^{4A} NHC(O)N$G^{4A}G^{4A}$, NG^{4A}C(O)G^{4A}, NG^{4A}C(O)OG^{4A}, NG^4C(O)NHG^{4A}, NG^{4A}C(O)N$G^{4A}G^{4A}$ SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-12 (e.g., 3-7) membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-12 (e.g., 3-7) membered ring is a C_{3-7} cycloalkyl. In some embodiments, the 3-12 (e.g., 3-7) membered ring is a 4-7 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 (e.g., 3-7) membered ring is phenyl. In some embodiments, the 3-12 (e.g., 3-7) membered ring is a 5-membered heteroaryl having 1-4, such as 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 (e.g., 3-7) membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 membered ring is a 3-7 membered

ring as defined herein. In some embodiments, the 3-12 membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, or phenyl. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-17, as defined herein. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-18, as defined herein. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-19, as defined herein. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-19', as defined herein. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-19", as defined herein. For example, in some embodiments, the compound of Formula A can have a structure according to Formula I-1-c, I-1-d, I-1-x, or I-1-y:

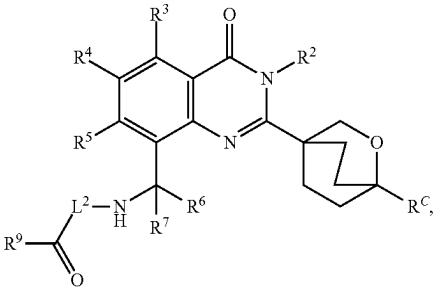
Formula I-1-c



Formula I-1-d



Formula I-1-x



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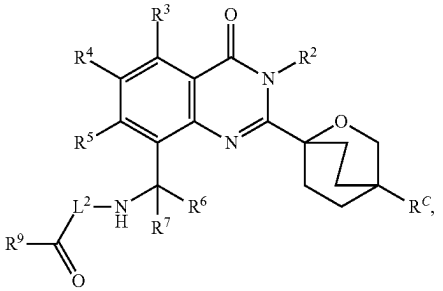
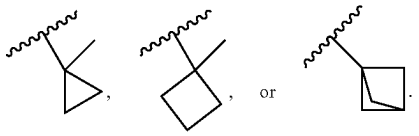
Formula I-1-y

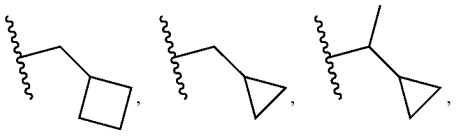


wherein the variables L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^9, and R^C are defined herein.

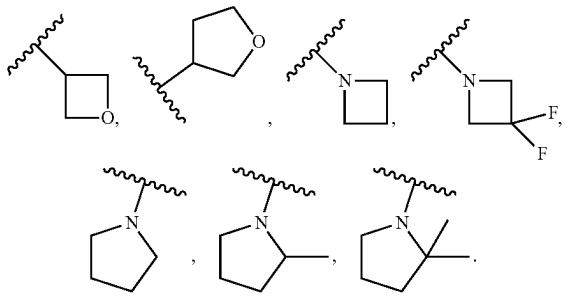
[0110] In some embodiments, R^C in any of the applicable formulae herein (e.g., Formulae I-1-c, I-1-d, I-1-x, I-1-y, or M-17, M-18, M-19, M-19', or M-19", etc.) can be CN. In some embodiments, R^C is H, halogen, such as F, Cl, or Br, OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, CH_2OCH_3, CHF_2, CH_3, or OCH_3. In some embodiments, R^C is G^{4A}. In some embodiments, R^C is $C(O)G^{4A}$. In some embodiments, R^C is $C(O)NHG^{4A}$ or $C(O)NG^{4A}G^{4A}$. In some embodiments, R^C is $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, $NHC(O)NHG^{4A}$ or $NHC(O)NG^{4A}G^{4A}$. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



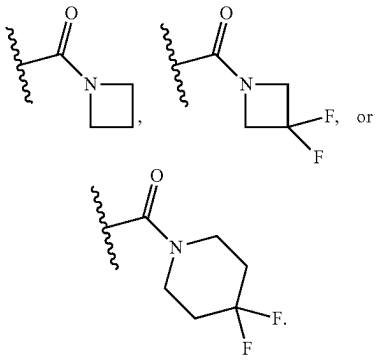
etc. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is (C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



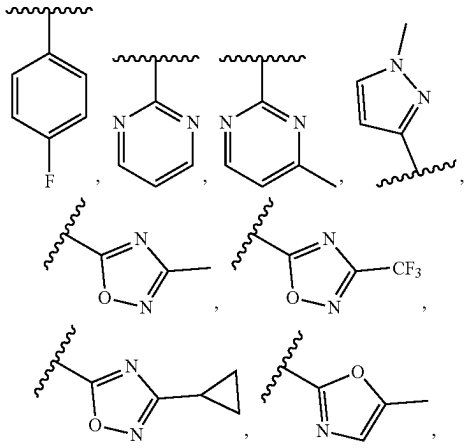
etc. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



etc., typically, when the 4-6 membered heterocyclic attaches through a ring nitrogen, R^C is $C(O)G^{4A}$, for example, in some embodiments, R^C is



[0111] In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is phenyl or 5- or 6-membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



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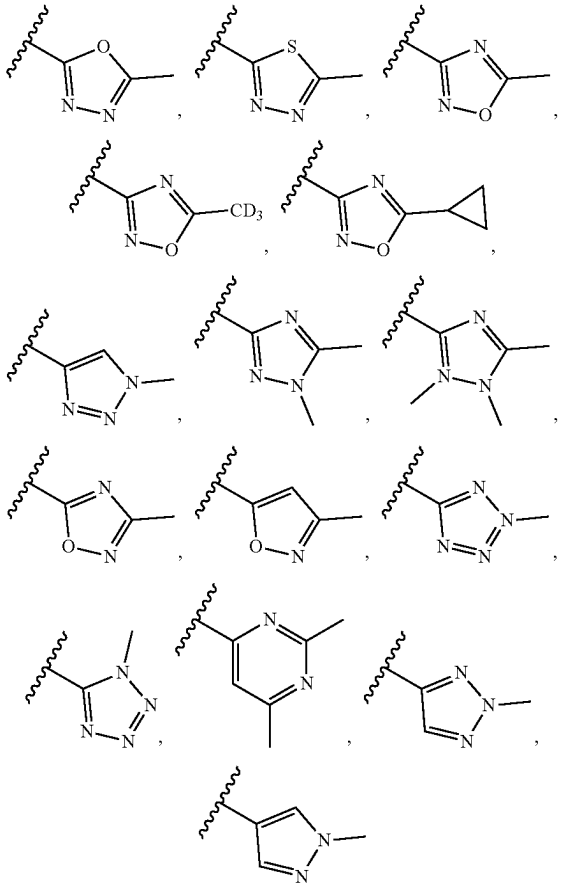
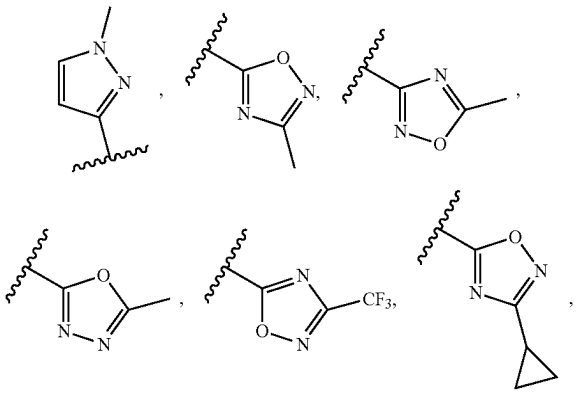


etc. In some embodiments, R^C is $C(O)NG^{4A}G^{4A}$ or $NHC(O)NG^{4A}G^{4A}$, wherein one instance of G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. In some embodiments, R^C is



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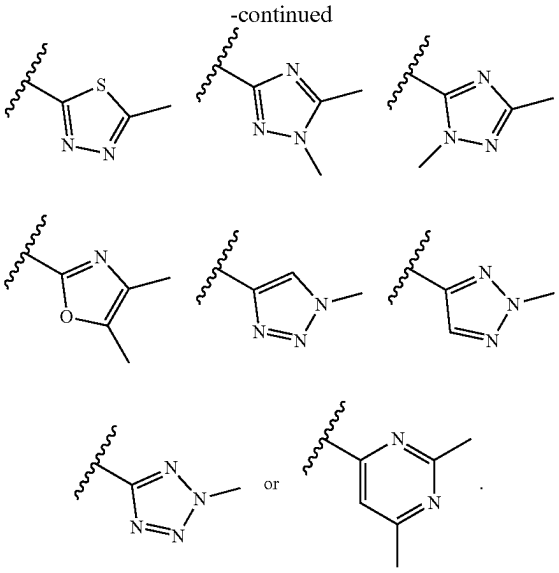
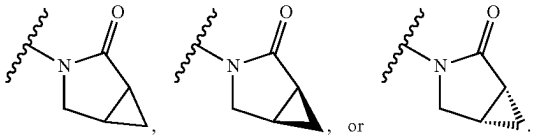
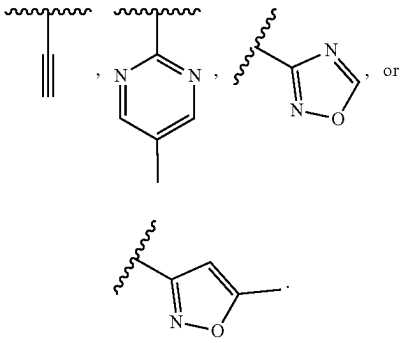


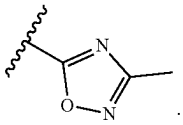
[0112] In some embodiments, R^C is



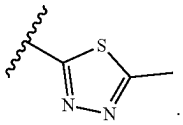
In some embodiments, R^C is



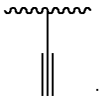
In some embodiments, R^C is F. In some embodiments, R^C is CHF_2. In some embodiments, R^C is CN. In some embodiments, R^C is



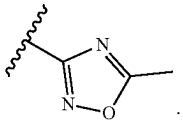
In some embodiments, R^C is



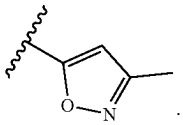
In some embodiments, R^C is



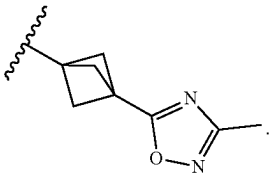
In some embodiments, R^C is



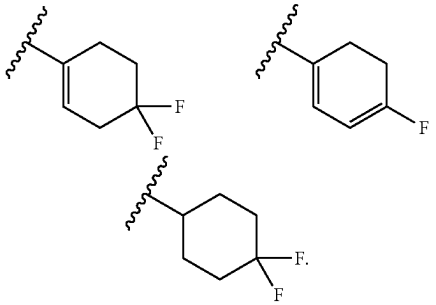
In some embodiments, R^C is



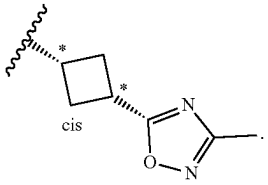
[0113] In some preferred embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



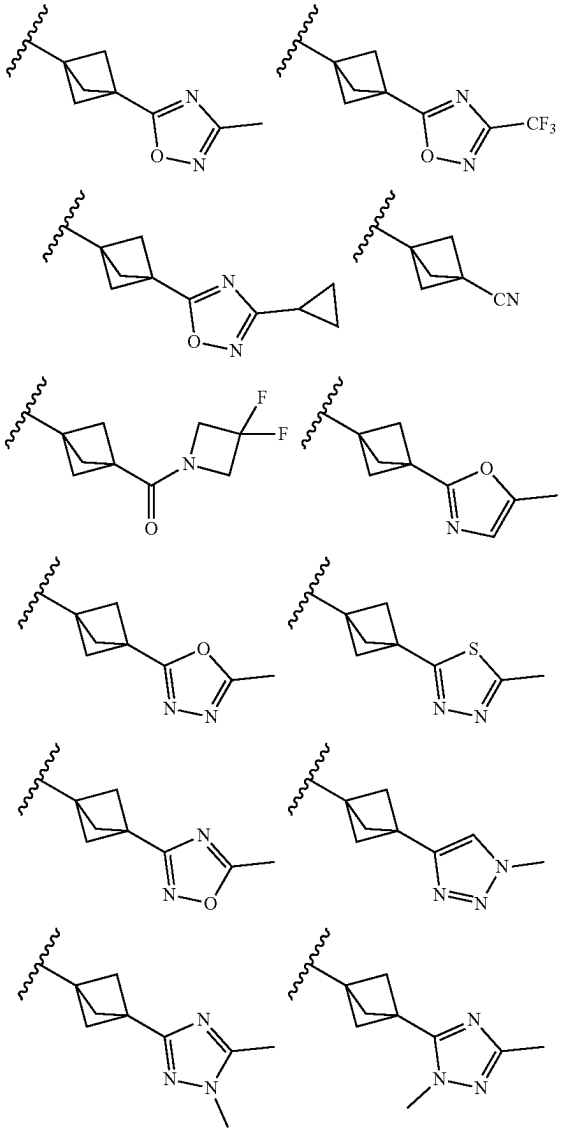
[0114] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be selected from



[0115] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-16 as defined herein, for example, can be



In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-17 as defined herein, for example, can be selected from



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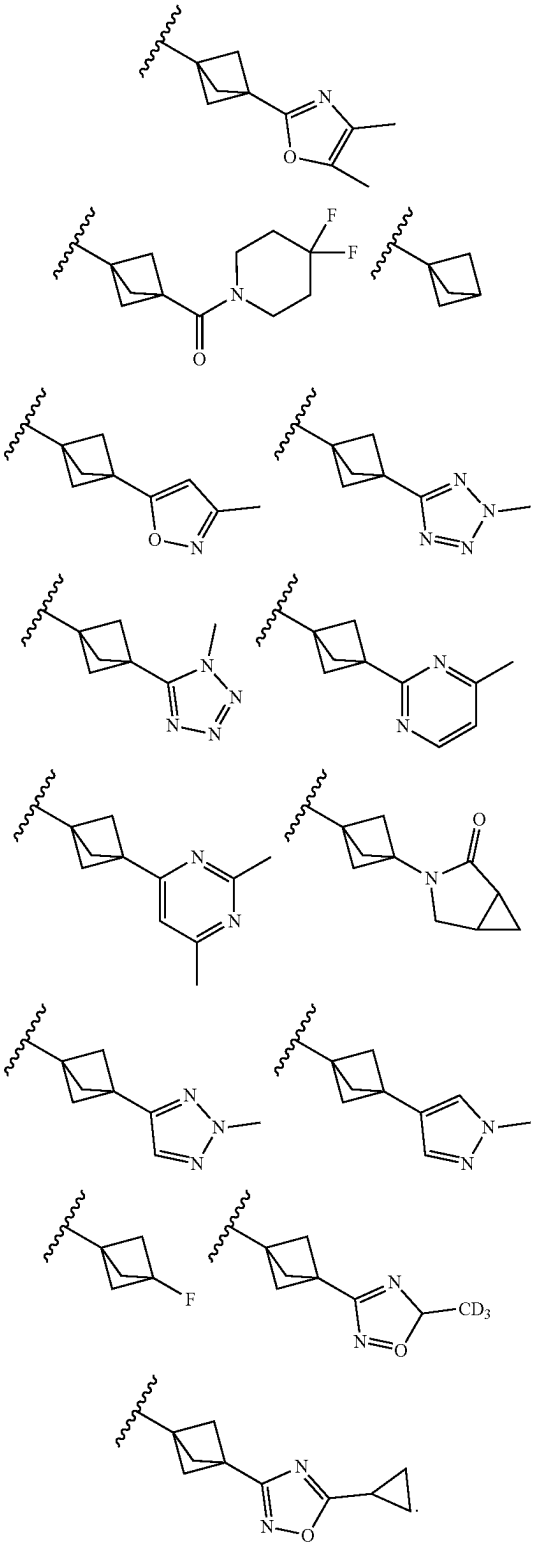
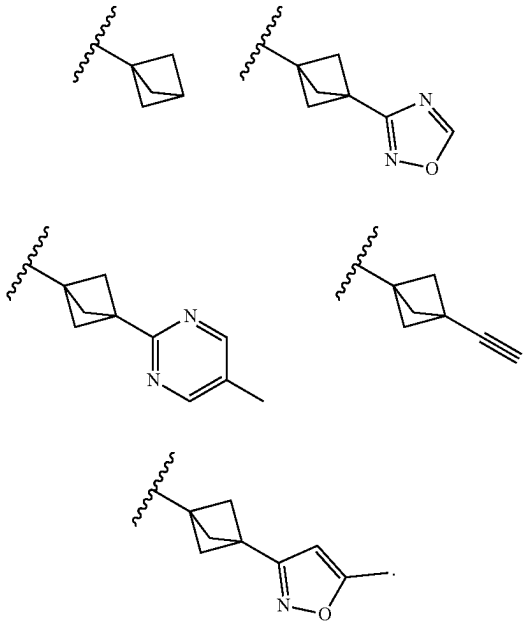
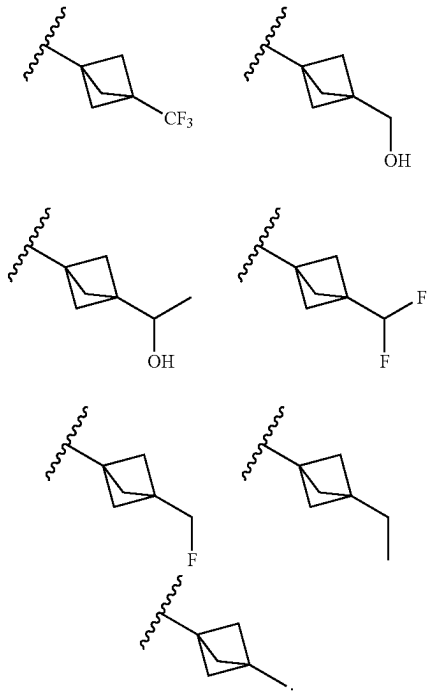


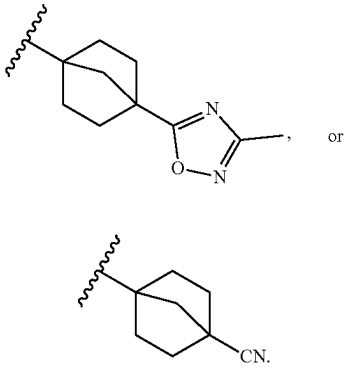
In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-17 as defined herein, for example, can be selected from



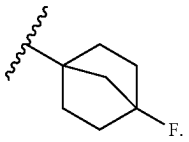
[0116] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-17 as defined herein, for example, can be selected from



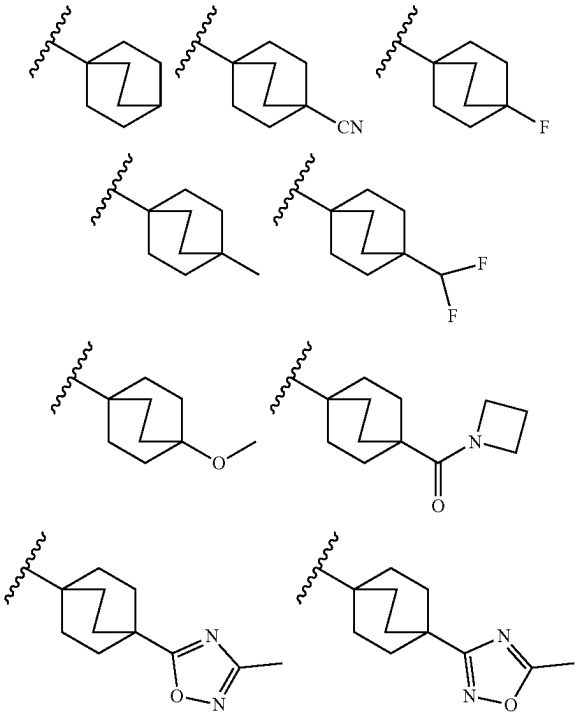
[0117] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-18 as defined herein, for example, can be



In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-18 as defined herein, for example, can be



[0118] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-19 as defined herein, for example, can be selected from



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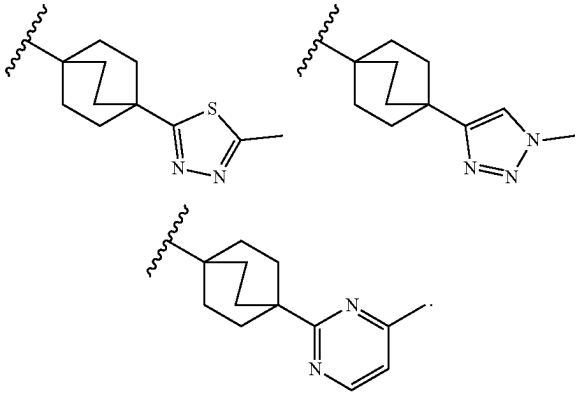
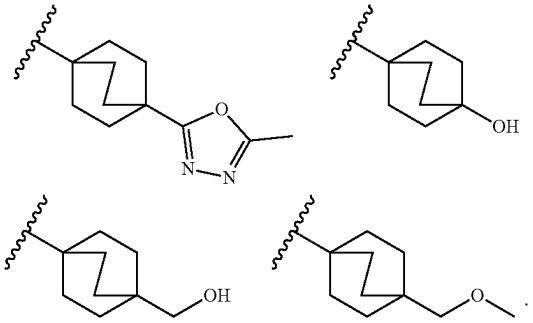
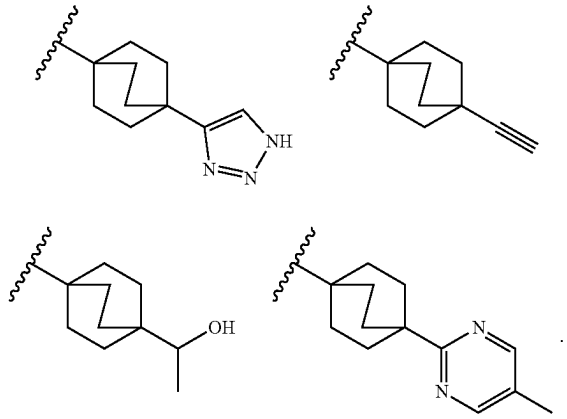


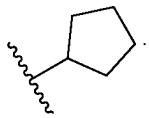
In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-19 as defined herein, for example, can be selected from



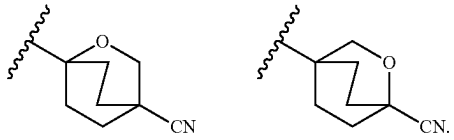
In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-19 as defined herein, for example, can be selected from



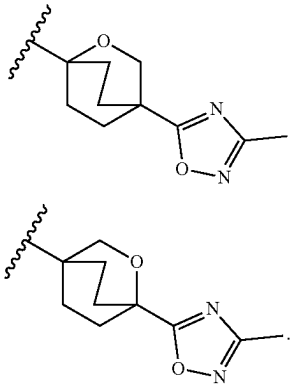
[0119] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be a cycloalkyl, such as



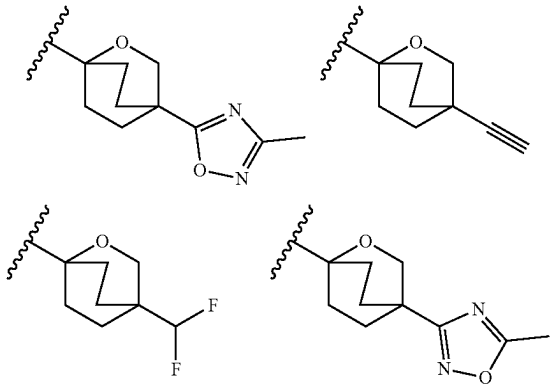
[0120] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be a bridged heterocyclyl, such as



In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be a bridged heterocyclyl, such as



In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be a bridged heterocyclyl, such as



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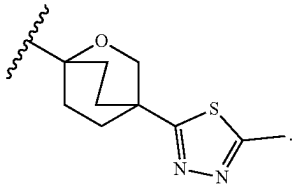
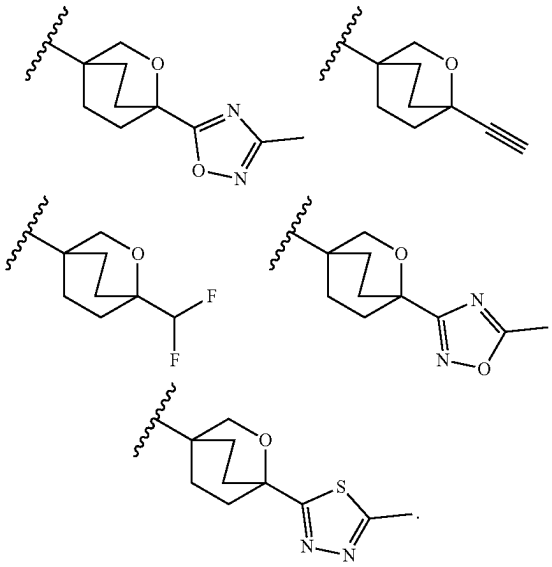
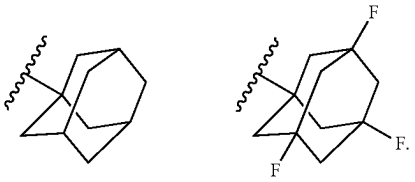


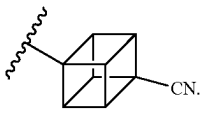
In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be a bridged heterocyclyl, such as



[0121] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be selected from

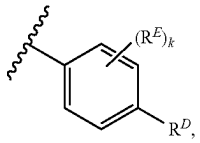


[0122] In some particular embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be selected from



[0123] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be an optionally substituted phenyl. When substituted, the phenyl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

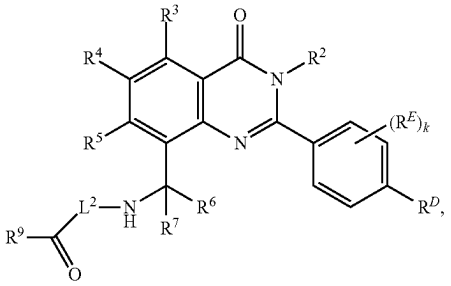
[0124] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



wherein R^D is halogen, CN, G^{4B}, OG^{4B}, NHG^{4B}, $NG^{4B}G^{4B}$, $C(O)G^{4B}$, $OC(O)G^{4B}$, $NHC(O)G^{4B}$, $NG^{4B}C(O)G^{4B}$, $C(O)OG^{4B}$, $C(O)NHG^{4B}$, $C(O)NG^{4B}G^{4B}$, $OC(O)OG^{4B}$, $OC(O)NHG^{4B}$, $OC(O)NG^{4B}G^{4B}$, $NHC(O)OG^{4B}$, $NHC(O)NHG^{4B}$ $NHC(O)NG^{4B}G^{4B}$, $NG^{4B}C(O)OG^{4B}$, $NG^{4B}C(O)NHG^{4B}$, $NG^{4B}C(O)NG^{4B}G^{4B}$ SO_2G^{4B}, SO_2NHG^{4B}, or $SO_2NG^{4B}G^{4B}$, wherein G^{4B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; wherein R^E at each occurrence is independently F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, C_{1-4} heteroalkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and k is 0, 1, or 2. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the

C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-8 membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-8 membered ring is a C_{3-8} cycloalkyl. In some embodiments, the 3-8 membered ring is a 4-8 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 (e.g., 3-8) membered ring is phenyl. In some embodiments, the 3-12 (e.g., 3-8) membered ring is a 5-membered heteroaryl having 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 (e.g., 3-8) membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 (e.g., 3-8) membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, or phenyl. In some embodiments, k is 0. In some embodiments, k is 1, and R^E is defined herein, such as F. In some embodiments, the compound of Formula A can have a structure according to Formula I-1-e:

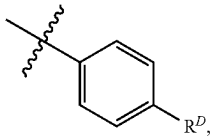
Formula I-1-e



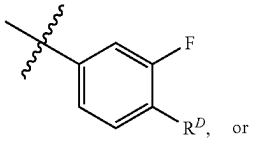
wherein the variables k, L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^D and R^E are defined herein.

[0125] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can have a structure according to:

(M-20)



(M-21)



or

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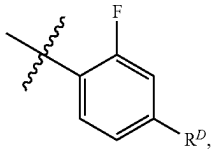
(M-22)

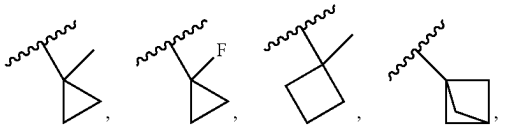


wherein R^D is halogen, CN, G^{5B}, NHG^{1B}, $NG^{5B}G^{5B}$, $C(O)G^{5B}$, $C(O)OG^{5B}$, $C(O)NHG^{5B}$, $C(O)NG^{5B}G^{5B}$, SO_2G^{5B}, SO_2NHG^{5B}, or $SO_2NG^{5B}G^{5B}$, wherein G^{5B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring, such as —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1} or one or more (e.g., 1, 2, or 3) G^{B2}, wherein G^{B1} is defined herein, and wherein G^{B2} at each occurrence is independently deuterium, F, Cl, CN, OH, NH_2, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-20, as defined herein. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-21, as defined herein. In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) has a structure according to M-22, as defined herein.

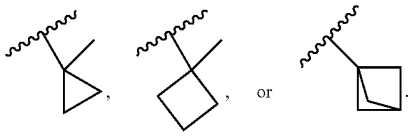
[0126] In some preferred embodiments, R^D in the structures herein (e.g., M-20, M-21, or M-22, or M-23 to M-25 as described hereinbelow) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B},

[0127] wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl.

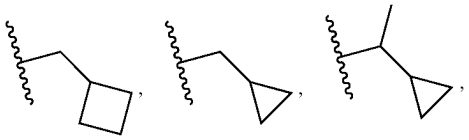
[0128] In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



etc. In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be $C(O)G^{5B}$ or $C(O)OG^{5B}$, wherein G^{5B} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,

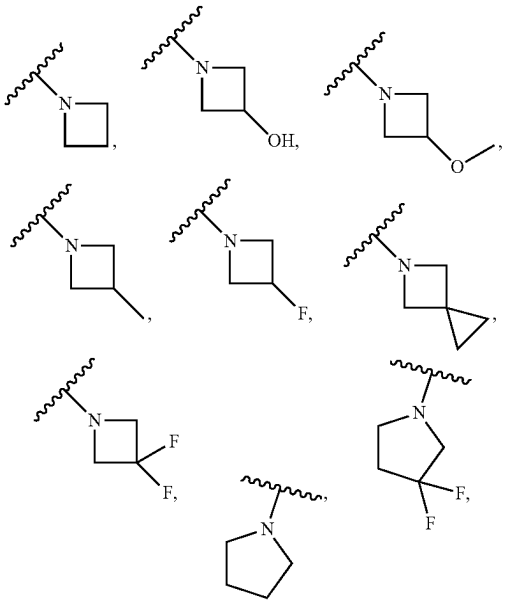


[0129] In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



etc.

[0130] In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is 4-7 membered heterocyclic (e.g., having 1 or 2 ring heteroatoms each independently O or N), such as azetidinyl, pyrrolidinyl, piperidinyl, oxazolidinyl, etc., which is optionally substituted with 1 or 2 substituents each independently OH, OCH_3, F, or methyl, such as



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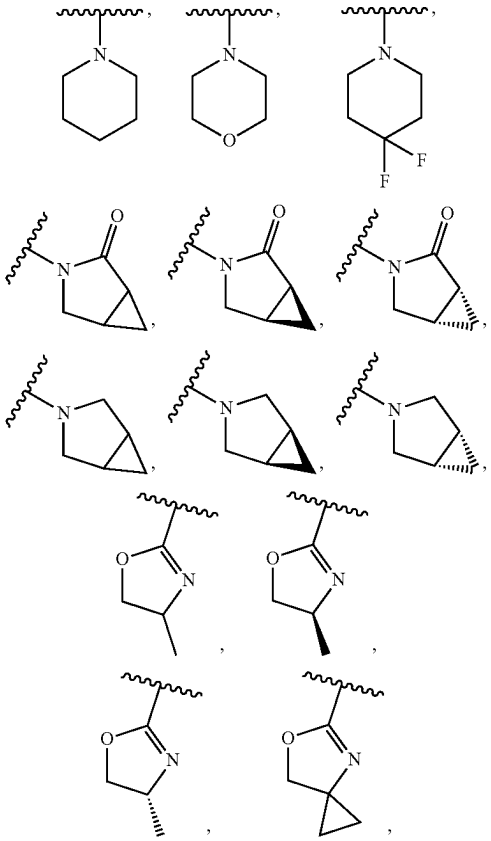
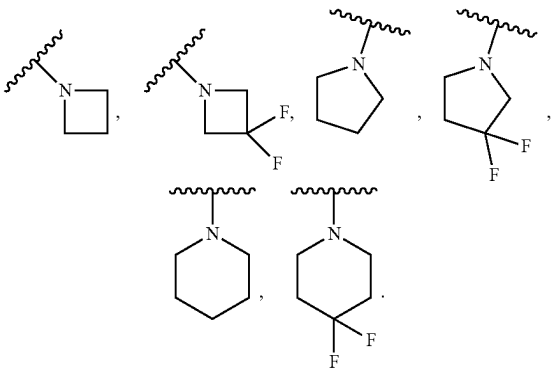
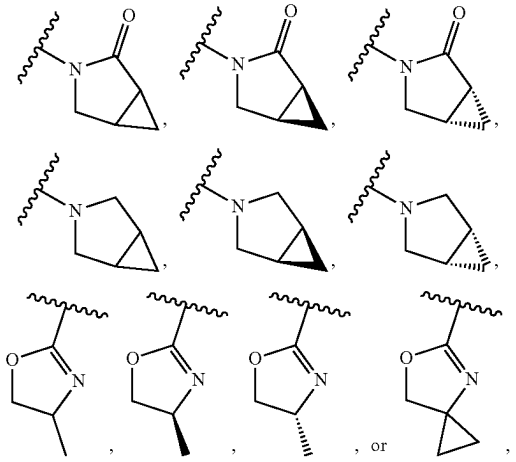


etc. In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be $C(O)G^{5B}$, wherein G^{5B} is 4-7 membered heterocyclic (e.g., having 1 or 2 ring heteroatoms each independently O or N), such as N-linked azetidinyl, pyrrolidinyl, or piperidinyl, which is optionally substituted with 1 or 2 substituents each independently F or methyl, such as

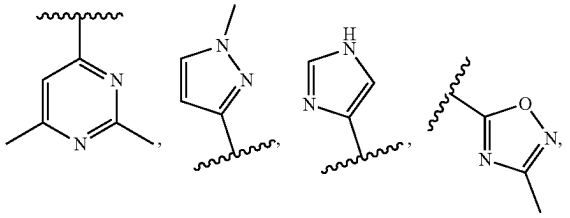


In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be 4-7 membered heterocyclic (e.g., having 1 or 2 ring heteroatoms each independently O or N), such as

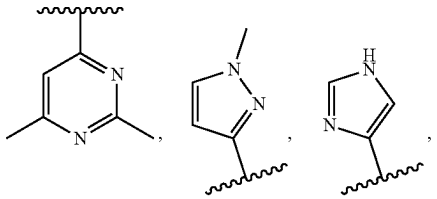


etc.

[0131] In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is 5- or 6-membered heteroaryl, such as pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, etc., which is optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



etc. For example, in some embodiments, R^D in the structures herein (e.g., M-20 to M-25) is a 5- or 6-membered heteroaryl, such as pyrazolyl, oxazolyl, imidazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, etc., which is optionally substituted, for example, with 1 or 2 methyl, such as



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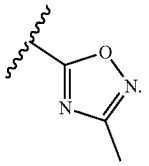
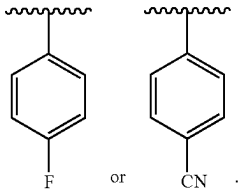


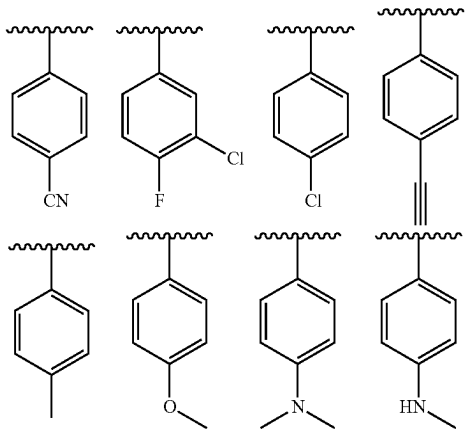
[0132] In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be NHG^{5B} or $C(O)NHG^{5B}$, wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). For example, in some embodiments, R^D can be $NHCH_3$.

[0133] In some preferred embodiments, R^D in the structures herein (e.g., M-20 to M-25) can be $C(O)NG^{5B}G^{5B}$, wherein one instance of G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. For example, in some embodiments, R^D can be $CON(CH_3)_2$.

[0134] In some embodiments, R^1 can be a phenyl, which is optionally substituted with 1-3 substituents independently selected from deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, and C_{1-4} alkyl optionally substituted with 1-3F. For example, in some embodiments, R^1 can be



[0135] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted phenyl, such as those having a structure according to M-20 to M-22, for example, R^1 can be selected from:



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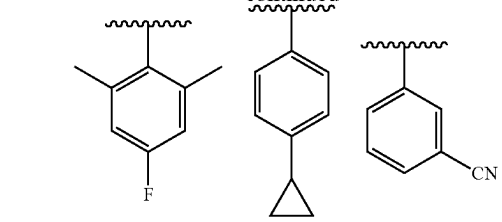

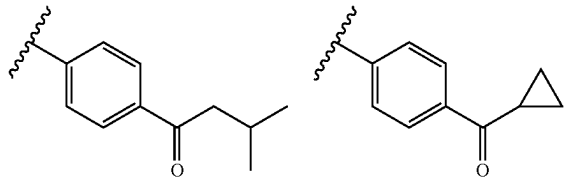

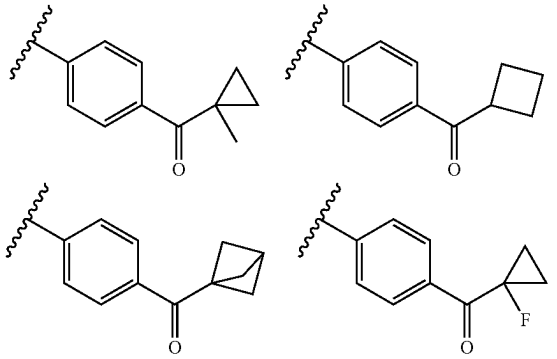

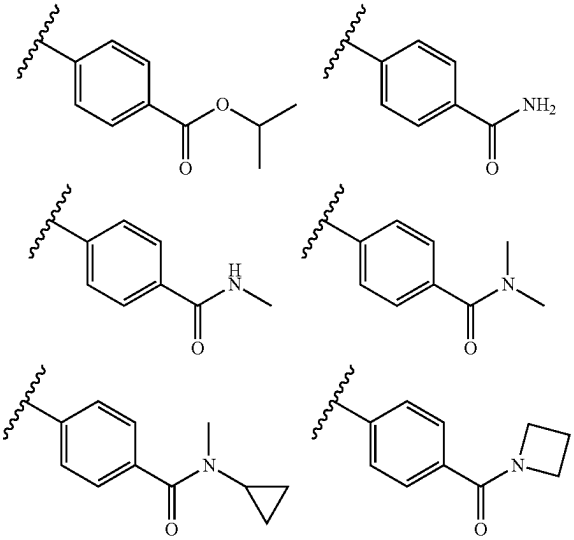

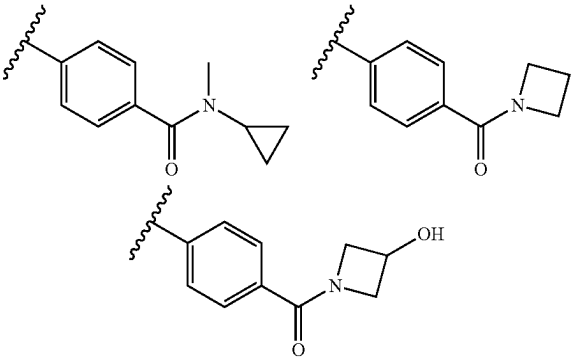

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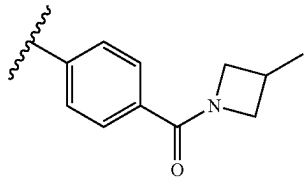

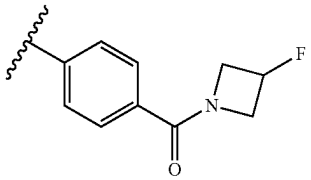

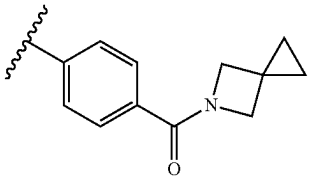

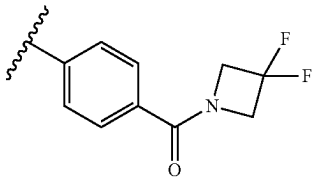

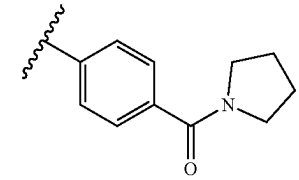

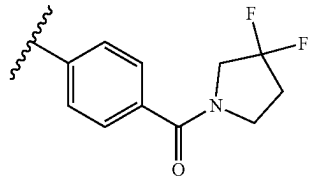

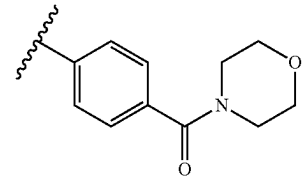

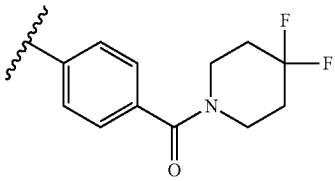

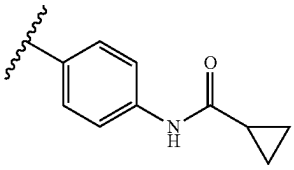

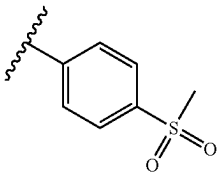

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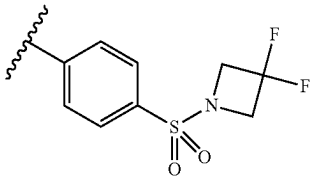

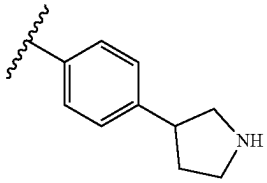

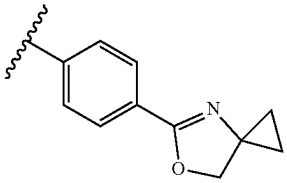

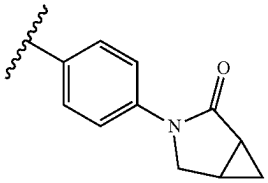

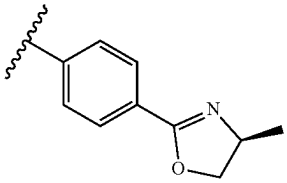

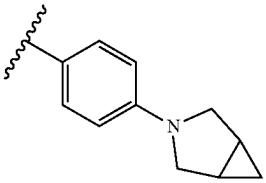

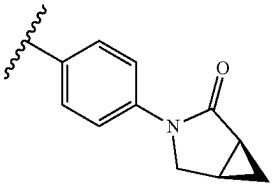

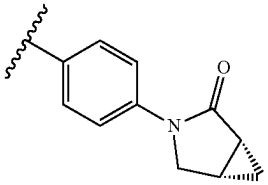

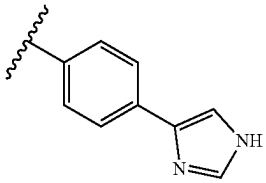

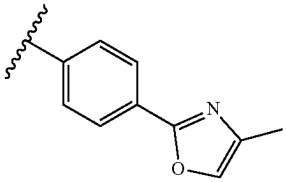

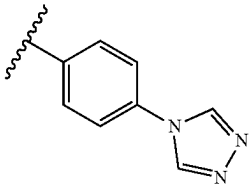

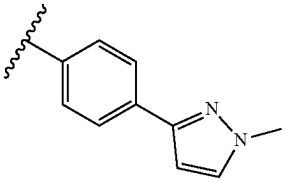

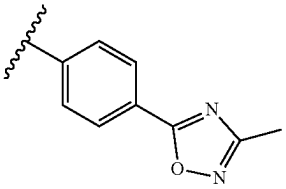

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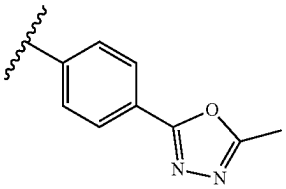

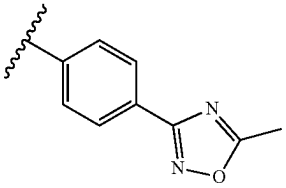

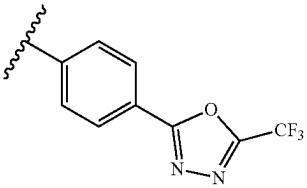

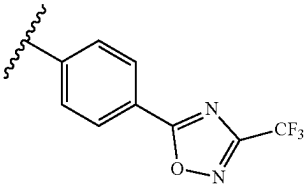

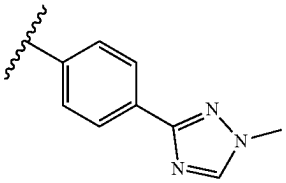

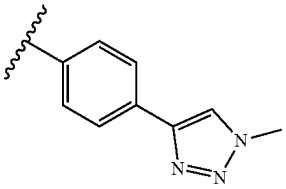

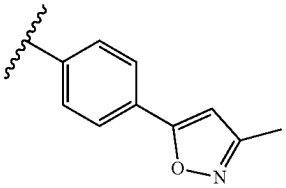

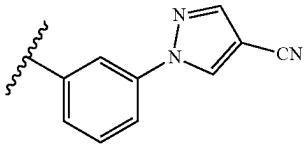

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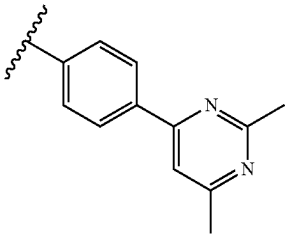

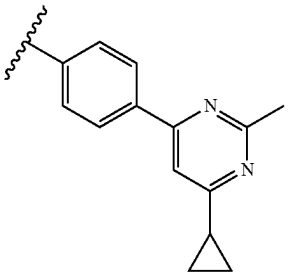

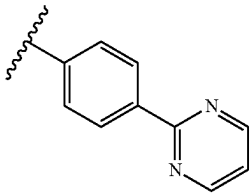

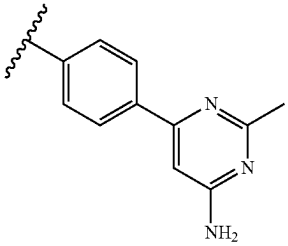

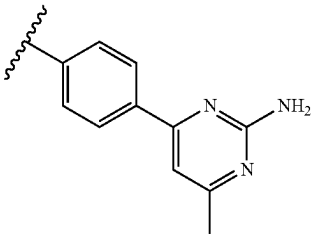

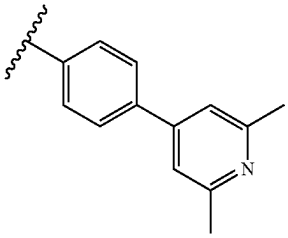

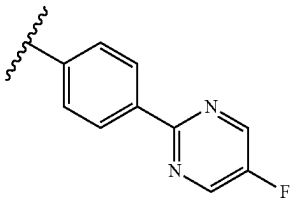

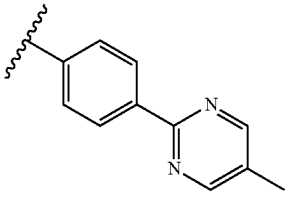

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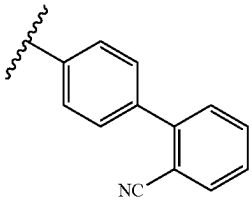
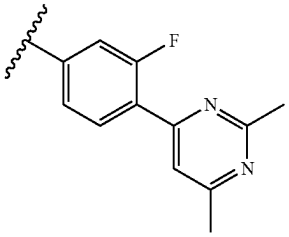
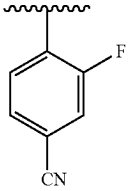
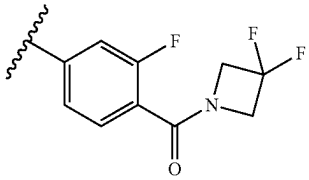
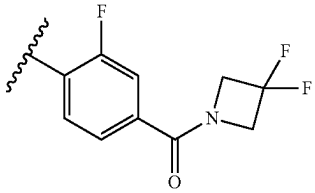
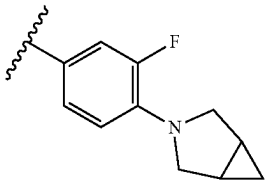


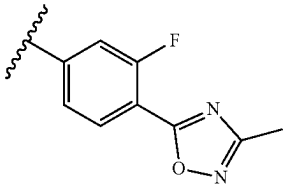


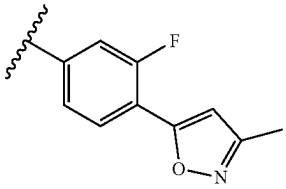


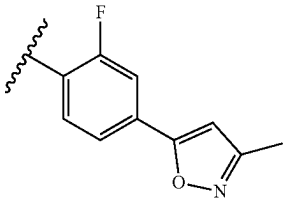




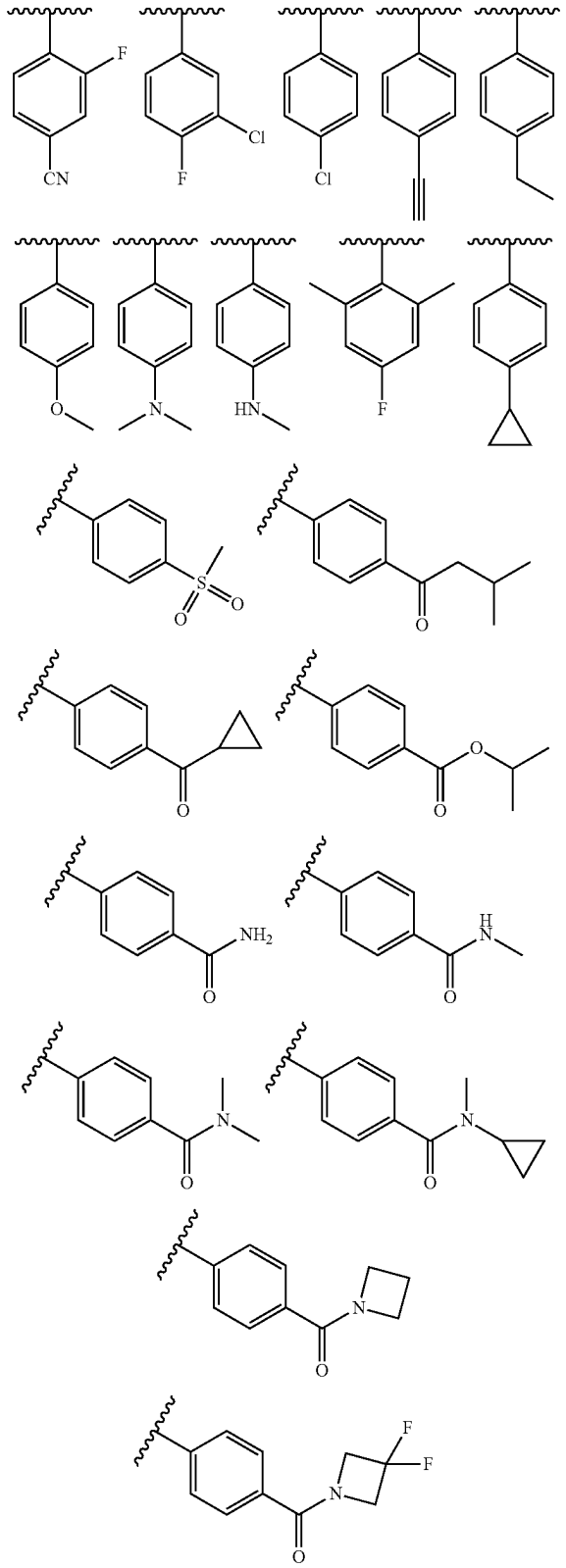








[0136] In some embodiments, R^1 can be selected from:



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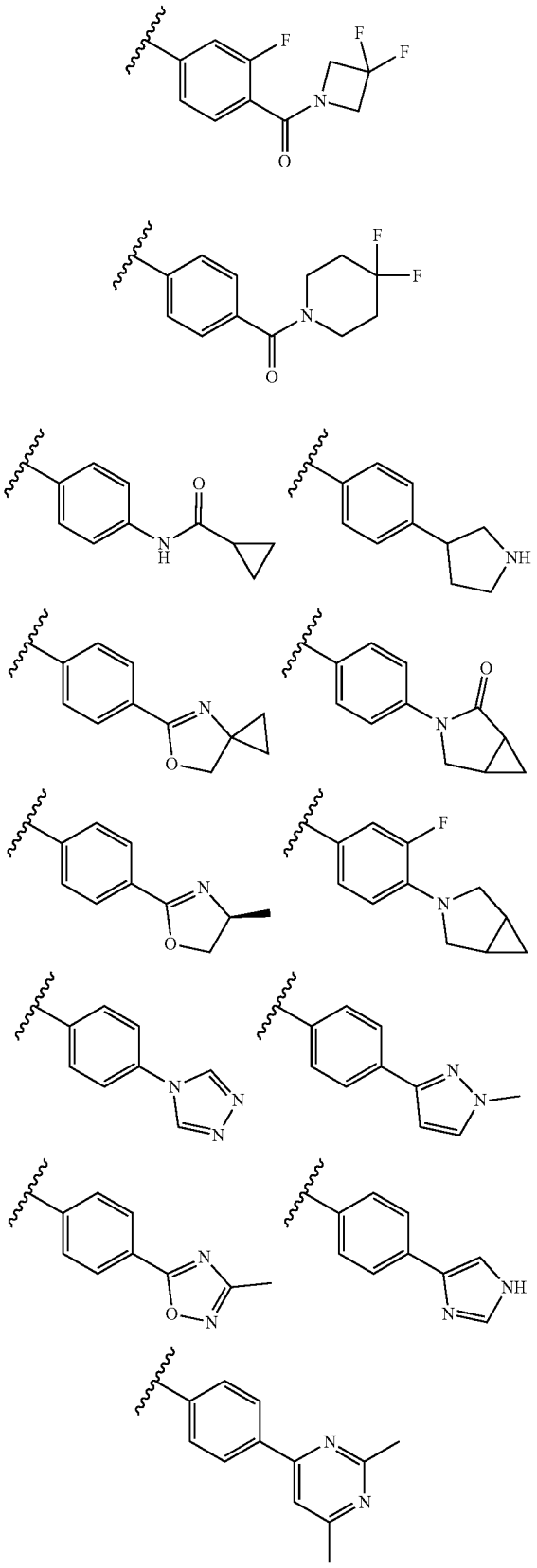

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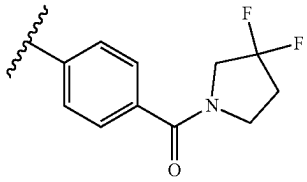
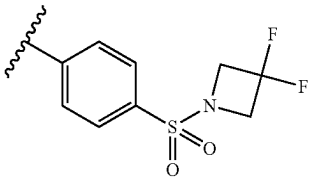
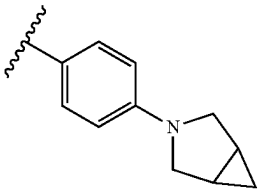
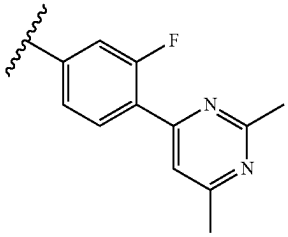
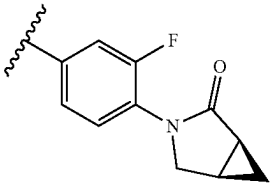
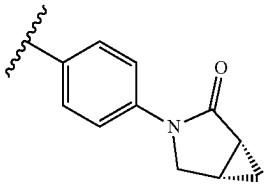


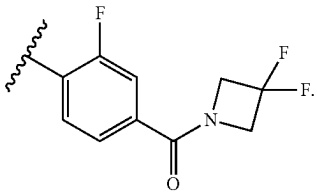




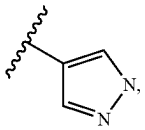




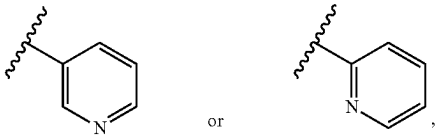




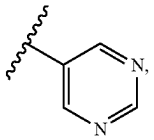
[0137] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be an optionally substituted 5- or 6-membered heteroaryl, such as those having 1, 2, or 3 ring heteroatoms selected from N, S, and O. For example, in some embodiments, R^1 is an optionally substituted 5-membered heteroaryl having 1 or 2 ring heteroatoms, such as two ring nitrogens. In some embodiments, R^1 is an optionally substituted 6-membered heteroaryl having 1 or 2 ring nitrogens. In some embodiments, R^1 is pyrazolyl, e.g.,



which is optionally substituted. In some embodiments, R^1 is pyridyl, e.g.,



which is optionally substituted. In some embodiments, R^1 is pyrimidinyl, e.g.,

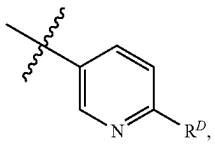


which is optionally substituted. Similarly, the 5-membered heteroaryl can be attached to the remainder of Formula A through a carbon or N ring atom, as valency permits, and when substituted, can be substituted at any available positions including at ring nitrogen atoms. When substituted, the 5- or 6-membered heteroaryl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—C(O)G^4, C(O)G^4, C(O)OG^4, C(O)NHG^4, C(O)NG^4G^4, OC(O)NHG^4, OC(O)NG^4G^4, NHC(O)NHG^4, or N(G^4)C(O)NG^4G^4,

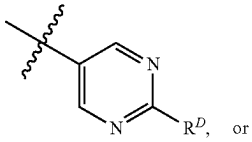
[0138] wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0139] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can have a structure according to:

(M-23)



(M-24)



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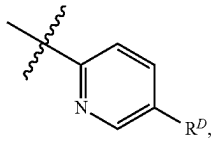
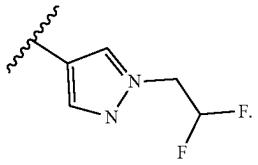
(M-25)

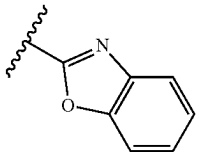


wherein R^D is halogen, CN, G^{4B}, OG^{4B}, NHG^{4B}, $NG^{4B}G^{4B}$, $C(O)G^{4B}$, $OC(O)G^{4B}$, $NHC(O)G^{4B}$, $NG^{4B}C(O)G^{4B}$, $C(O)OG^{4B}$, $C(O)NHG^{4B}$, $C(O)NG^{4B}G^{4B}$, SO_2G^{4B}, SO_2NHG^{4B} or $SO_2NG^{4B}G^{4B}$, wherein G^{4B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{41}, wherein G^{41} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. In some embodiments, R^D in M-23, M-24, or M-25 can also be any of those R^D described herein.

[0140] In some embodiments, R^1 is



[0141] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can also be an optionally substituted bicyclic heteroaryl, such as benzoxazolyl, benzimidazolyl, triazolopyridinyl, e.g.,



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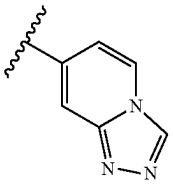

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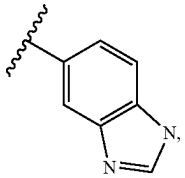
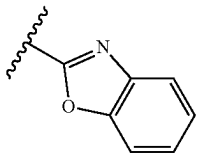


which is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^4, wherein G^4 at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. For example, in some embodiments, R^1 is



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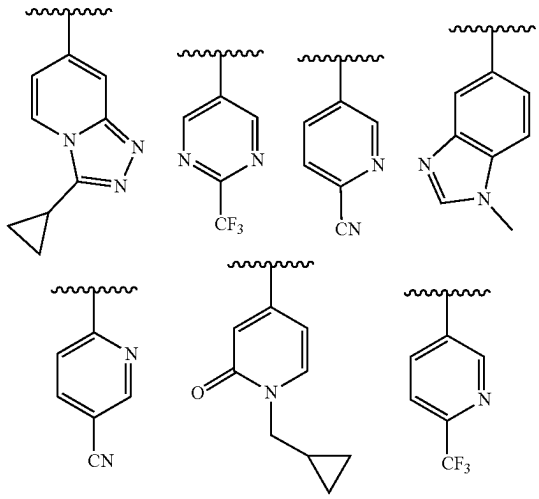
[0142] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be selected from:



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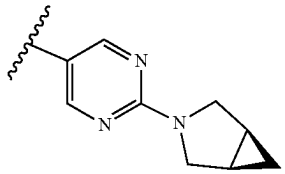

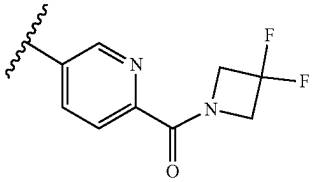

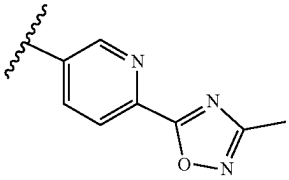

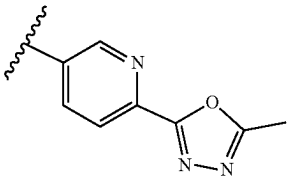

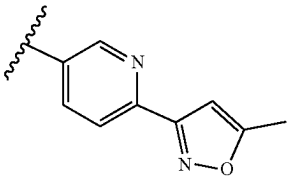

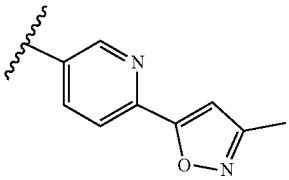

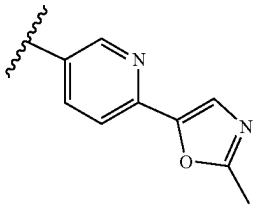

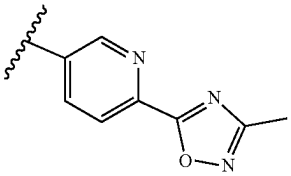

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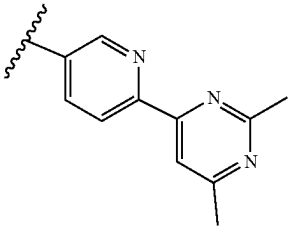

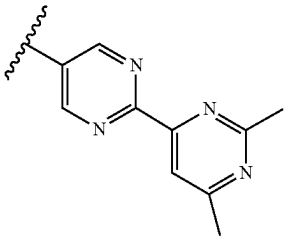

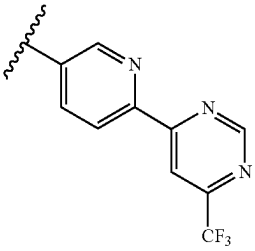

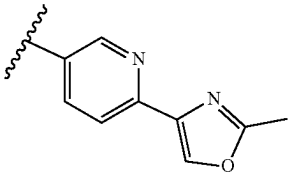

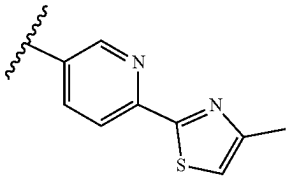

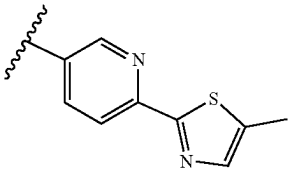

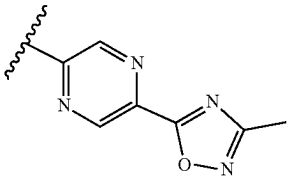

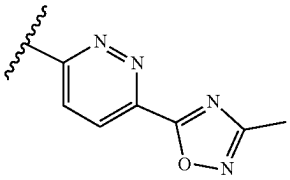

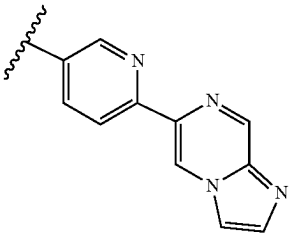

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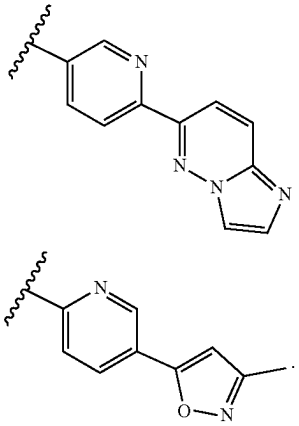
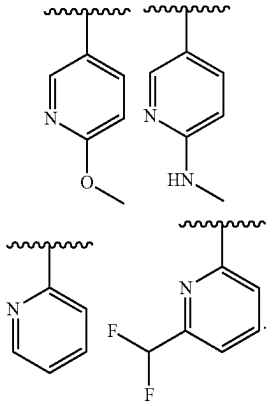
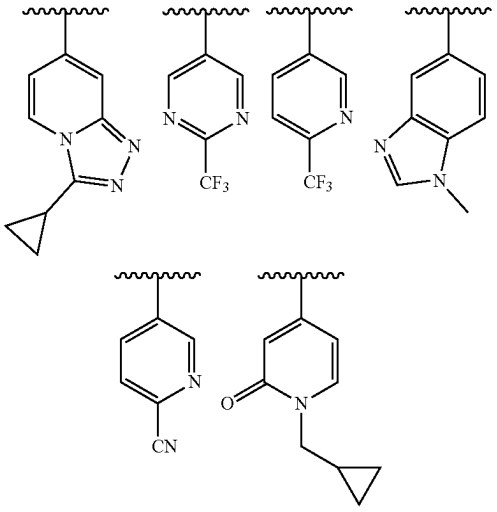


[0143] In some embodiments, R^1 in Formula A (e.g., Formula I, I-1, or I-1-a) can be selected from:



[0144] For example, R^1 can be selected from:



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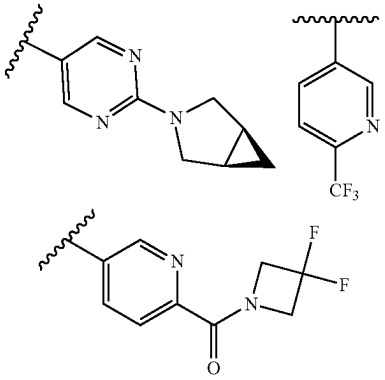


[0145] R^2 in Formula A (e.g., Formula I, I-1, or I-1-a) is typically a small group. For example, in some embodiments, R^2 in Formula A (e.g., Formula I, I-1, or I-1-a) is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F.

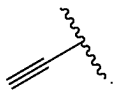
[0146] In some preferred embodiments, R^2 in Formula A (e.g., Formula I, I-1, or I-1-a) is a C_{1-4} alkyl optionally substituted with 1-3F, more preferably, R^2 is methyl, or R^2 is CD_3 or CF_3.

[0147] In some embodiments, R^4 in Formula A (e.g., Formula I, I-1, or I-1-a) is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0148] In some preferred embodiments, R^4 in Formula A (e.g., Formula I, I-1, or I-1-a) is a C_{1-4} alkyl optionally substituted with 1-3F, more preferably, R^4 is methyl, or R^4 is CD_3 or CF_3.

[0149] In some preferred embodiments, R^4 in Formula A (e.g., Formula I, I-1, or I-1-a) is a halogen, more preferably, R^4 is F. In some embodiments, R^4 is Cl or Br.

[0150] In some embodiments, R^4 in Formula A (e.g., Formula I, I-1, or I-1-a) can be



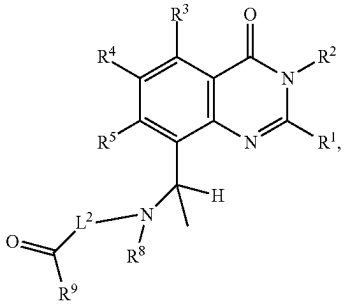
[0151] In some embodiments, R^5 in Formula A (e.g., Formula I, I-1, or I-1-a) is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0152] In some preferred embodiments, R^5 in Formula A (e.g., Formula I, I-1, or I-1-a) is hydrogen.

[0153] R^6 and R^7 in Formula A (e.g., Formula I, I-1, or I-1-a) can be the same or different. In some embodiments, both R^6 and R^7 can be hydrogen. In some embodiments, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, which is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, or C_{1-4} alkoxy optionally substituted with 1-3F. In some embodiments, one of R^6 and R^1 is hydrogen, and the other of R^6 and R^7 is a 3-6 membered ring having 0, 1, or 2 ring heteroatoms, such as cyclopropyl, which is optionally substituted with one or more such as 1 or 2 substituents each independently deuterium, F, CN, OH, or C_{1-4} alkyl optionally substituted with 1-3F. In some preferred embodiments, one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is C_{1-4} alkyl, more preferably, one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is methyl.

[0154] In some preferred embodiments, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, more preferably, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl. For example, in some embodiments, the compound of Formula I-1-a can be characterized as having a structure of Formula I-1-a-1:

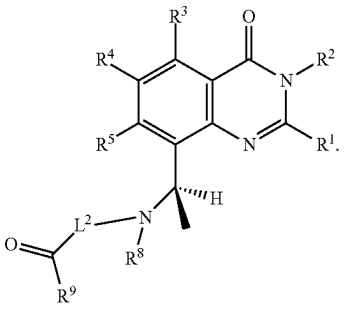
Formula I-1-a-1



wherein L^2, R^1, R^2, R^3, R^4, R^5, R^6, and R^9 are defined herein. As would be understood by those of ordinary skilled in the art, when R^6 and R^7 are different, such as in Formula I-1-a-1, the compound has a chiral center. The present disclosure is not limited to any particular enantiomer (with respect to the chiral carbon bonded with both R^6 and R^7), and encompasses both enantiomers and a mixture thereof in any ratio.

[0155] In some embodiments, the compound of Formula I-1-a-1 can have a configuration according to Formula I-1-a-1R,

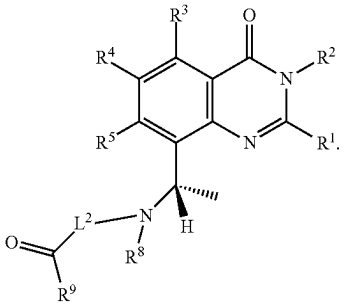
Formula I-1-a-1R



[0156] In some embodiments, the compound of Formula I-1-a-1R can have an enantiomeric purity characterized by an enantiomeric excess ("ee"), with respect to the as-drawn chiral center, of greater than 50%, such as 80% ee or higher, preferably, 90% ee or higher, such as 95% ee, 98% ee, 99% ee, or higher. In some embodiments, the compound of Formula I-1-a-1R can also exist in a racemic mixture.

[0157] In some embodiments, the compound of Formula I-1-a can have a configuration according to Formula I-1-a-1S,

Formula I-1-a-1S

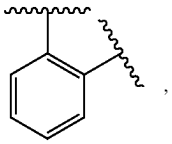


[0158] In some embodiments, the compound of Formula I-1-a-1S can have an enantiomeric purity characterized by greater than 50% ee, with respect to the as-drawn chiral center, such as 80% ee or higher, preferably, 90% ee or higher, such as 95% ee, 98% ee, 99% ee, or higher. In some embodiments, the compound of Formula I-1-a-1S can also exist in a racemic mixture.

[0159] When U in Formula A is NR^8, such as in Formula I, I-1, or I-1-a, R^8 is typically hydrogen. In some embodiments, R^8 can be a C_{1-4} alkyl optionally substituted with 1-3 fluorine. In some embodiments, R^1 can be a nitrogen protecting group as described herein.

[0160] L^2 in Formula A (e.g., Formula I, I-1, or I-1-a) is typically an optionally substituted phenylene or 5- or 6-membered heteroarylene.

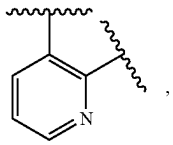
[0161] For example, in some embodiments, L^2 is an optionally substituted phenylene. Typically, in such cases, the R^{100} (such as $C(O)R^9$) and U (such as NR^1) are ortho to each other. For example, L^2 can be a 1,2-phenylene represented by



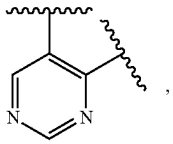
which is optionally substituted (i.e., the remaining four positions of the benzene ring can be optionally further substituted). When substituted, the phenylene can be typically substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN,

OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F.

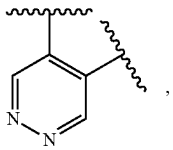
[0162] In some embodiments, L^2 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted 6-membered heteroarylene. Typically, the 6-membered heteroarylene contains 1 or 2 ring nitrogen atoms, such as pyridylene, pyrazinylene, pyrimidinylene, or pyridazinylene. Typically, in such cases, the R^{100} (such as $C(O)R^9$) and U (such as NRs) are ortho to each other. For example, L^2 can be



which is optionally substituted. In some embodiments, L^2 can be

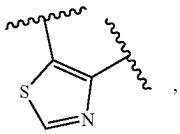


which is optionally substituted. In some embodiments, L^2 can be



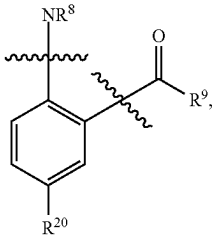
which is optionally substituted. When substituted, the 6-membered heteroarylene can be typically substituted with one or more substituents (e.g., 1 or 2) each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F.

[0163] In some embodiments, L^2 in Formula A (e.g., Formula I, I-1, or I-1-a) can be an optionally substituted 5-membered heteroarylene. Typically, the 5-membered heteroarylene contains 1 or 2 ring heteroatoms. For example, in some embodiments, L^2 can be



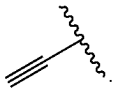
which is optionally substituted. When substituted, the 5-membered heteroarylene can be typically substituted with one or more substituents (e.g., 1 or 2) each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0164] In some preferred embodiments, L^2 in Formula I, or a subformula such as I-1, or I-1-a can be

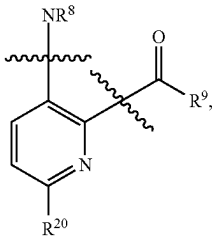


[0165] (NR^1 and $C(O)R^9$ are shown to show direction of attachment to the remainder of the molecule),

[0166] wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. In some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3. In some embodiments, R^{20} is



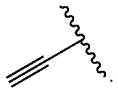
[0167] In some preferred embodiments, L^2 in Formula I, or a subformula such as I-1, or I-1-a can be



[0168] (NR^8 and $C(O)R^9$ are shown to show direction of attachment to the remainder of the molecule),

[0169] wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4}

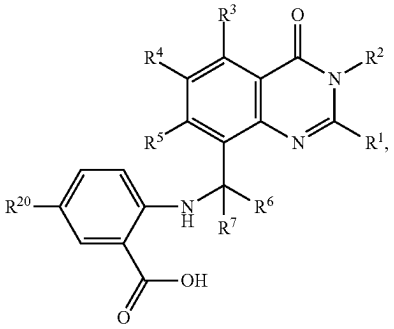
alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. In some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3. In some embodiments, R^{20} is



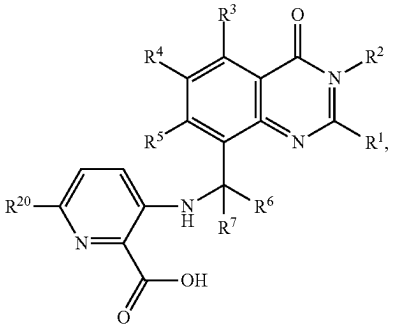
[0170] When R^{100} in Formula A is $C(O)R^9$, such as in Formula I, I-1, or 1-1-a, R^9 is typically OH. In some embodiments, R^9 can be OG^3, wherein G^3 is defined herein. In some embodiments, R^9 can be NH_2, NHG^3, NG^3G^3, or $NHSO_2G^3$, wherein G^3 is defined herein. For example, in some embodiments, G^3 at each occurrence is independently a C_{1-4} alkyl.

[0171] In some embodiments, the compound of Formula I-1-a can be characterized as having a structure according to Formula I-1-a-2 or I-1-a-3:

Formula III-1-a-2



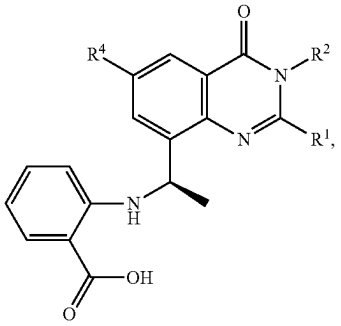
Formula III-1-a-3



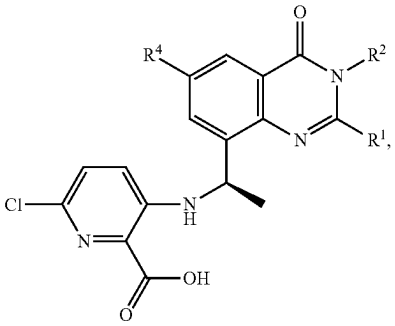
[0172] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined herein. In some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3.

[0173] In some embodiments, the compound of Formula I-1-a can be characterized as having a structure according to Formula I-1-a-4 or I-1-a-5:

Formula I-1-a-4



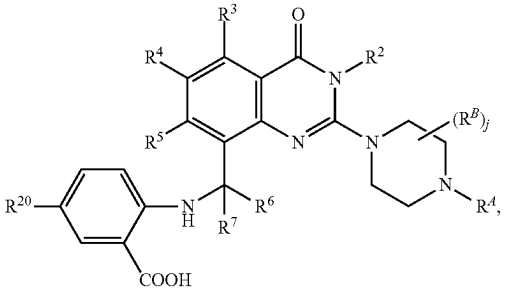
Formula I-1-a-5



wherein R^1, R^2, and R^4 are defined herein. In some embodiments, the compound of Formula I-1-a-4 or I-1-a-5 can have an enantiomeric purity characterized by greater than 50% ee, with respect to the as-drawn chiral center, such as 80% ee or higher, preferably, 90% ee or higher, such as 95% ee, 98% ee, 99% ee, or higher. In some embodiments, the compound of Formula I-1-a-4 or I-1-a-5 can also exist in a racemic mixture.

[0174] In some embodiments, the compound of Formula I-1-a-2 can be characterized as having a structure according to Formula I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, or I-1-a-2-d:

Formula I-1-a-2-a



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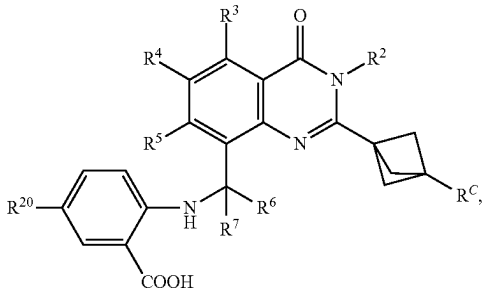
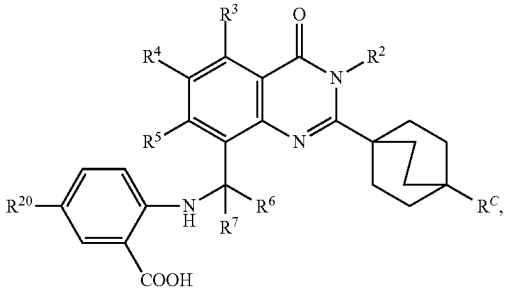
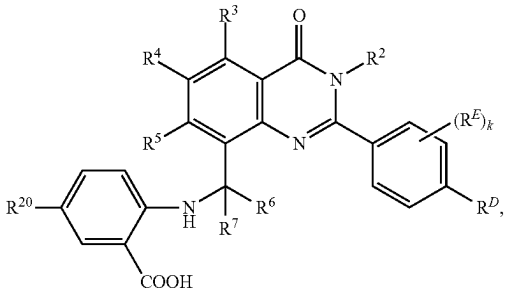
Formula I-1-a-2-b



Formula I-1-a-2-c



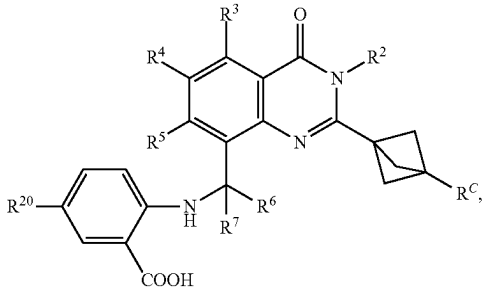
Formula I-1-a-2-d



[0175] wherein j, k, R^A, R^C, R^D, R^E, R^2, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined herein. In some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3. In some preferred embodiments, R^{20} is hydrogen.

[0176] In some embodiments, the compound of Formula I-1-a-2 or I-1-a-3 can have a structure according to Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f:

Formula I-1-a-2-b



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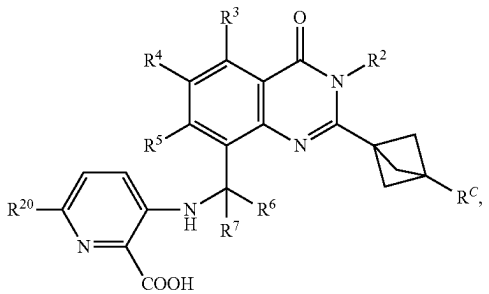
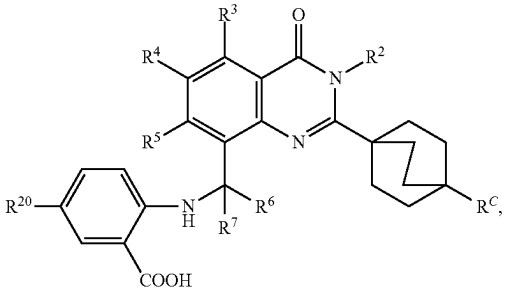
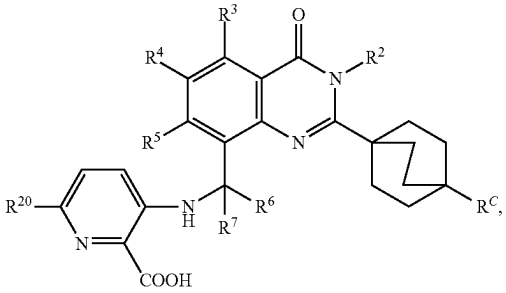
Formula I-1-a-3-b



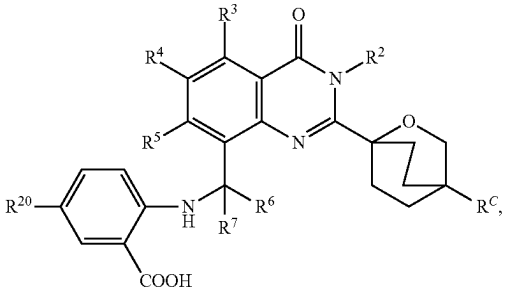
Formula I-1-a-2-c



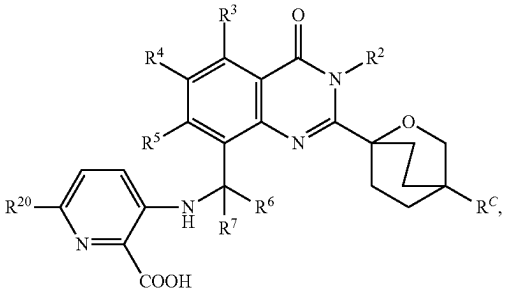
Formula I-1-a-3-c



Formula I-1-a-2-e



Formula I-1-a-3-e



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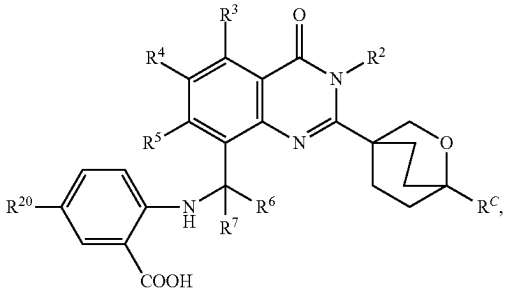
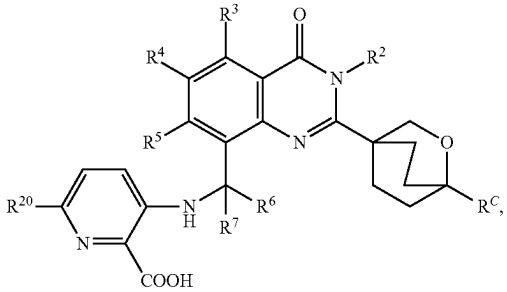
Formula I-1-a-2-f



Formula I-1-a-3-f



[0177] wherein:

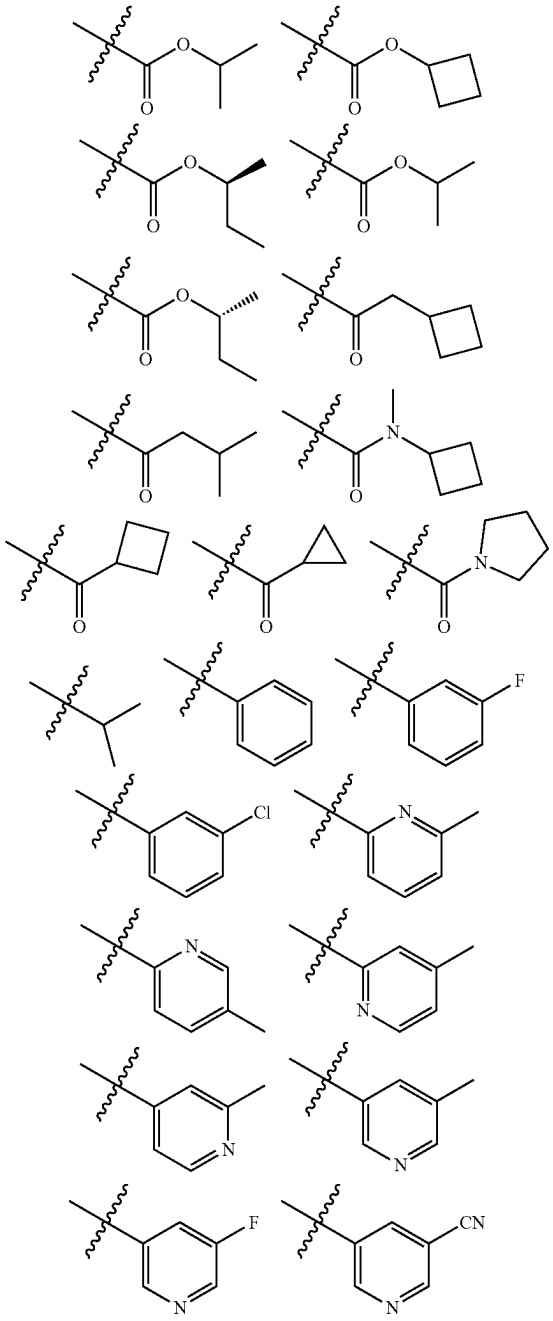
[0178] R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4}alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F; and

[0179] R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^AL, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl

[0180] wherein the variables R^2, R^3, R^4, R^5, R^6, and R^7 are defined herein.

In some embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3. For example, in some embodiments, R^{20} can be hydrogen. In some embodiments, R^{20} can be F or Cl.

[0181] In some embodiments, in Formula I-1-a-2-a, R^A can be selected from



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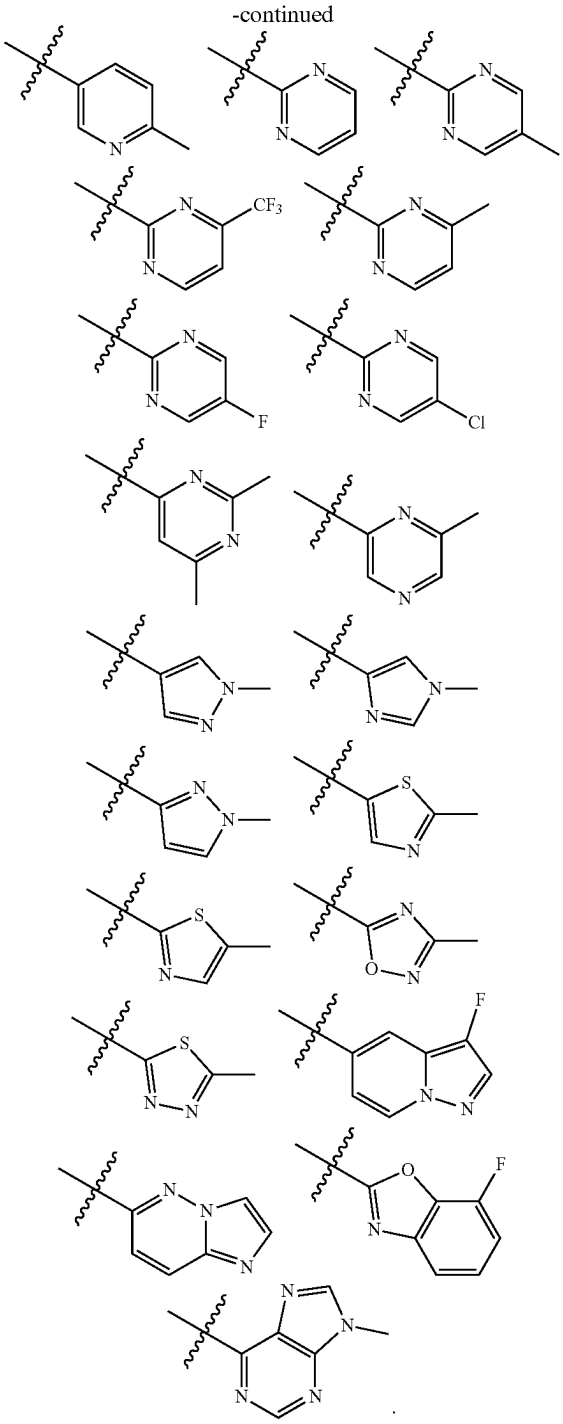
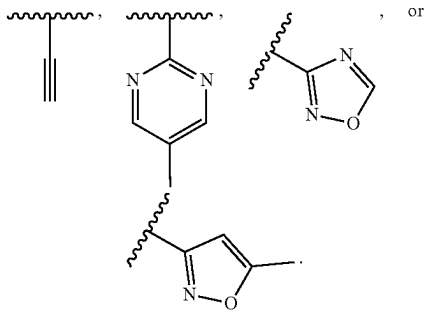
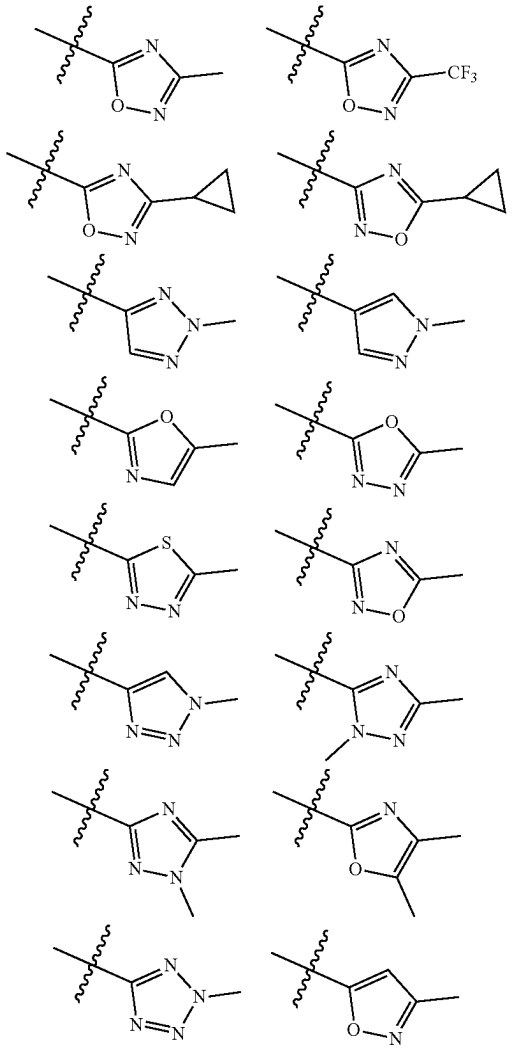


[0182] In some embodiments, in Formula I-1-a-2-a, j can be 0, or R^B is methyl and j can be 1.

[0183] In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, or CH_2OCH_3. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is selected from:



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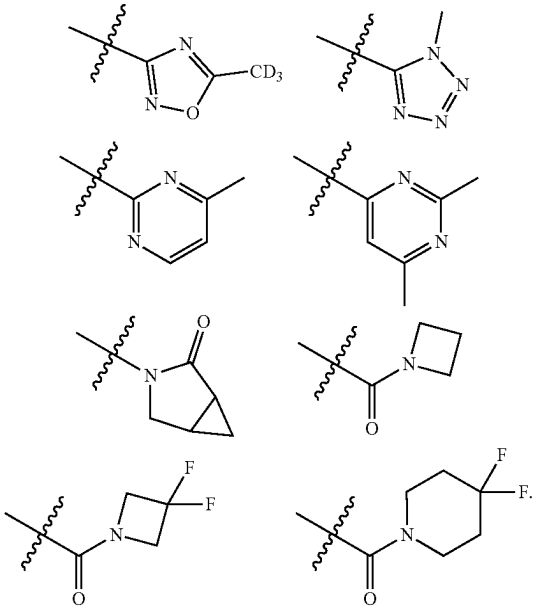
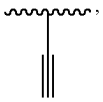
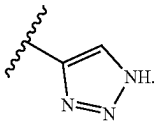


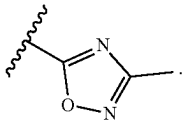
In some preferred embodiments, R^C in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f can be H, F, CN,



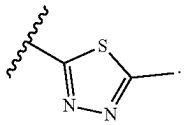
or a 5-membered heteroaryl which is optionally substituted, for example, a triazole, an thiadiazole, or an oxadiazole optionally substituted with methyl, CD_3, CF_3, or cyclopropyl. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is selected from CH_3, CH_2F, CHF_2, CF_3, CH_2OH, CH_2CH_3, or $CH(OH)CH_3$. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



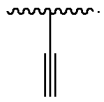
In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is F. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is CHF_2. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is CN. In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



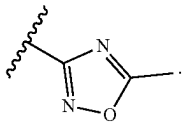
In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



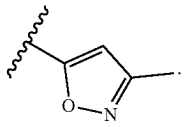
In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



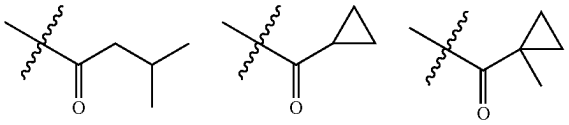
In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



In some embodiments, in Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^C is



[0184] In some embodiments, in Formula I-1-a-2-d, R^D is H, F, CN, acetenyl, methyl, ethyl, OCH_3, $NHCH_3$, or cyclopropyl. In some embodiments, in Formula I-1-a-2-d, R^D is selected from:



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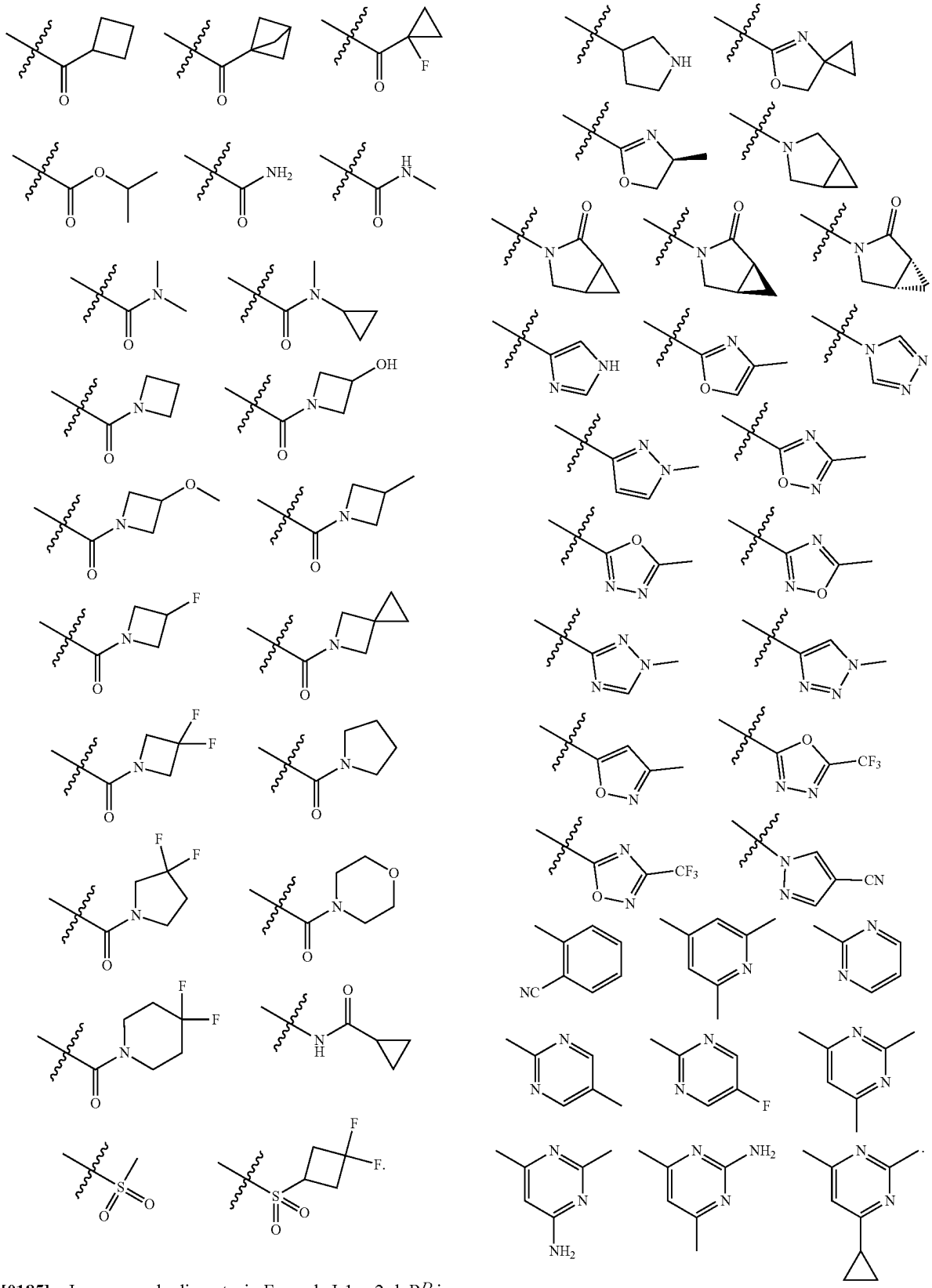


[0185] In some embodiments, in Formula I-1-a-2-d, R^D is selected from

[0186] In some embodiments, in Formula I-1-a-2-d, k is 0, or R^E is F, Cl, CN, methyl and k is 1, or each R^E is independently F or methyl and k is 2.

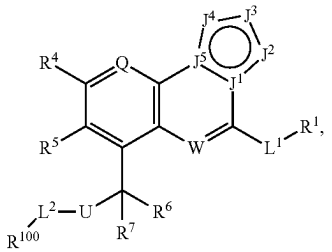
[0187] In some embodiments, in Formula I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^{20} is H. In some embodiments, in Formula I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f, R^{20} is Cl.

[0188] Further specific definitions of the variables for Formula A, such as Formula I, I-1, or I-1-a, include those respective atom/group/structures shown in the exemplified compounds herein, see e.g., those shown in Table A and Examples section.

Formula B

[0189] In some embodiments, the present disclosure provides a compound of Formula B, or a pharmaceutically acceptable salt thereof:

Formula B



[0190] wherein:

[0191] W is CR^{10} or N, wherein R^{10} is hydrogen, deuterium, halogen, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or C_{1-4} alkoxy optionally substituted with 1-3 fluorine;

[0192] Q is N or CR^3, wherein R^3 is hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0193] U is null, O, S, S(O), SO_2, or NR^8, wherein R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0194] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0195] R^1 is hydrogen or a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0196] J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5- or 6-membered ring having 2 or 3 ring heteroatoms, preferably, 2 or 3 ring nitrogen atoms, preferably, an optionally substituted 5-membered heteroaryl wherein J^4 is N, and J^5 is C or N;

[0197] R^4 and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0198] R^6 and R^7 are each independently hydrogen, deuterium, halogen, CN, G^2, or OG^2,

[0199] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0200] R^{100} is —R^{102}-R^{103}, wherein R^{102} is null, O, NH, C_{1-4} alkylene or C_{1-4} heteroalkylene having 1 or 2 heteroatoms, and R^{103} is hydrogen, COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, $SO_2NG^3G^3$, or a 5- or 6-membered ring having a hydrogen bond donor, e.g., a tetrazolyl;

[0201] wherein:

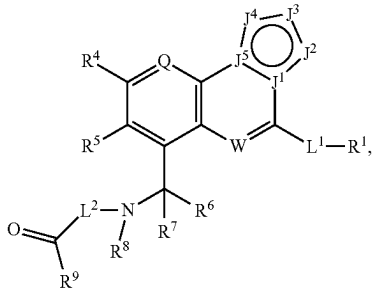
[0202] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0203] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0204] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

[0205] In some embodiments, the compound of Formula B can be characterized as having a structure according to Formula II:

Formula II



[0206] wherein:

[0207] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

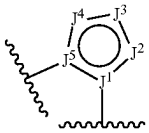
[0208] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0209] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$,

[0210] wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure,

[0211] wherein W, Q, L^1, L^2, J^1, J^2, J^3, J^4, J^5, R^6, R^4, and R^5 are defined herein.

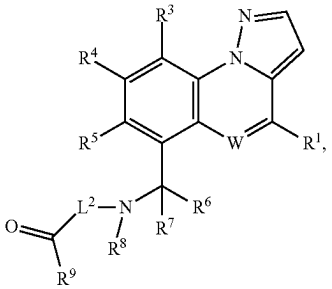
[0212] For the moiety of



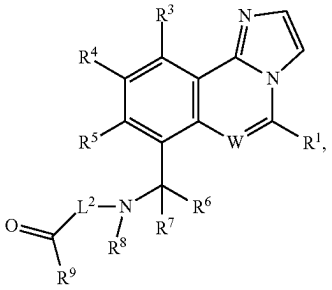
shown in the formulae herein (including Formula B, D, II, IV, etc.), it should be understood that when J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5-membered ring having 2 or 3 ring heteroatoms, each of J^1, J^2, J^3, J^4, and J^5 contains one ring atom of the 5-membered ring, such as a ring carbon or ring nitrogen atom. And when J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 6-membered ring having 2 or 3 ring heteroatoms, one of J^1, J^2, J^3, J^4, and J^5 contains two ring atoms of the 6-membered ring, and each of the remaining of J^1, J^2, J^3, J^4, and J^5 contains one ring atoms of the 6-membered ring. Preferably, J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5-membered or 6-membered heteroaryl ring, more preferably, 5-membered heteroaryl, in which J^4 is N, and J^5 is C or N.

[0213] In some specific embodiments, the compound of Formula B can be characterized as having a structure according to Formula II-1, II-2, or II-3:

Formula II-1



Formula II-2



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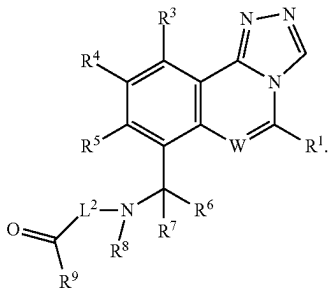
Formula II-3



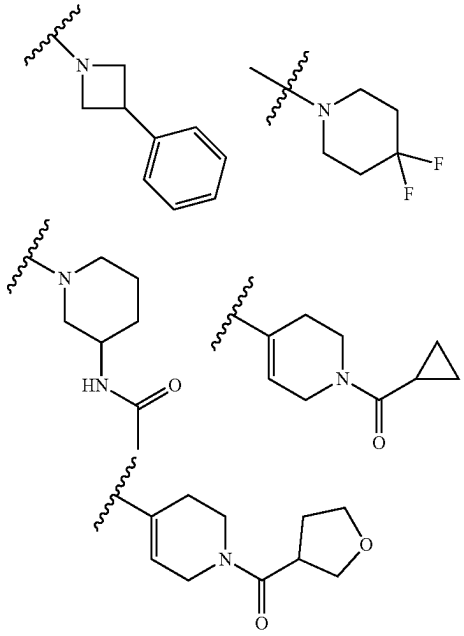
wherein the variables W, L^2, R^1, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined and preferred herein.

[0214] Suitable definitions and preferred definitions of the variables in Formula B (such as those in subformulae, e.g., Formula II, II-1, II-2, or II-3) include any of those described for the corresponding variables (i.e., those having the same identifiers, such as U, W, Q, L^1, L^2, R^1, R^3, R^4, R^5, R^6, R^7, R^8, and R^9) for Formula A and its subformulae.

[0215] For example, in some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), W can be N.

[0216] In some specific embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), R^1 can be any of those defined herein in connection with Formula A and its subformulae. For example, in some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), R^1 can have a structure according to any of M-1 to M-25 as described herein in connection with Formula A and its subformulae.

[0217] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), R^1 can be selected from



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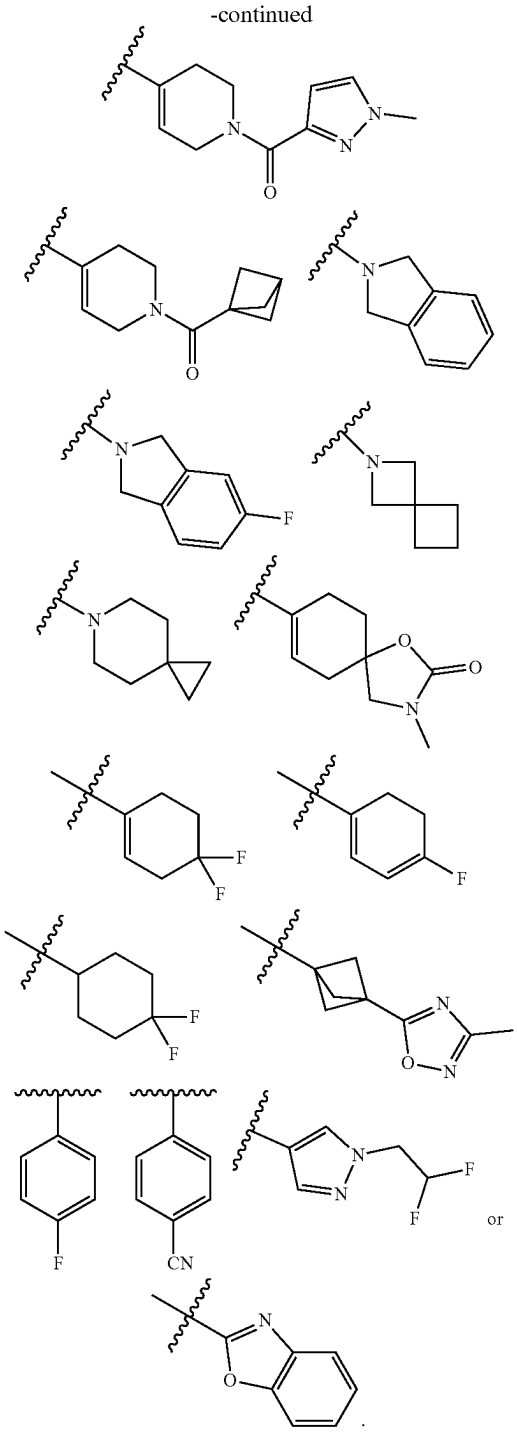
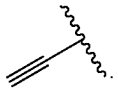


[0218] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), Q is CR^3 and R^3 can be methyl. In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), Q is CR^3 and R^3 can be hydrogen.

[0219] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), R^4 can be methyl.

[0220] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), R^4 can be F, Cl, Br, or



[0221] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), R^5 can be hydrogen.

[0222] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), both R^6 and R^7 can be hydrogen.

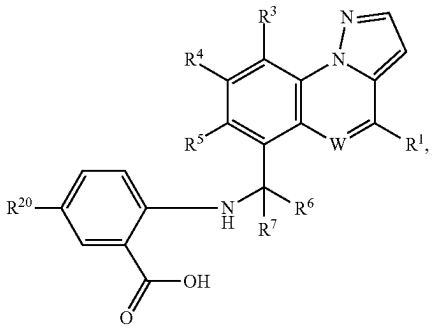
[0223] In some embodiments according to Formula B (such as a subformula, e.g., Formula II, II-1, II-2, or II-3), one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, more preferably, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl.

[0224] In some embodiments, U in Formula B is NR^8, such as in Formula II, II-1, II-2, or II-3, R^8 is typically hydrogen.

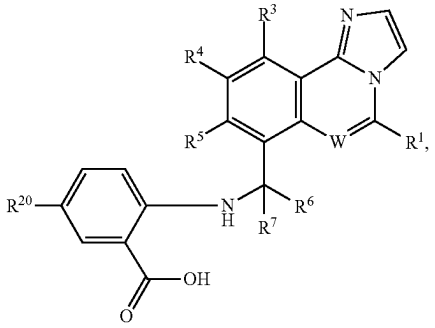
[0225] In some embodiments, R^{100} in Formula B is C(O) R^9, such as in Formula II, II-1, II-2, or II-3, R^9 is typically OH.

[0226] In some specific embodiments, the compound of Formula B can be characterized as having a structure according to Formula II-1-a, II-2-a, or II-3-a:

Formula II-1-a



Formula II-2-a



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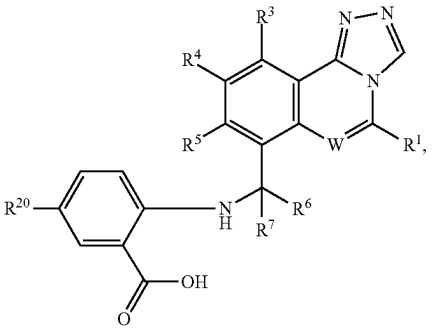
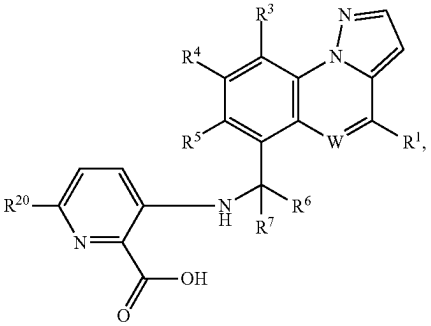
Formula II-3-a



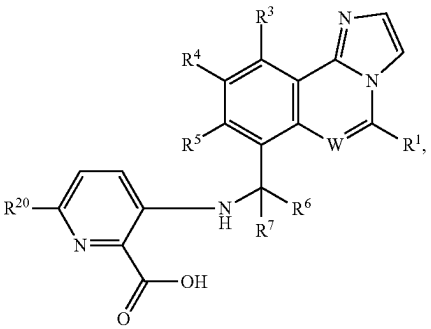
wherein the variables W, R^1, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined and preferred herein. For example, in some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3. In some embodiments, R^{20} is hydrogen.

[0227] In some specific embodiments, the compound of Formula B can be characterized as having a structure according to Formula II-1-b, II-2-b, or II-3-b:

Formula II-1-b



Formula II-2-b



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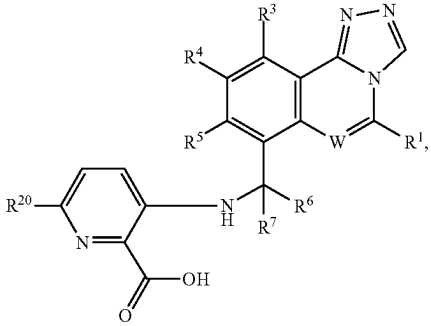
Formula II-3-b



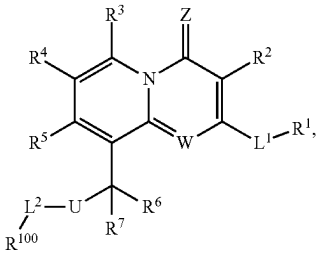
wherein the variables W, R^1, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined and preferred herein. For example, in some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3. In some embodiments, R^{20} is Cl.

[0228] Further specific definitions of the variables for Formula B, such as Formula II, II-1, II-2, or II-3, include those respective atom/group/structures shown in the exemplified compounds herein.

Formula C

[0229] In some embodiments, the present disclosure provides a compound of Formula C, or a pharmaceutically acceptable salt thereof:

Formula C



[0230] wherein:

[0231] W is CR^{10} or N, wherein R^{10} is hydrogen, deuterium, halogen, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or C_{1-4} alkoxy optionally substituted with 1-3 fluorine;

[0232] Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy;

[0233] U is null, O, S, S(O), SO_2, or NR^8, wherein R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0234] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0235] R^1 is hydrogen or a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12

membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0236] R^2, R^3, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0237] R^6 and R^7 are each independently hydrogen, deuterium, halogen, CN, G, or OG^2;

[0238] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0239] R^{100} is —R^{102}-R^{103}, wherein R^{102} is null, O, NH, C_{1-4} alkylene or C_{1-4} heteroalkylene having 1 or 2 heteroatoms, and R^{103} is hydrogen, COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, $SO_2NG^3G^3$, or a 5- or 6-membered ring having a hydrogen bond donor, e.g., a tetrazolyl;

[0240] wherein:

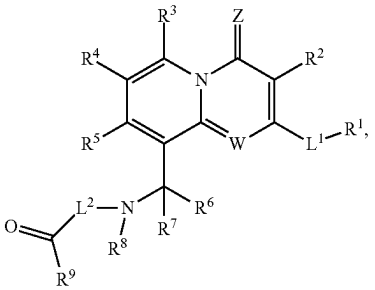
[0241] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0242] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0243] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

[0244] In some embodiments, the compound of Formula C can be characterized as having a structure according to Formula III:

Formula III



[0245] wherein:

[0246] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

[0247] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0248] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$,

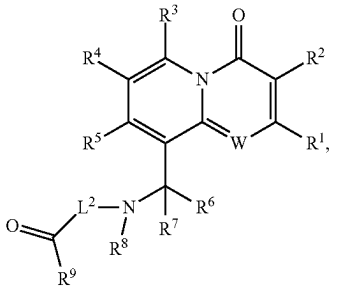
[0249] wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure,

[0250] wherein W, Z, L^1, L^2, R^1, R^2, R^3, R^4, and R^5, are defined herein.

[0251] In some embodiments, Z in Formula C or III is O.

[0252] In some embodiments, the compound of Formula III can be characterized as having a structure according to Formula III-1:

Formula III-1



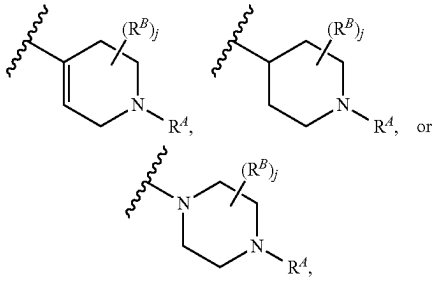
wherein W, L^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

[0253] Suitable definitions and preferred definitions of the variables in Formula C (such as those in subformulae, e.g., Formula III or III-1) include any of those described for the corresponding variables (i.e., those having the same identifiers, such as U, W, Z, L^1, L^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9) for Formula A and its subformulae.

[0254] For example, in some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1), W can be N.

[0255] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1), R^1 can be any of those defined herein in connection with Formula A and its subformulae. For example, in some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1), R^1 can have a structure according to any of M-1 to M-25 as described herein in connection with Formula A and its subformulae. The exemplified description of variables below for Formula C, such as R^1, is not to be understood as limiting in any way, and additional useful or preferred definitions of the variables are described herein, such as those described in connection with Formula A and its subformulae.

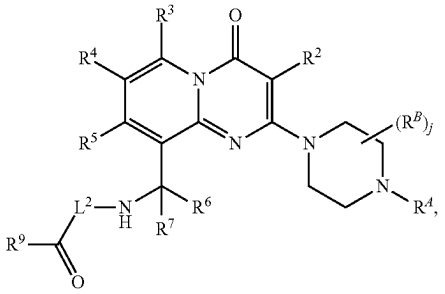
[0256] In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be



wherein R^A is G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$ wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; wherein R^B at each occurrence is independently F, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and j is 0, 1, or 2. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-12 membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-12 membered ring is a C_{3-7} cycloalkyl. In some embodiments, the 3-12 membered ring is a 4-7 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is phenyl. In some embodiments, the 3-12 membered ring is a 5-membered heteroaryl having 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, or phenyl. In some embodiments, j is 0. In some embodiments, j is 1 or 2, and R^B is defined herein, for example, in some embodiments, R^B is methyl. In some embodiments, R^A can also have the definition described herein for the variable R^C or R^D.

[0257] For example, in some embodiments, the compound of Formula C can have a structure according to Formula III-2:

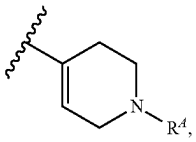
Formula III-2



wherein the variables j, L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^A and R^B are defined herein.

[0258] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-1:

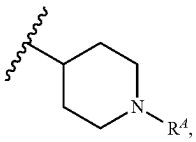
(M-1)



wherein R^A is defined herein.

[0259] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-2:

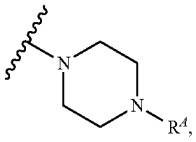
(M-2)



wherein R^A is defined herein.

[0260] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-3:

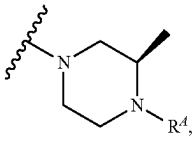
(M-3)



wherein R^A is defined herein.

[0261] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-4:

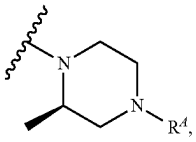
(M-4)



wherein R^A is defined herein.

[0262] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-5:

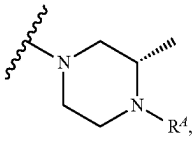
(M-5)



wherein R^A is defined herein.

[0263] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-6:

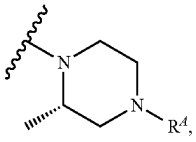
(M-6)



wherein R^A is defined herein.

[0264] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-7:

(M-7)

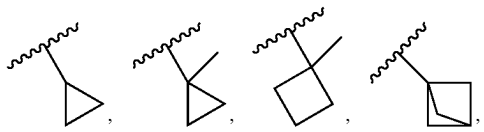


wherein R^A is defined herein.

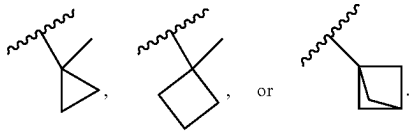
[0265] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)NHG^{5A}$, $C(O)NG^{5A}G^{5A}$, SO_2G^{5A}, SO_2NHG^{5A}, or $SO_2NG^{5A}G^{5A}$, wherein G^{5A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4}alkenyl, or C_{2-4} alkynyl; (ii) 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1}, wherein G^{B1} at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or cyclopropyl.

[0266] For example, in some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl. In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be C_{1-4} alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl.

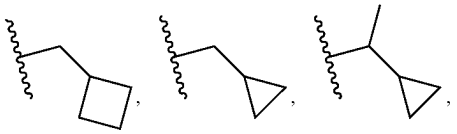
[0267] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)N(CH_3)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



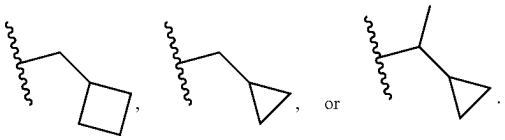
etc. In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



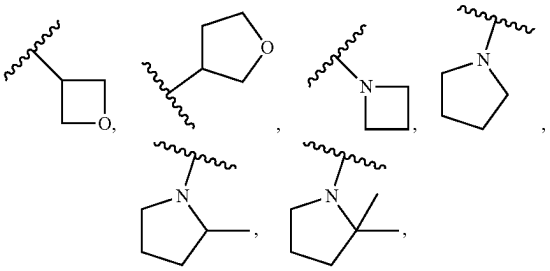
[0268] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)N(CH_3)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



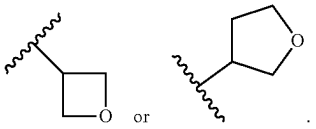
etc. In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be $C(O)G^{5A}$ or $C(O)OG^{5A}$, wherein G^{5A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



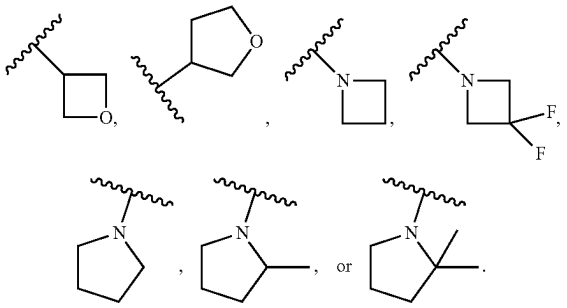
[0269] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)N(CH_3)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



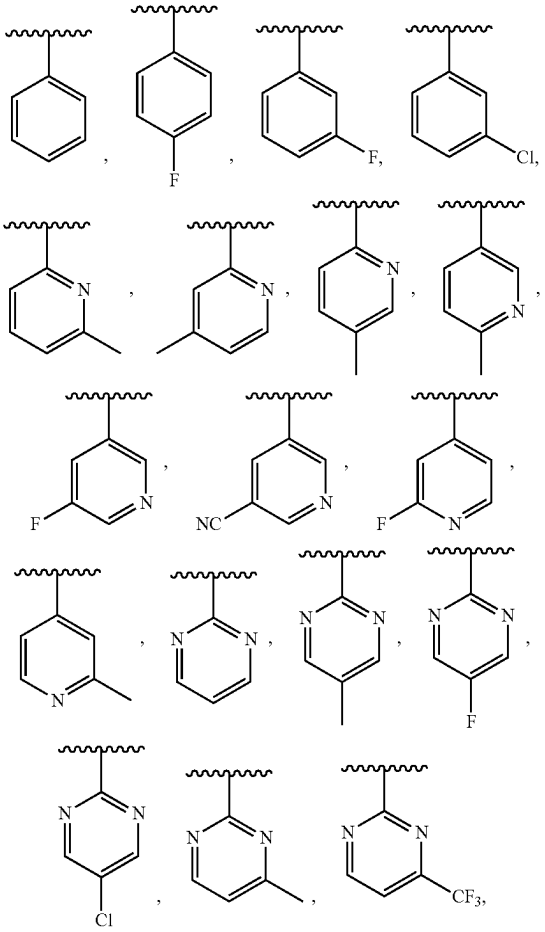
etc. Preferably, the 4-6 membered heterocyclic does not connect to a heteroatom through a ring heteroatom. For example, in some embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A} which can be



In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be $C(O)G^{5A}$, wherein G^{5A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



[0270] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A}, $C(O)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is phenyl or 5-10 membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



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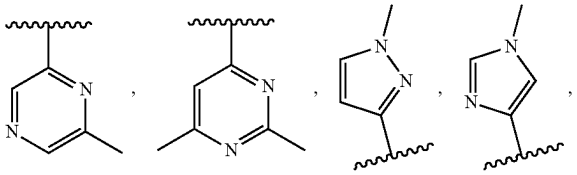
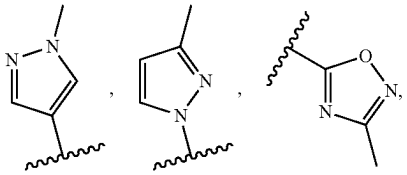
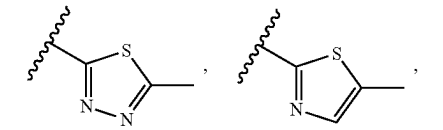
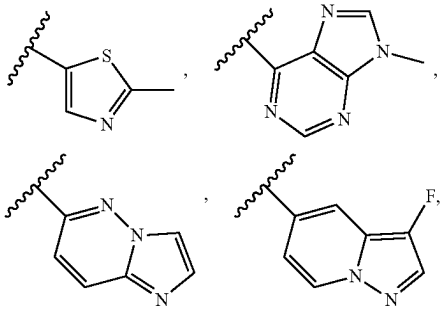
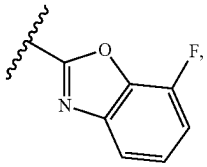


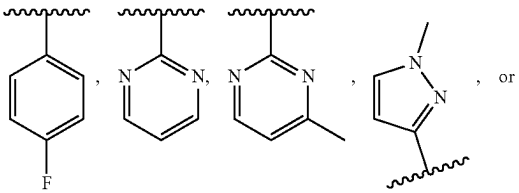








etc. In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be G^{5A} or $C(O)G^{5A}$, wherein G^{5A} is phenyl or 5- or 6-membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



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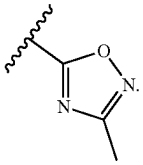
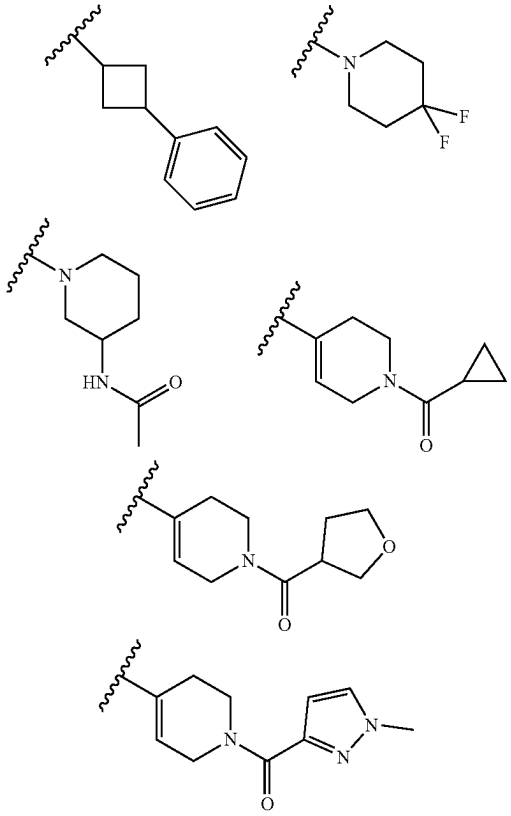


[0271] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be $C(O)NHG^{5A}$ wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). For example, R^A can be CONH (isopropyl).

[0272] In some preferred embodiments, R^A in the structures herein (e.g., Formula III-2) can be $C(O)NG^{5A}G^{5A}$, wherein one instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. For example, R^A can be $CON(CH_3)_2$.

[0273] In some specific embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be selected from:



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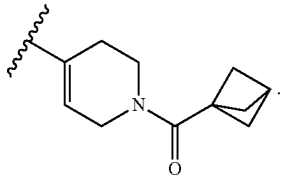
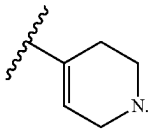
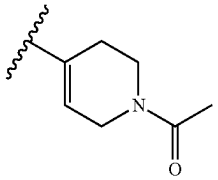
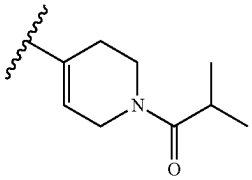


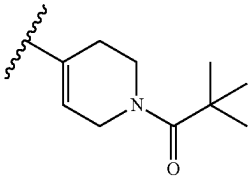
[0274] In some specific embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be an optionally substituted

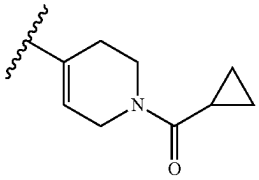


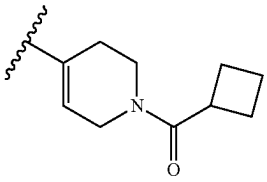
For example, R^1 can be selected from:

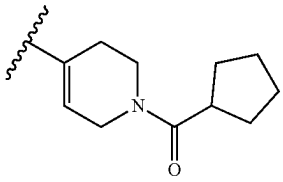


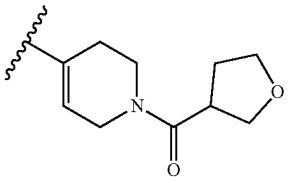


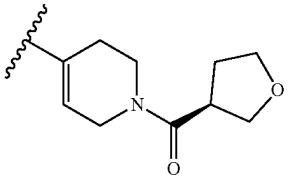












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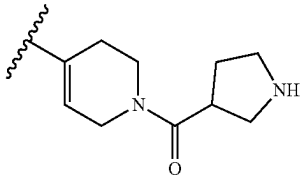

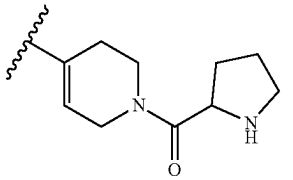

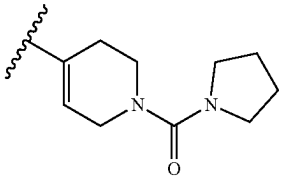

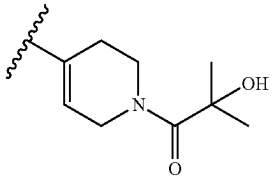

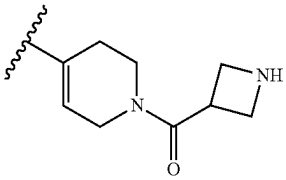

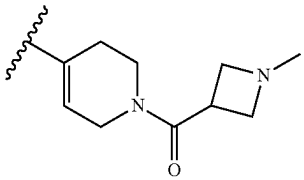

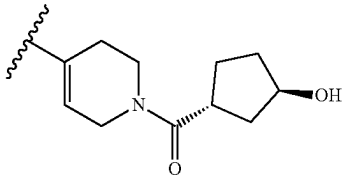

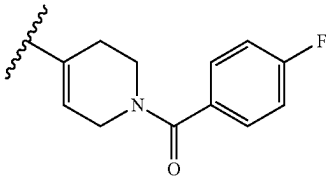

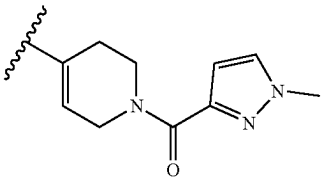

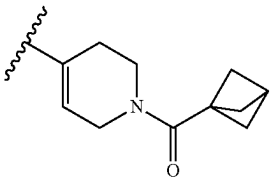

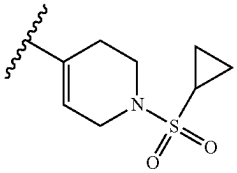

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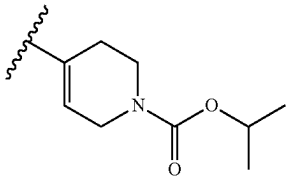

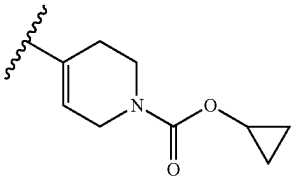

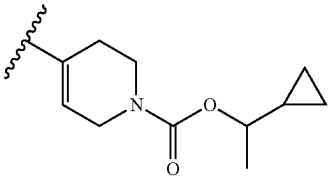

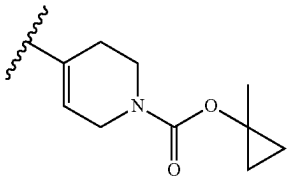

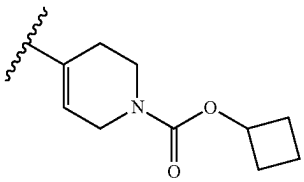

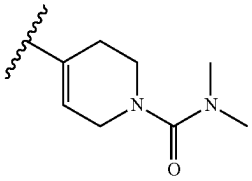

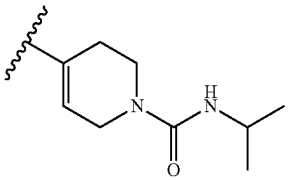

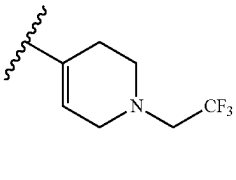

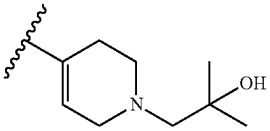

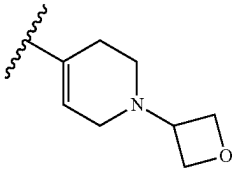

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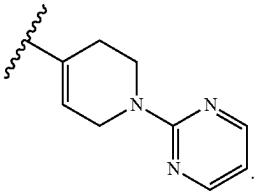
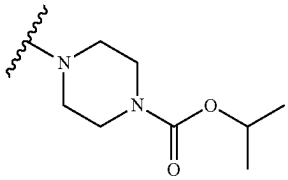
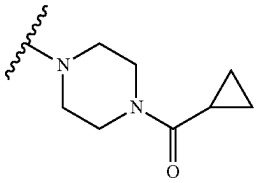
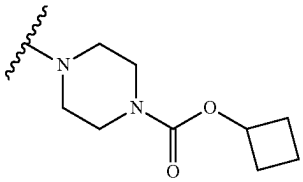
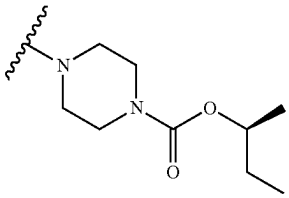


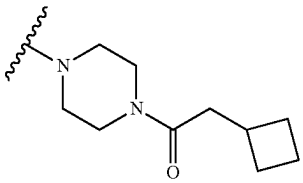
[0275] In some specific embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be an optionally substituted piperazine, for example, R^1 can be selected from:

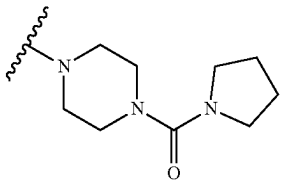












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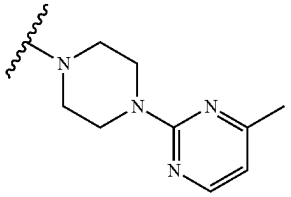
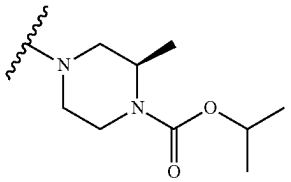
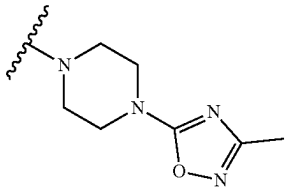
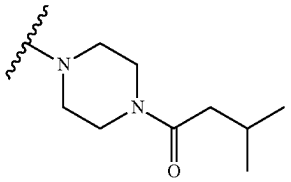
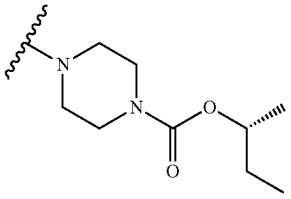
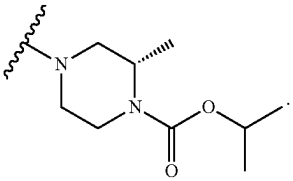




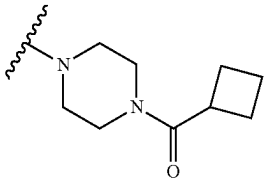


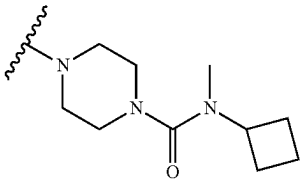






[0276] For example, R^1 can be selected from:





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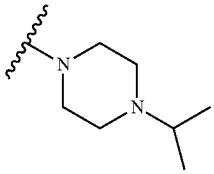

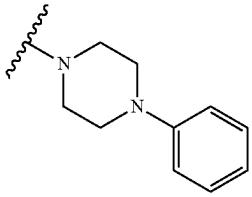

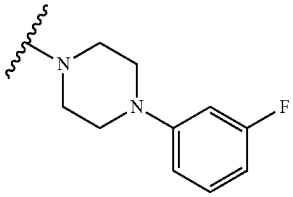

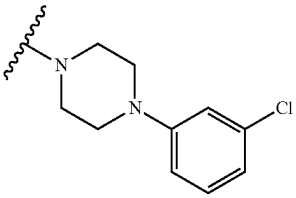

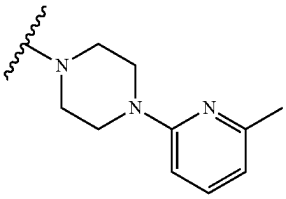

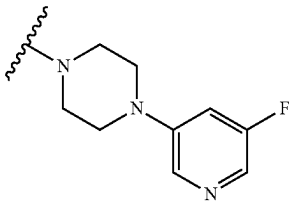

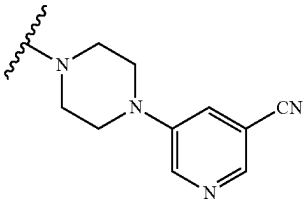

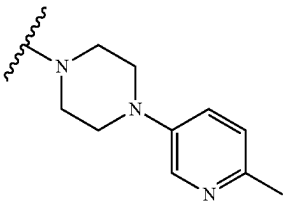

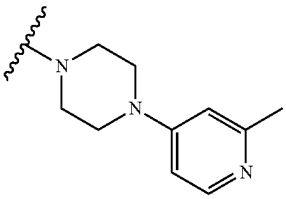

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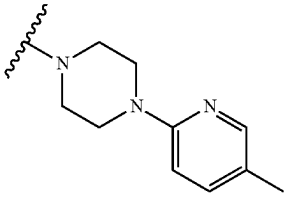

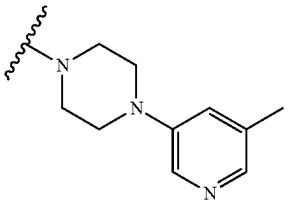

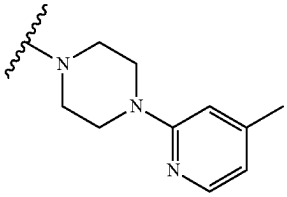

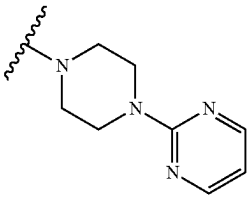

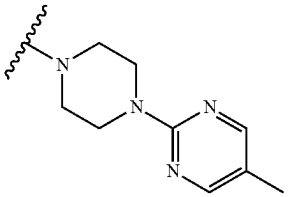

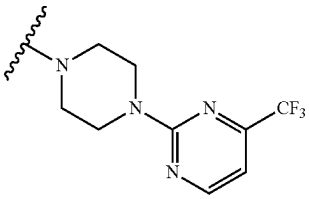

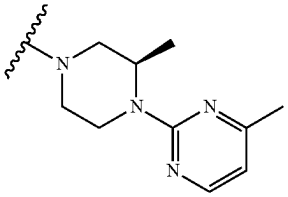

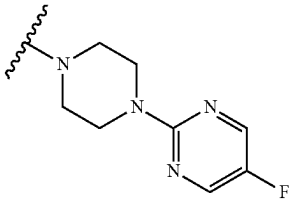

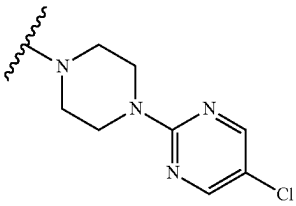

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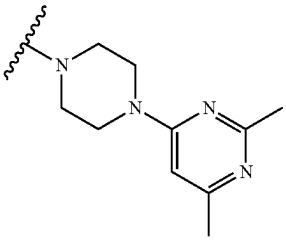

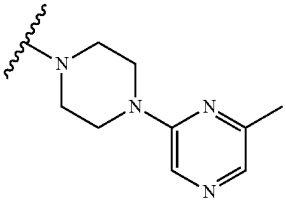

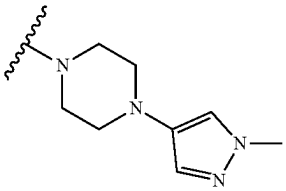

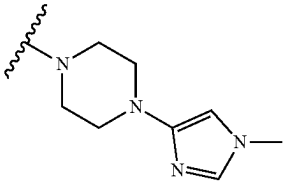

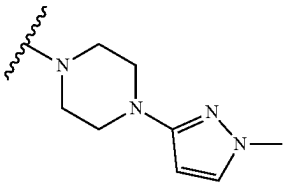

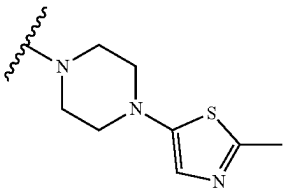

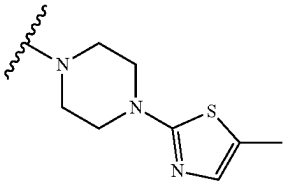

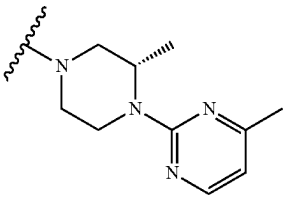

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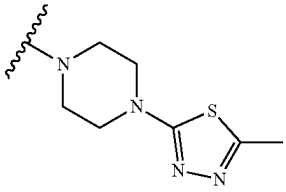
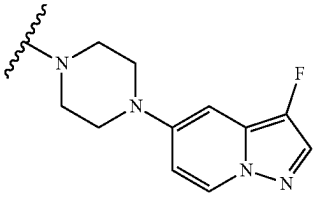
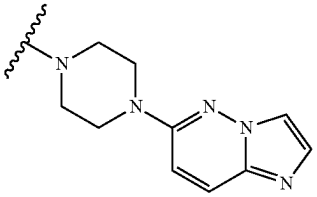
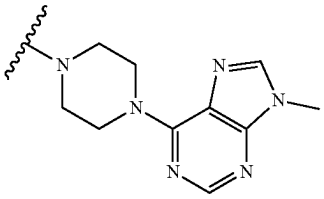
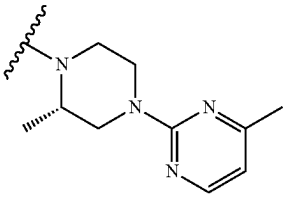
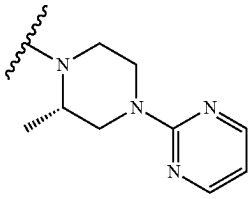


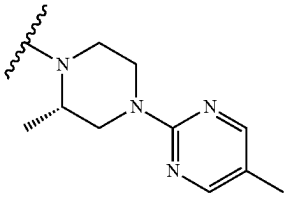


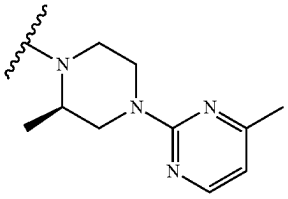


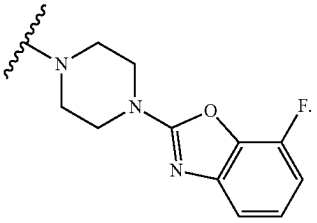




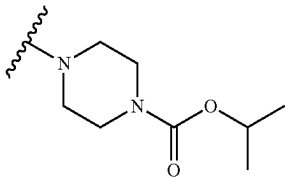


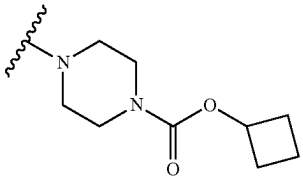


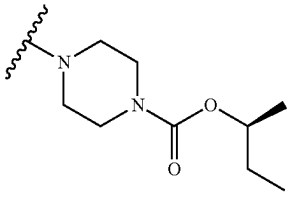


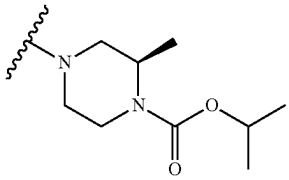


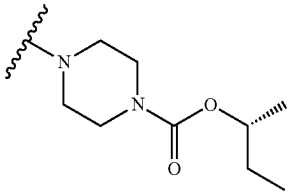
[0277] In some embodiments, R^1 can be selected from:

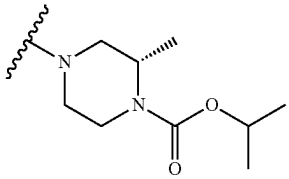


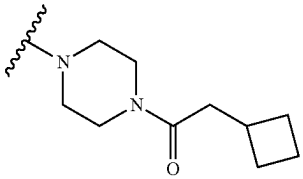


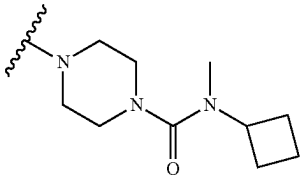


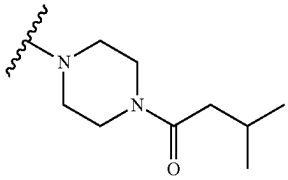


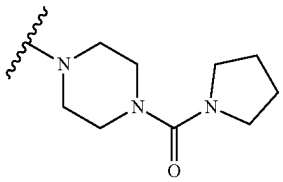












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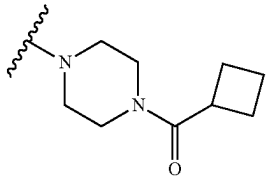

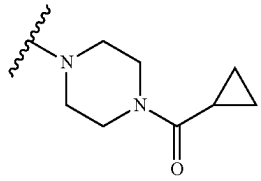

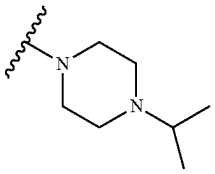

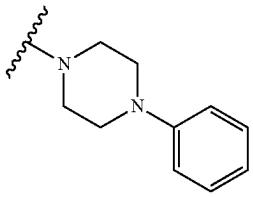

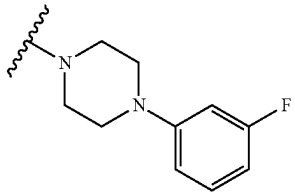

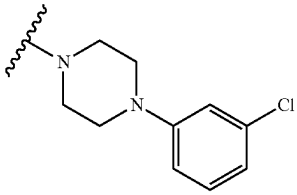

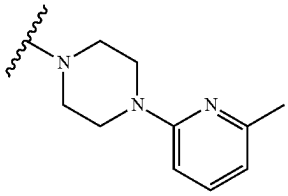

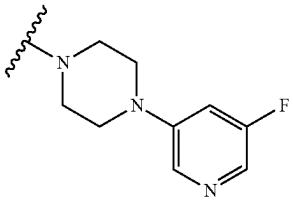

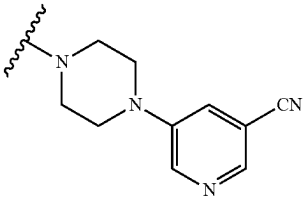

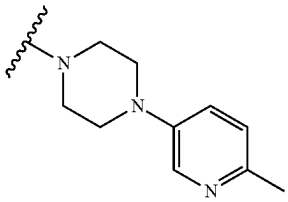

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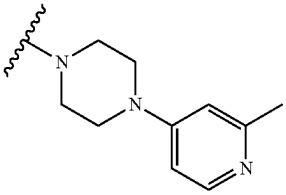

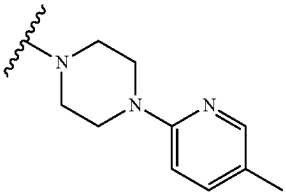

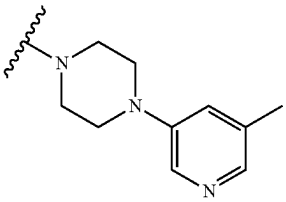

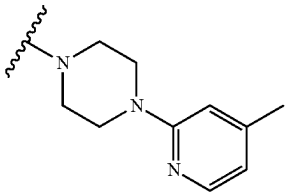

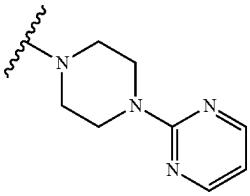

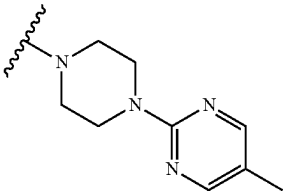

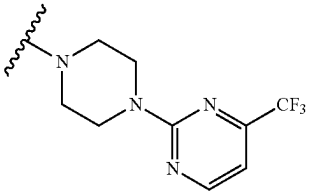

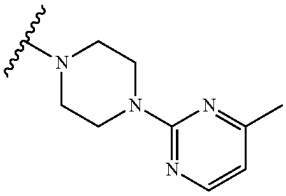

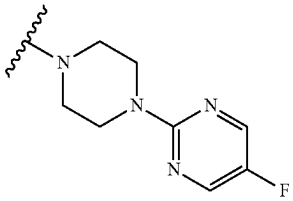

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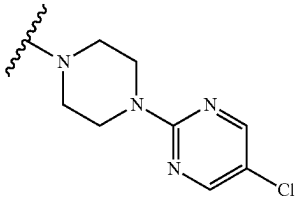

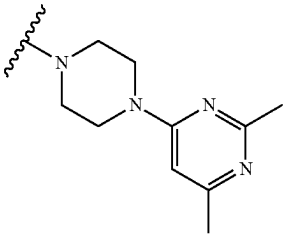

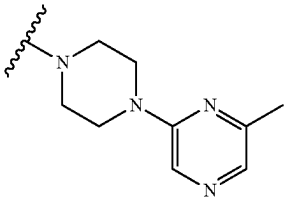

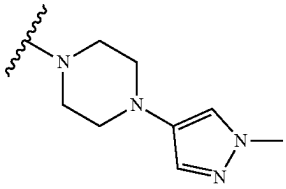

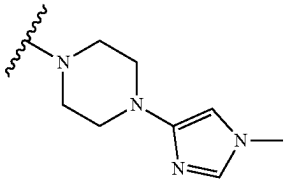

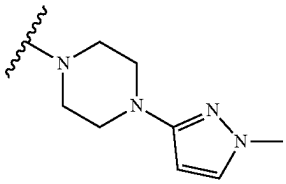

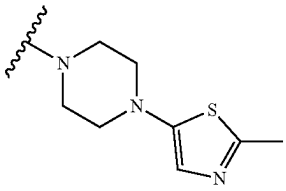

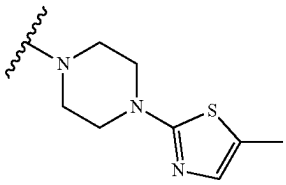

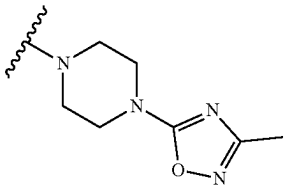

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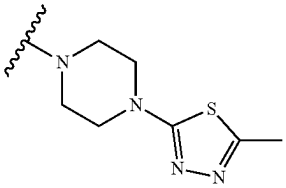

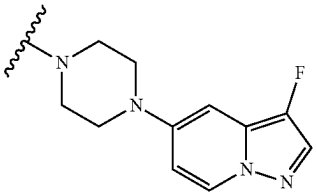

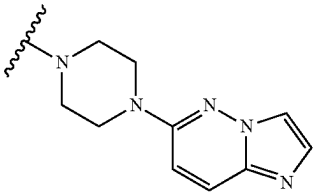

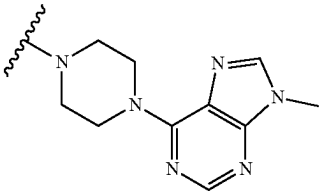

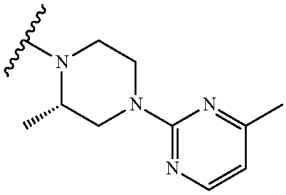

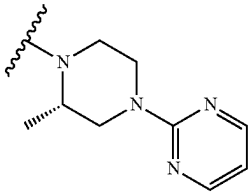

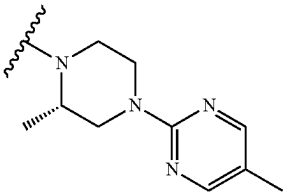

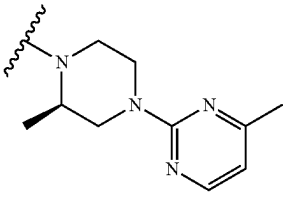

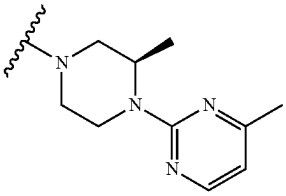

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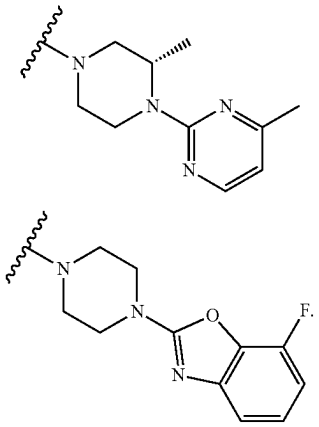
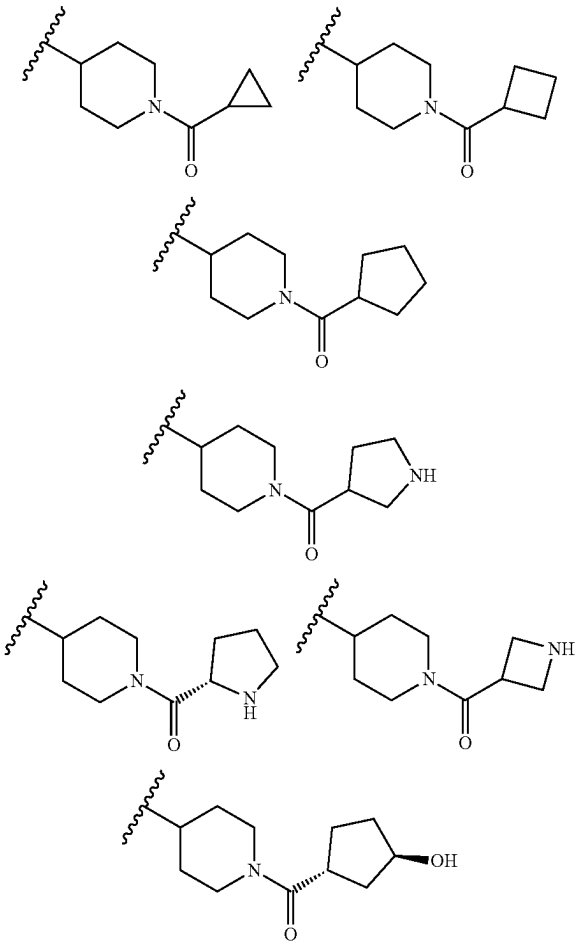


[0278] In some specific embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be an optionally substituted piperidine, for example, R^1 can be selected from:



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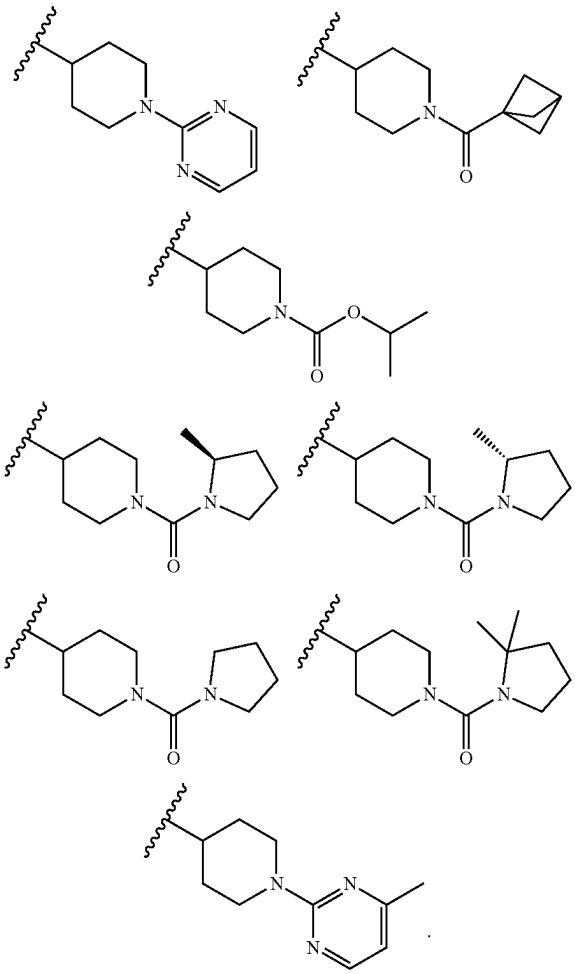
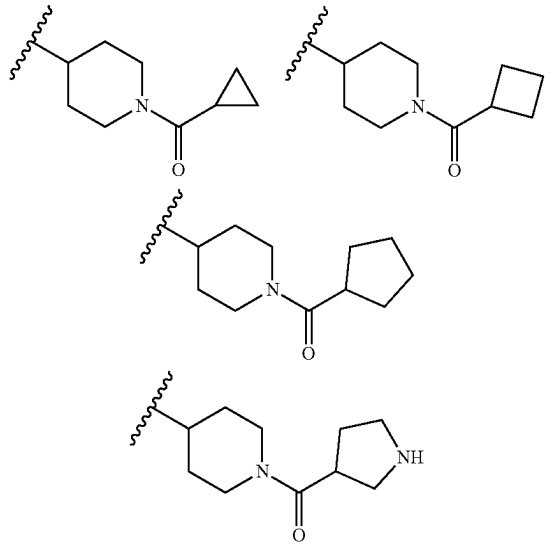


[0279] In some embodiments, R^1 can be selected from:



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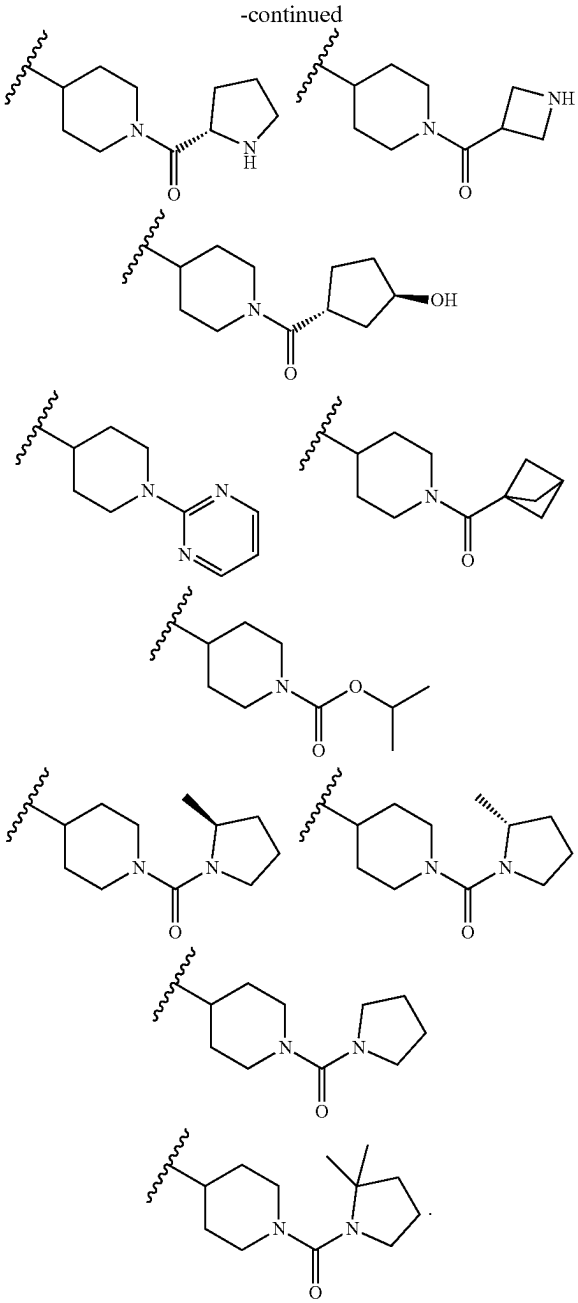
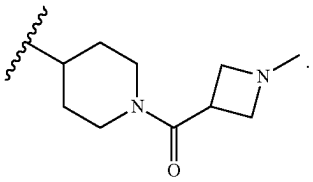
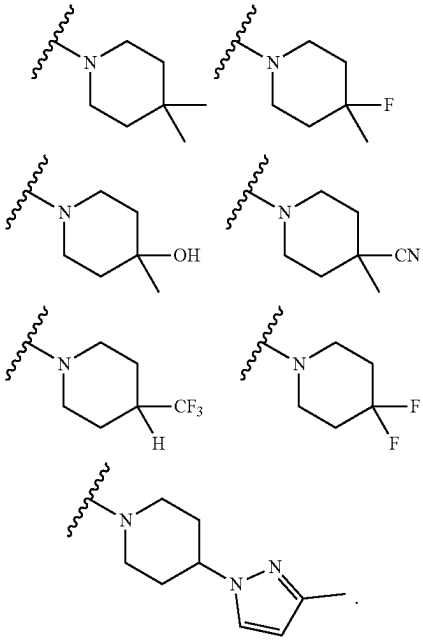


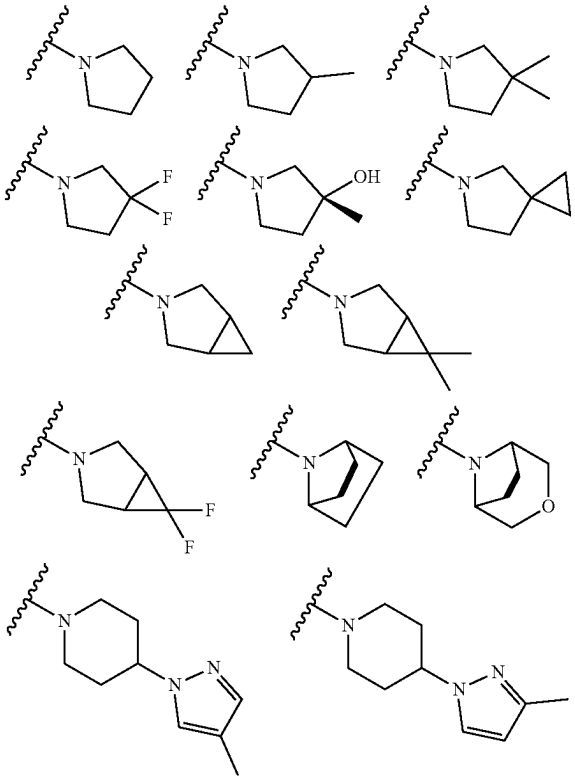
[0280] In some embodiments, R^1 can be selected from:



[0281] In some specific embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be an optionally substituted piperidine, which attaches to the remainder of the molecule through the ring nitrogen, for example, in some embodiments, R^1 can be selected from:



[0282] In some embodiments, R^1 can be selected from:



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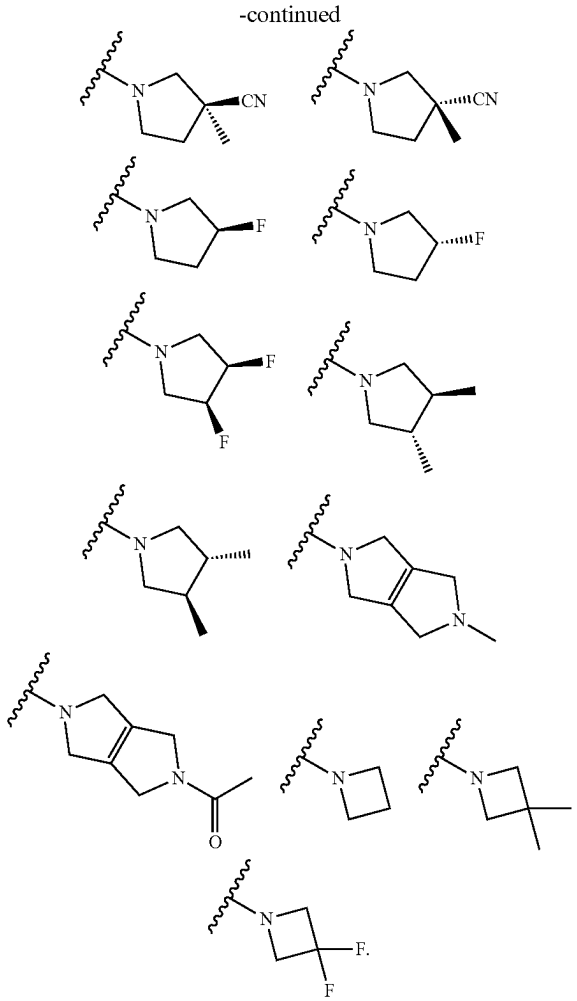
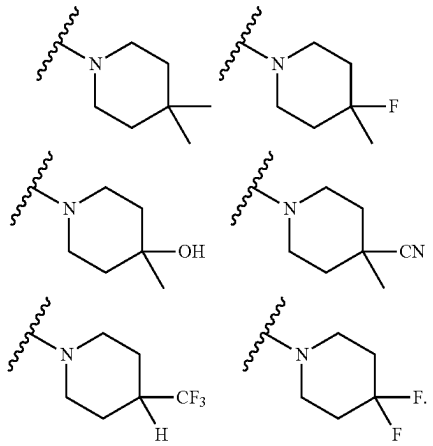
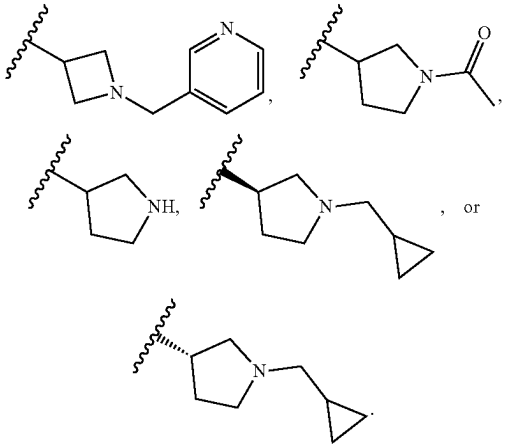


[0283] For example, R^1 can be selected from:

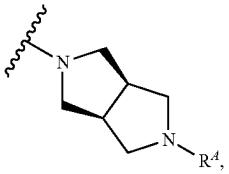


[0284] In some specific embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be selected from:

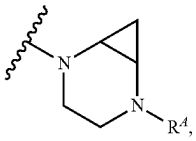


[0285] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can have a structure according to:

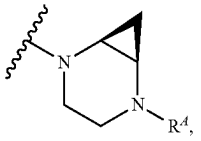
(M-8)



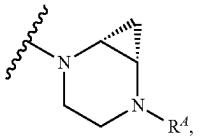
(M-9)



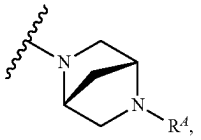
(M-10)



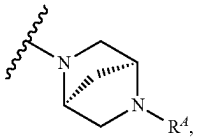
(M-11)



(M-12)



(M-13)



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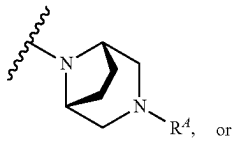
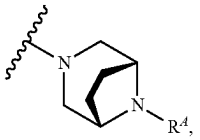
(M-14)

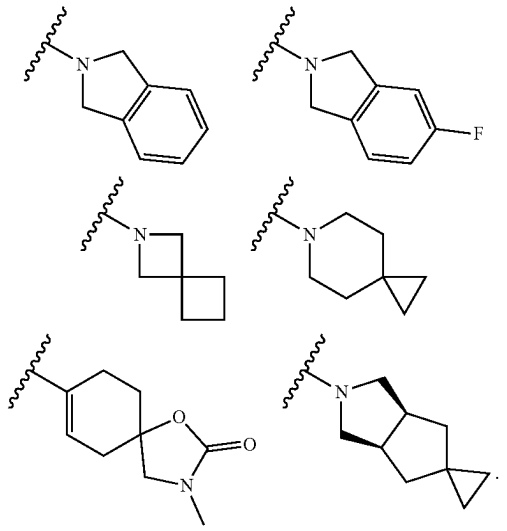


(M-15)

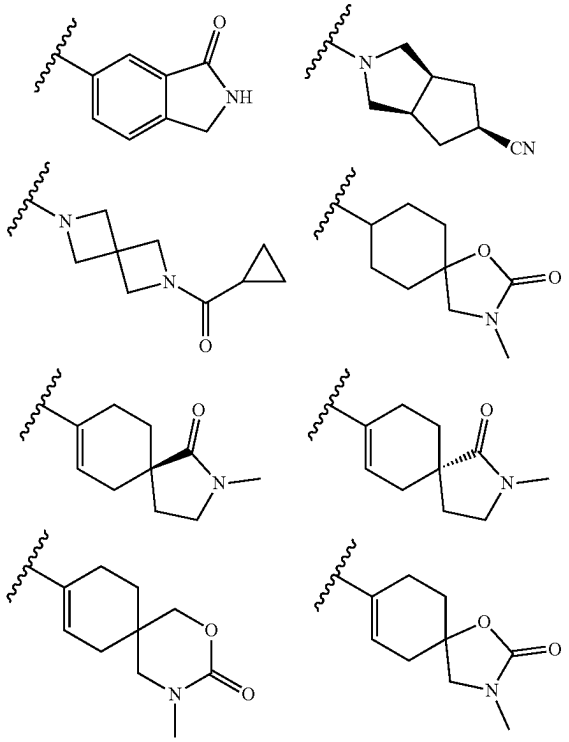


wherein R^A is G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1} wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-12 membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-12 membered ring is a C_{3-7} cycloalkyl. In some embodiments, the 3-12 membered ring is a 4-7 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is phenyl. In some embodiments, the 3-12 membered ring is a 5-membered heteroaryl having 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, or phenyl. In some embodiments, R^A in M-8 to M-15 can be any of those R^A described herein.

[0286] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) is selected from:



[0287] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) is selected from:



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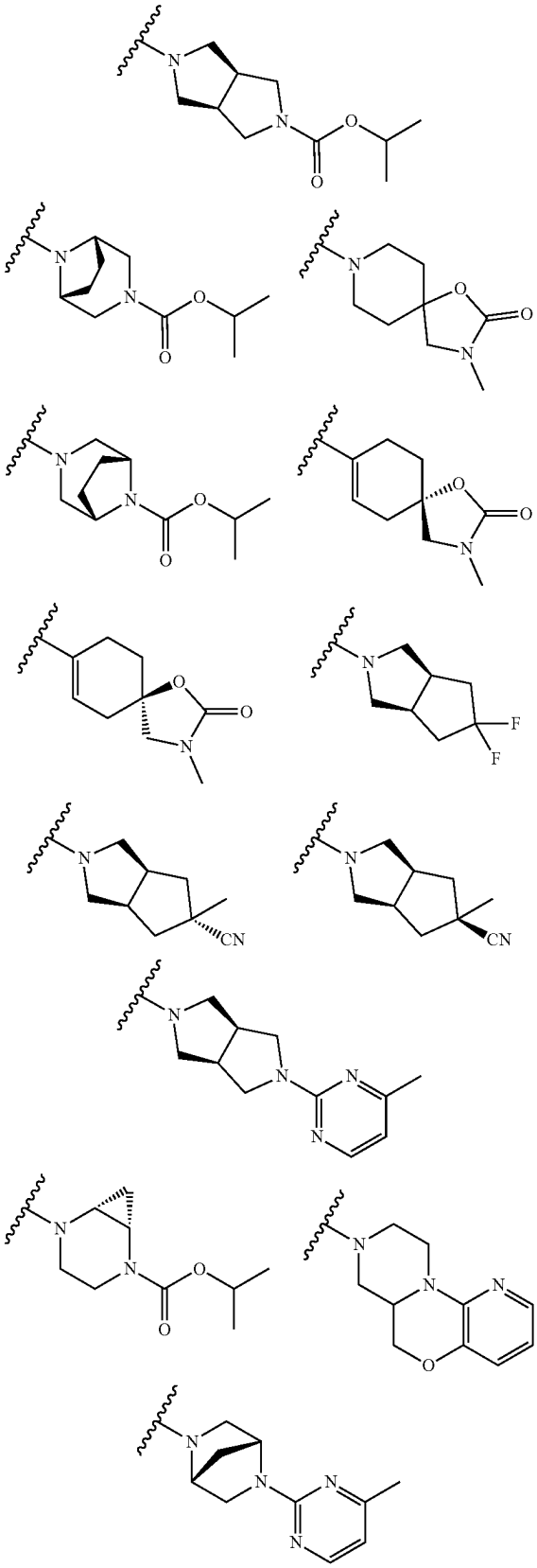

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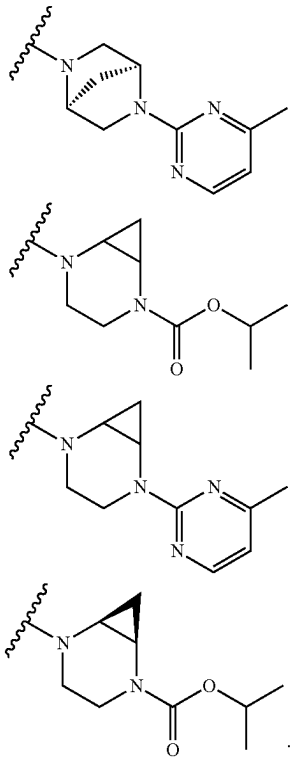
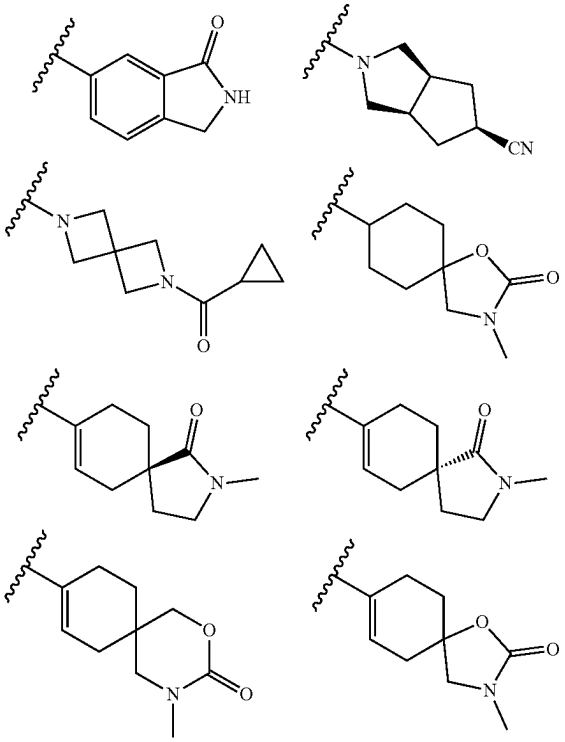


[0288] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) is selected from:



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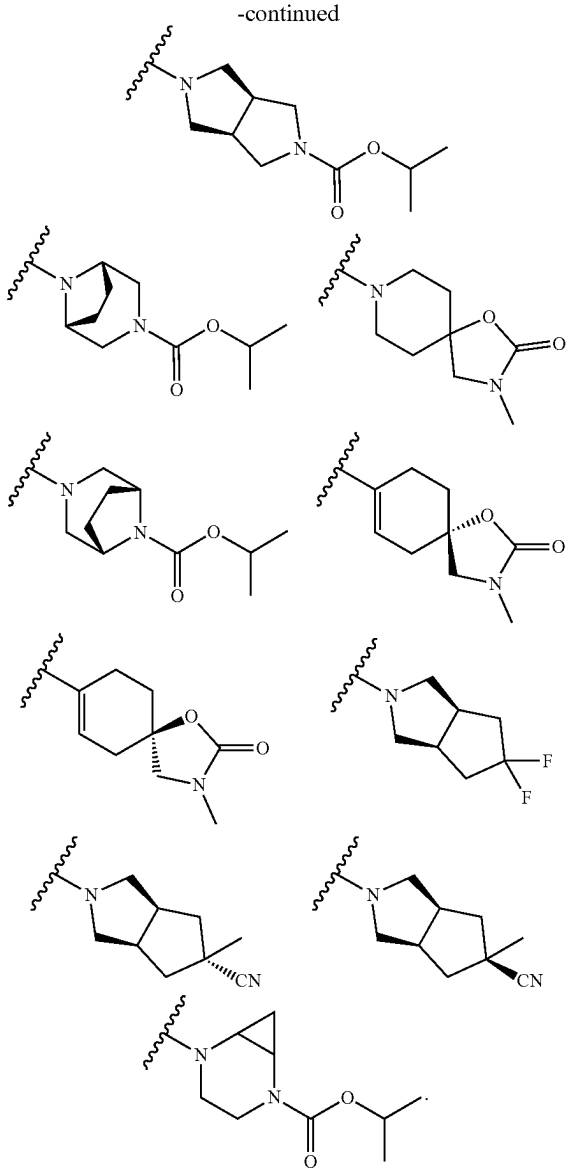
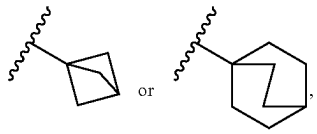
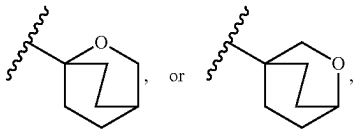


[0289] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be a bridged 5-12 membered ring structure, which is optionally substituted, wherein the bridged ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S. For example, in some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be a 5-12 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted. For example, in some embodiments, R^1 is a 5-8 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be a 5-12 membered (preferably, 7-10 membered, e.g., 7 or 8 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one ring heteroatom which is a ring oxygen. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be a 5-12 membered (preferably, 8-10 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one or two ring heteroatoms independently selected from S, O, and N. In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be

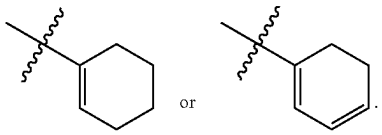


each of which is optionally substituted, e.g., as described herein. In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be

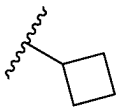


each of which is optionally substituted, e.g., as described herein.

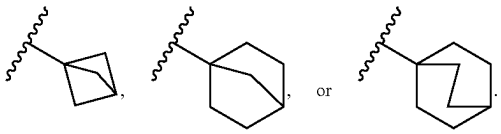
[0290] In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be a 4-10 membered carbocyclyl, which is optionally substituted. The 4-10 membered carbocyclyl can be monocyclic or polycyclic. In some embodiments, the 4-10 membered carbocyclyl has one or two carbon-carbon double bonds, such as



In some embodiments, the 4-10 membered carbocyclyl can also be fully saturated, such as



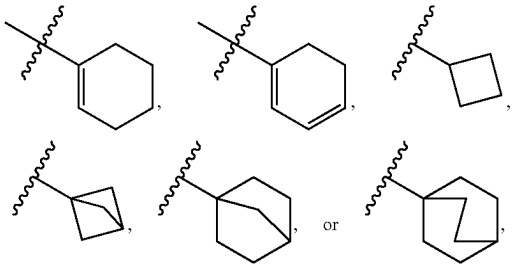
or cyclohexyl. In some embodiments, the 4-10 membered carbocyclyl can be a bridged ring, such as



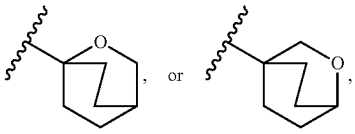
When substituted, the 4-10 membered carbocyclyl is typically substituted with one or more, such as 1-3, or 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$,

[0291] wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0292] In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be



or, or can be

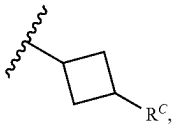


each of which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—$C(O)G^5$, or $C(O)G^5$,

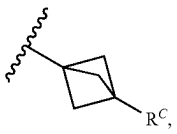
[0293] wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0294] In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be a structure of

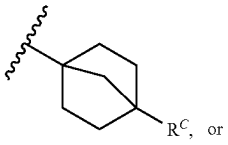
(M-16)



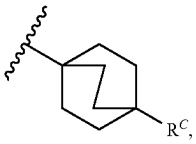
(M-17)



(M-18)

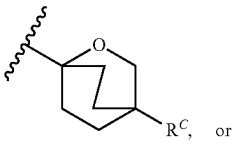


(M-19)

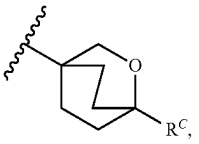


or can be a structure of

(M-19′)



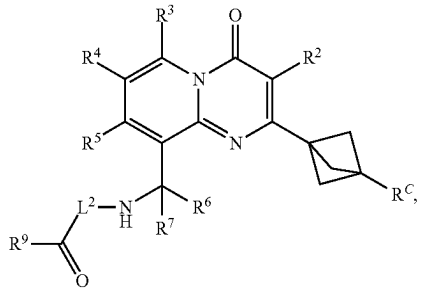
(M-19″)



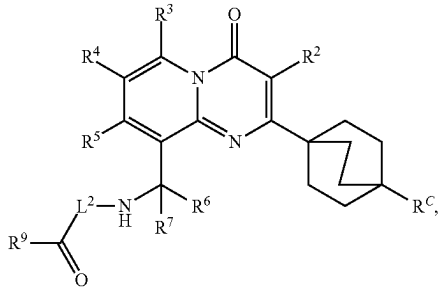
wherein R^C is hydrogen, halogen (e.g., F), CN, COOH, $CONH_2$, G^{4A}, OG^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, $NHC(O)NHG^{4A}$, $NHC(O)NG^{4A}G^{4A}$, $NG^{4A}C(O)G^{4A}$, $NG^{4A}C(O)OG^{4A}$, $NG^{4A}C(O)NHG^{4A}$ $NG^{4A}C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-

oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as (C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-17, as defined herein. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-18, as defined herein. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-19, as defined herein. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-19', as defined herein. In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-19", as defined herein. For example, in some embodiments, the compound of Formula C can have a structure according to Formula III-3, III-4, III-x, or III-y:

Formula III-3



Formula III-4



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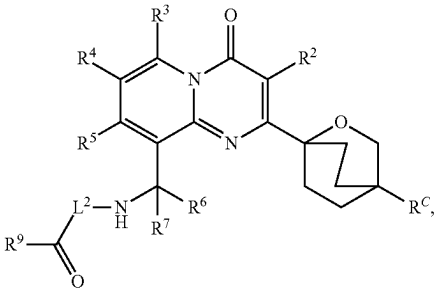
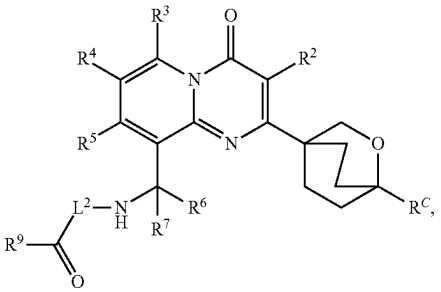
Formula III-x

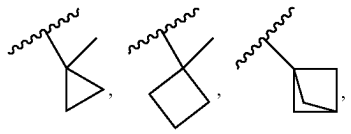


Formula III-y

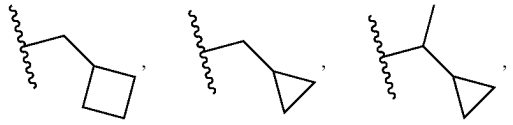


wherein the variables L^2, R^2, R^3, R^4, R^5, R^1, R^7, R^9, and R^C are defined herein.

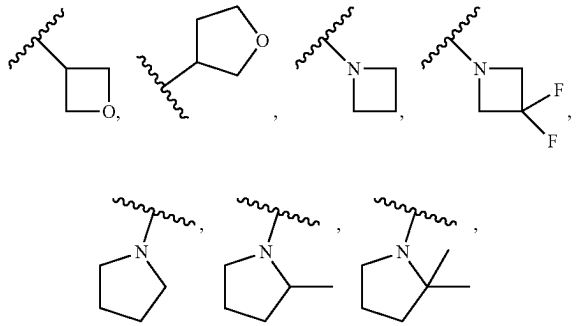
[0295] For example, in some embodiments, R^C is CN. In some embodiments, R^C is H, halogen, such as F, Cl, or Br, OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, CH_2OCH_3, CHF_2, CH_3, or OCH_3. In some embodiments, R^C is G^{4A}. In some embodiments, R^C is $C(O)G^{4A}$. In some embodiments, R^C is $C(O)NHG^{4A}$ or $C(O)NG^{4A}G^{4A}$. In some embodiments, R^C is $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, $NHC(O)NHG^{4A}$, or $NHC(O)NG^{4A}G^{4A}$. In some embodiments, R^C is G^4, $C(O)G^4$, $C(O)NHG^4$, $NHC(O)G^4$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



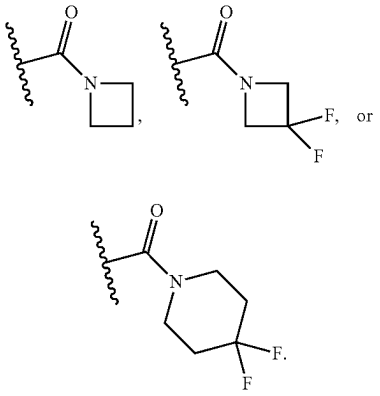
etc. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



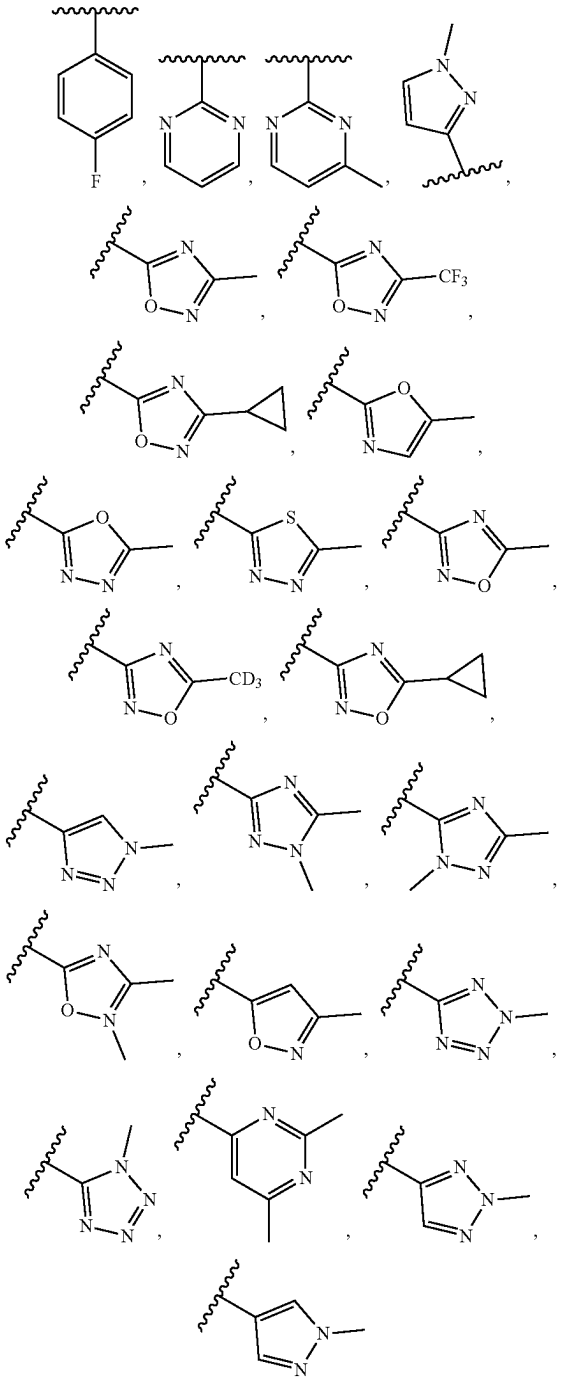
etc. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



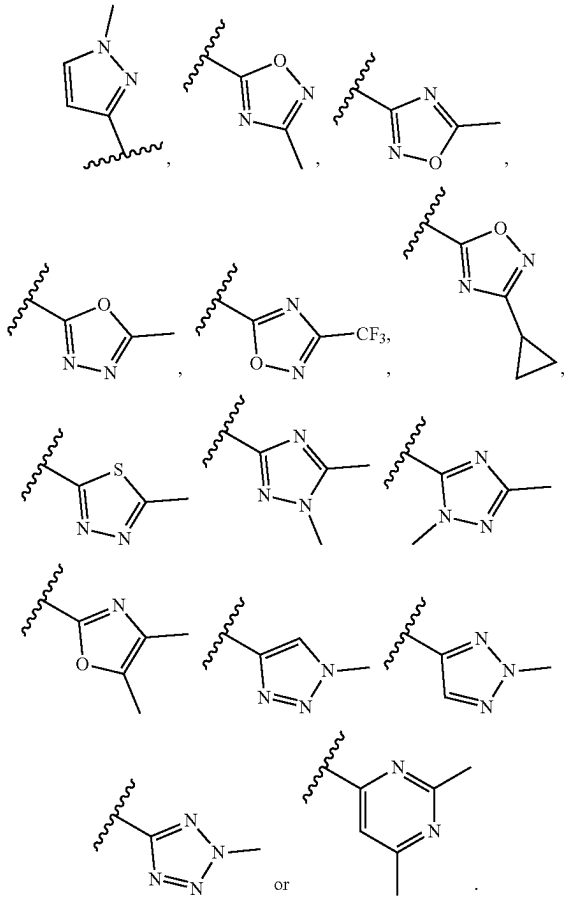
etc., typically, when the 4-6 membered heterocyclic attaches through a ring nitrogen, R^C is $C(O)G^{4A}$, for example, in some embodiments, R^C is



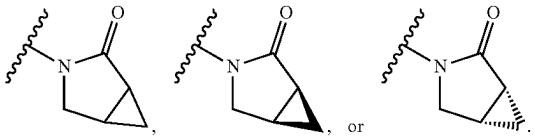
In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is phenyl or 5- or 6-membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



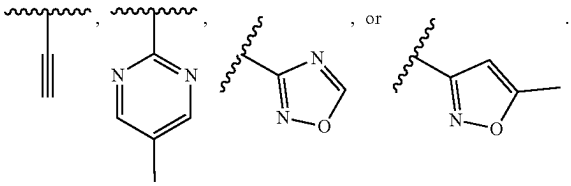
etc. In some embodiments, R^C is $C(O)NG^{4A}G^{4A}$ or $NHC(O)NG^{4A}G^{4A}$, wherein one instance of G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. In some embodiments, R^C is



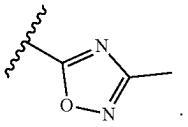
[0296] In some embodiments, R^C is



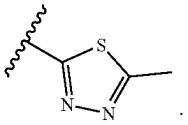
In some embodiments, R^C is



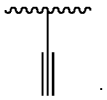
In some embodiments, R^C is F. In some embodiments, R^C is CHF_2. In some embodiments, R^C is CN. In some embodiments, R^C is



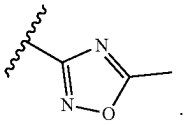
In some embodiments R^C is



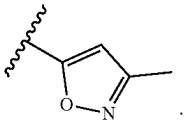
In some embodiments, R^C is



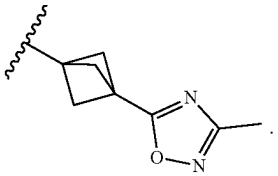
In some embodiments, R^C is



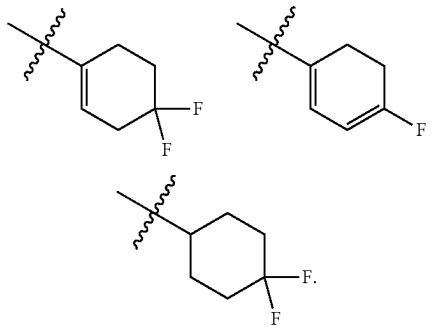
In some embodiments, R^C is



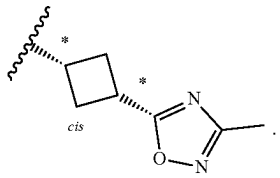
In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be



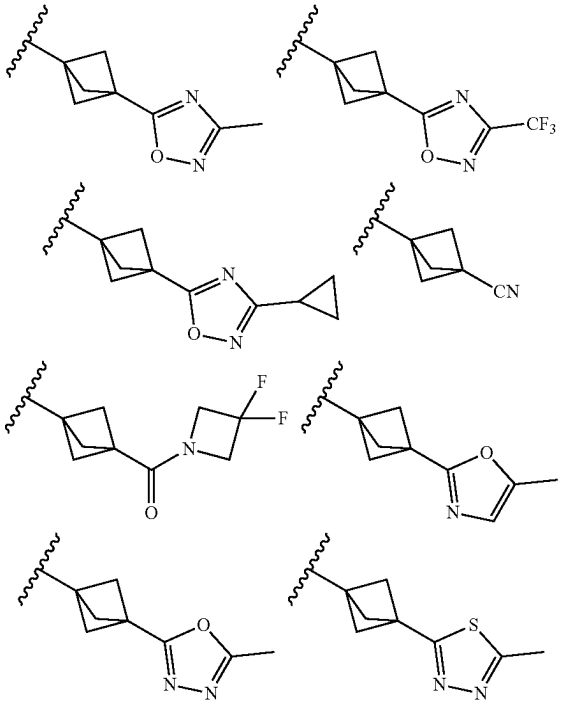
[0297] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be selected from



[0298] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-16 as defined herein, for example, can be



[0299] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-17 as defined herein, for example, can be selected from



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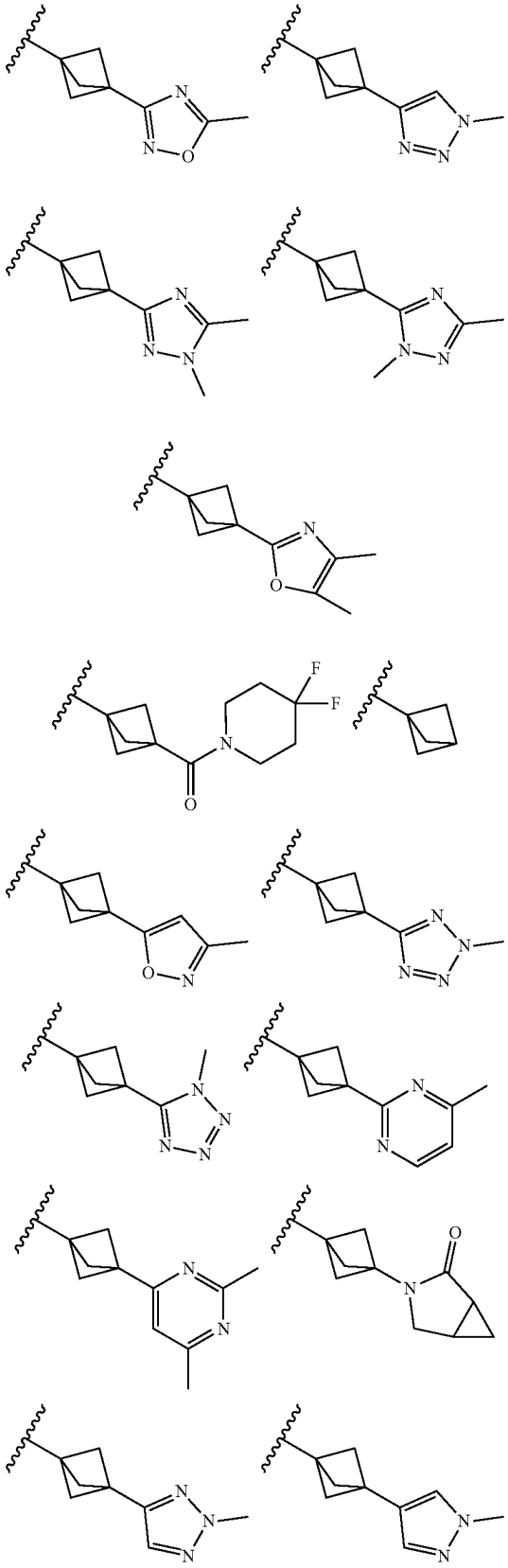

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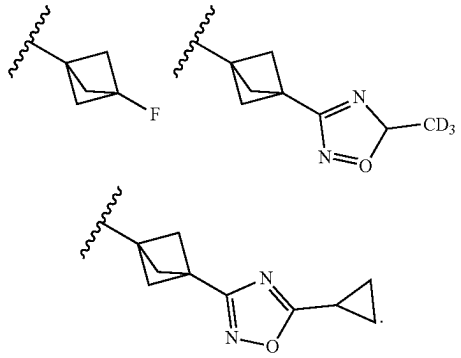
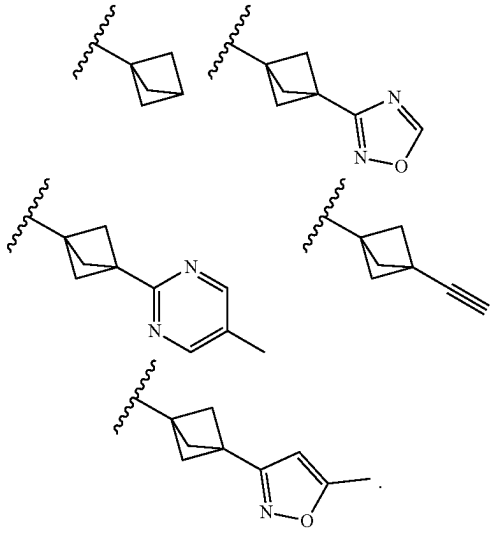
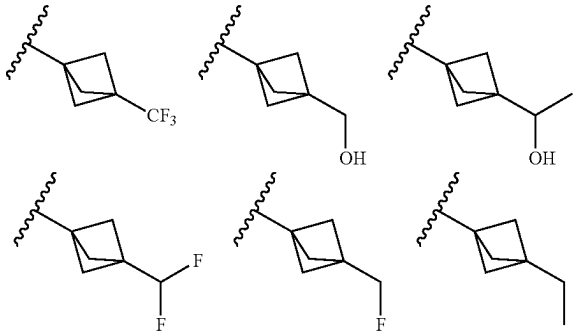


[0300] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-17 as defined herein, for example, can be selected from



In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-17 as defined herein, for example, can be selected from



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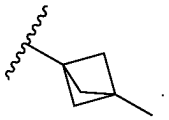
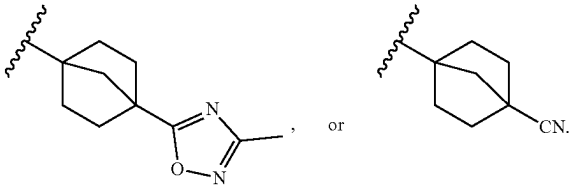
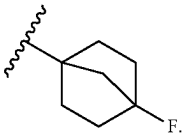


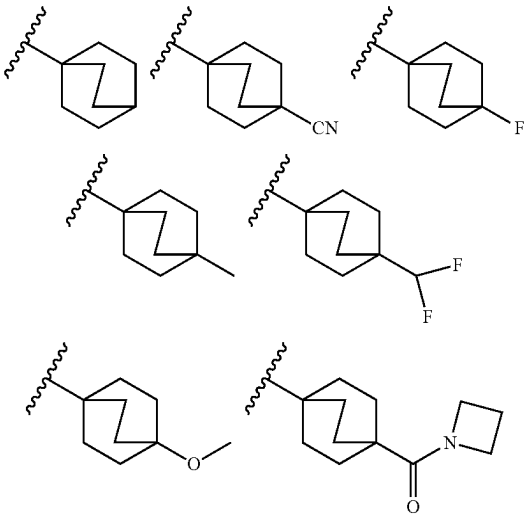
[0301] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-18 as defined herein, for example, can be



[0302] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-18 as defined herein, for example, can be



[0303] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-19 as defined herein, for example, can be selected from



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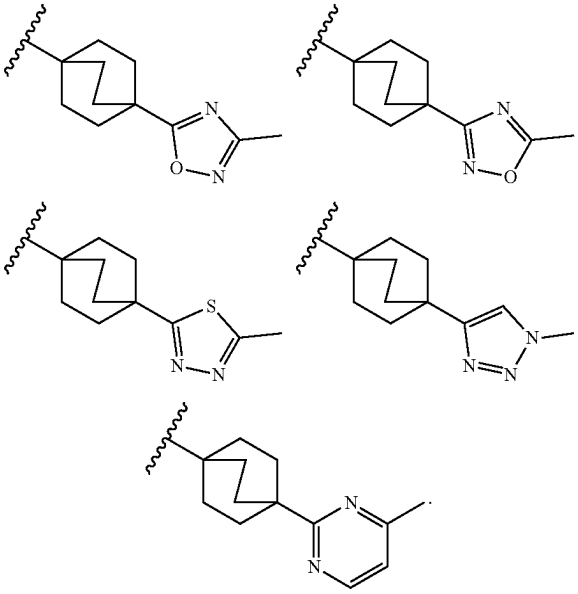
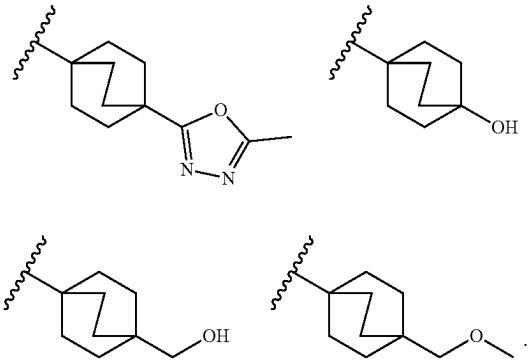
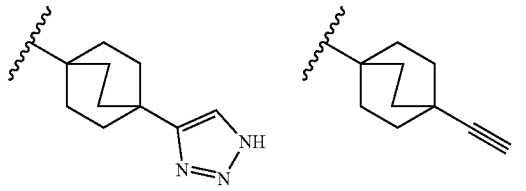


In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-19 as defined herein, for example, can be selected from



In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) has a structure according to M-19 as defined herein, for example, can be selected from



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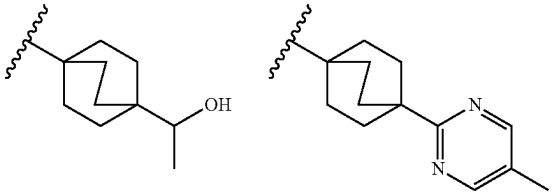
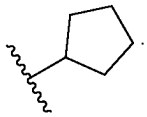
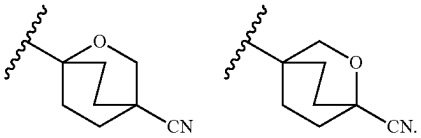


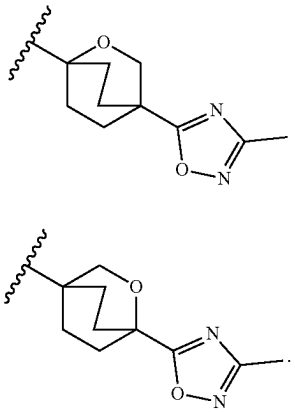
[0304] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be a cycloalkyl, such as



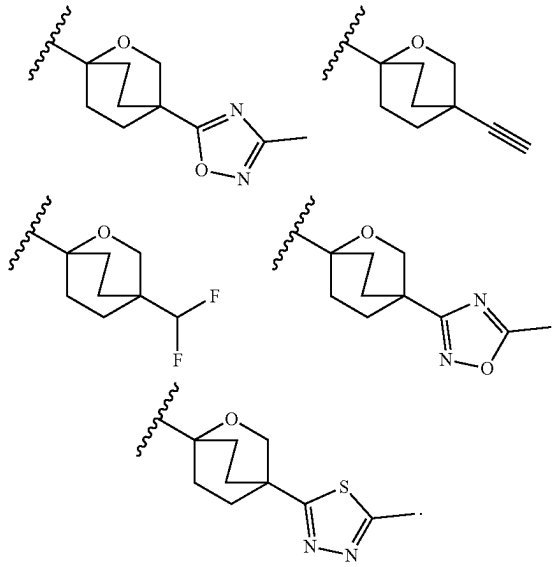
In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be selected from



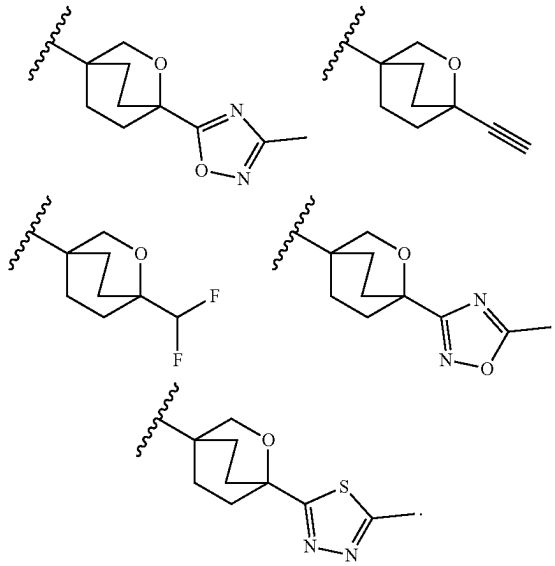
In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be a bridged heterocyclyl, such as



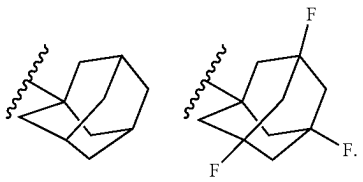
In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be a bridged heterocyclyl, such as



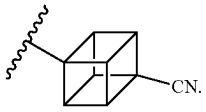
[0305] In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be a bridged heterocyclyl, such as



In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be selected from



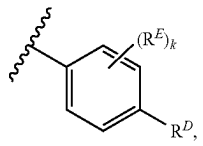
In some particular embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be selected from



[0306] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can also be an optionally substituted phenyl. When substituted, the phenyl is typically substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A,

[0307] wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

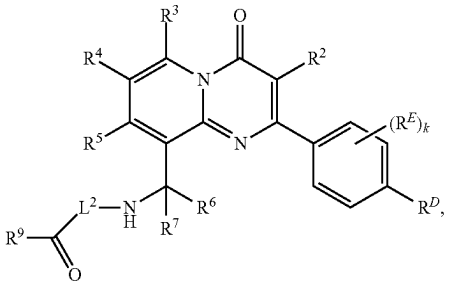
[0308] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be



wherein R^D is halogen, CN, G^{4B}, OG^{4B}, NHG^{4B}, $NG^{4B}G^{4B}$, $C(O)G^{4B}$, $OC(O)G^{4B}$, $NHC(O)G^{4B}$, $NG^{4B}C(O)G^{4B}$, $C(O)OG^{4B}$, $C(O)NHG^{4B}$, $C(O)NG^{4B}G^{4B}$, $OC(O)OG^{4B}$, $OC(O)NHG^{4B}$, $OC(O)NG^{4B}G^{4B}$, $NHC(O)OG^{4B}$, $NHC(O)NHG^{4B}$, $NHC(O)NG^{4B}G^{4B}$, $NG^{4B}C(O)OG^{4B}$, $NG^{4B}C(O)NHG^{4B}$, $NG^{4B}C(O)NG^{4B}G^{4B}$, SO_2G^{4B}, SO_2NHG^{4B}, or $SO_2NG^{4B}G^{4B}$, wherein G^{4B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroal-

kylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl a 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; wherein R^E at each occurrence is independently F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, C_{1-4} heteroalkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and k is 0, 1, or 2. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-12 membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-12 membered ring is a C_{3-8} cycloalkyl. In some embodiments, the 3-12 membered ring is a 4-8 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is phenyl. In some embodiments, the 3-12 membered ring is a 5-membered heteroaryl having 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, or phenyl. In some embodiments, k is 0. In some embodiments, k is 1, and R^E is defined herein, such as F. In some embodiments, the compound of Formula C can have a structure according to Formula III-5:

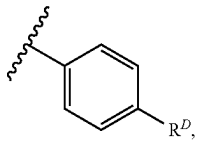
Formula III-5



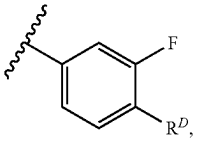
wherein the variables k, L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^D and R^E are defined herein.

[0309] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can have a structure according to:

(M-20)

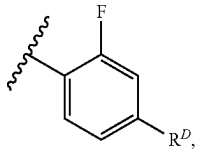


(M-21)



or

(M-22)

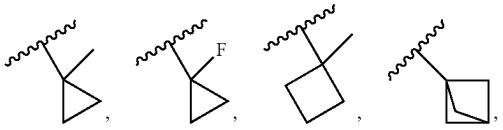


wherein R^D is halogen, CN, G^{5B}, NHG^{5B}, $NG^{5B}G^{5B}$, $C(O)G^{5B}$, $C(O)OG^{5B}$, $C(O)NHG^{5B}$, $C(O)NG^{5B}G^{5B}$, SO_2G^{5B}, SO_2NHG^{5B}, or $SO_2NG^{5B}G^{5B}$, wherein G^{5B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1} or one or more (e.g., 1, 2, or 3) G^{B2}, wherein G^{B1} is defined herein, and wherein G^{B2} at each occurrence is independently deuterium, F, Cl, CN, OH, NH_2, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. In some embodiments, R^1 in Formula C (e.g., Formula III or III-1) has a structure according to M-20, as defined herein. In some embodiments, R^1 in Formula C (e.g., Formula III or III-1) has a structure according to M-21, as defined herein. In some embodiments, R^1 in Formula C (e.g., Formula III or III-1) has a structure according to M-22, as defined herein.

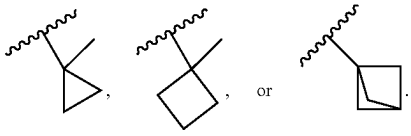
[0310] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl.

[0311] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is C_{3-6} cycloalkyl

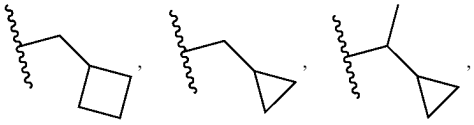
optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



etc. In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be $C(O)G^{5B}$ or $C(O)OG^{5B}$, wherein G^{5B} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,

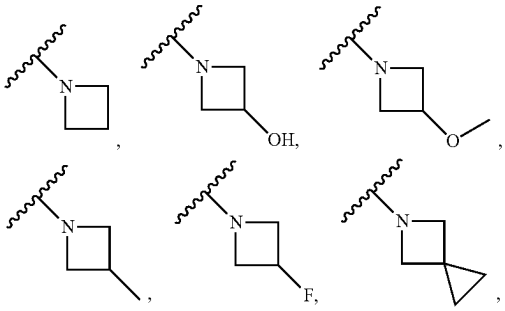


[0312] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



etc.

[0313] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is 4-7 membered heterocyclic (e.g., having 1 or 2 ring heteroatoms each independently O or N), such as azetidinyl, pyrrolidinyl, piperidinyl, oxazolidinyl, etc., which is optionally substituted with 1 or 2 substituents each independently OH, OCH_3, F, or methyl, such as



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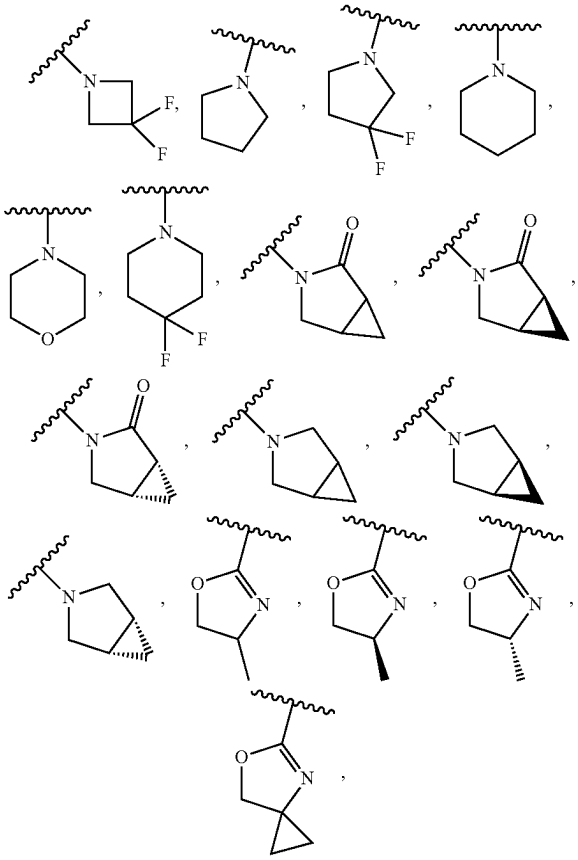
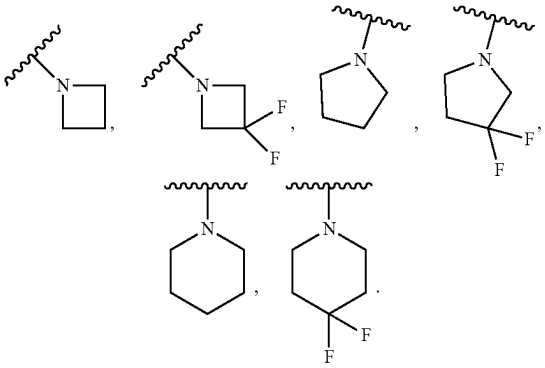
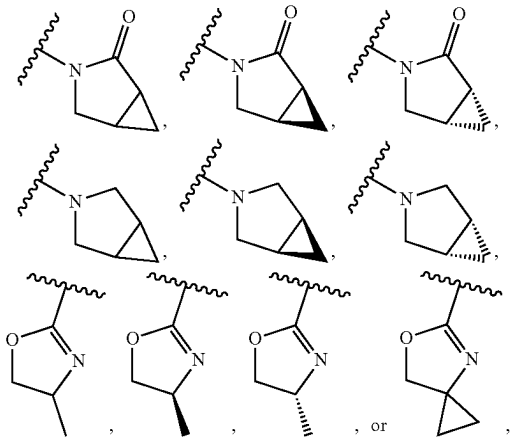


etc. In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be $C(O)G^{51}$, wherein G^{5B} is 4-7 membered heterocyclic (e.g., having 1 or 2 ring heteroatoms each independently O or N), such as N-linked azetidinyl, pyrrolidinyl, or piperidinyl, which is optionally substituted with 1 or 2 substituents each independently F or methyl, such as

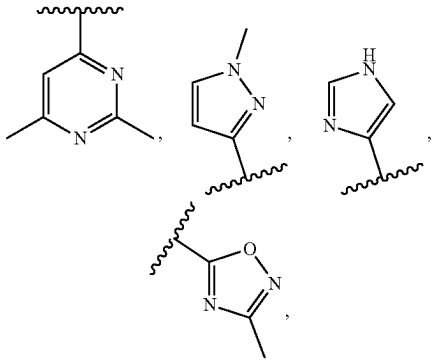


In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be 4-7 membered heterocyclic (e.g., having 1 or 2 ring heteroatoms each independently O or N), such as

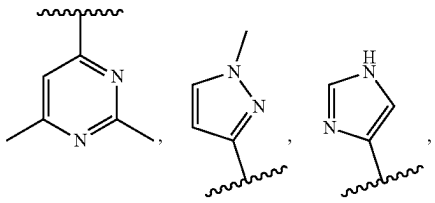


etc.

[0314] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is 5- or 6-membered heteroaryl, such as pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, etc., which is optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



etc. For example, in some embodiments, R^D in the structures herein (e.g., Formula III-5) is a 5- or 6-membered heteroaryl, such as pyrazolyl, oxazolyl, imidazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, etc., which is optionally substituted, for example, with 1 or 2 methyl, such as



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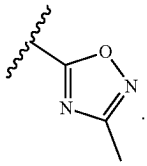
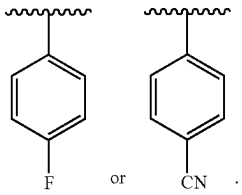


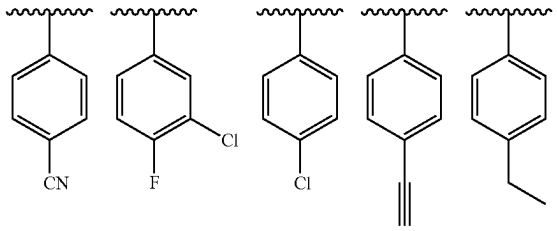
[0315] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be NHG^{5B} or $C(O)NHG^{5B}$, wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). For example, in some embodiments, R^D can be $NHCH_3$.

[0316] In some preferred embodiments, R^D in the structures herein (e.g., Formula III-5) can be $C(O)NG^{5B}G^{5B}$, wherein one instance of G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. For example, in some embodiments, R^D can be $CON(CH_3)_2$.

[0317] In some embodiments, R^1 can be a phenyl, which is optionally substituted with 1-3 substituents independently selected from deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, and C_{1-4} alkyl optionally substituted with 1-3F. For example, in some embodiments, R^1 can be



[0318] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be an optionally substituted phenyl, such as those having a structure according to M-20 to M-22, for example, R^1 can be selected from:



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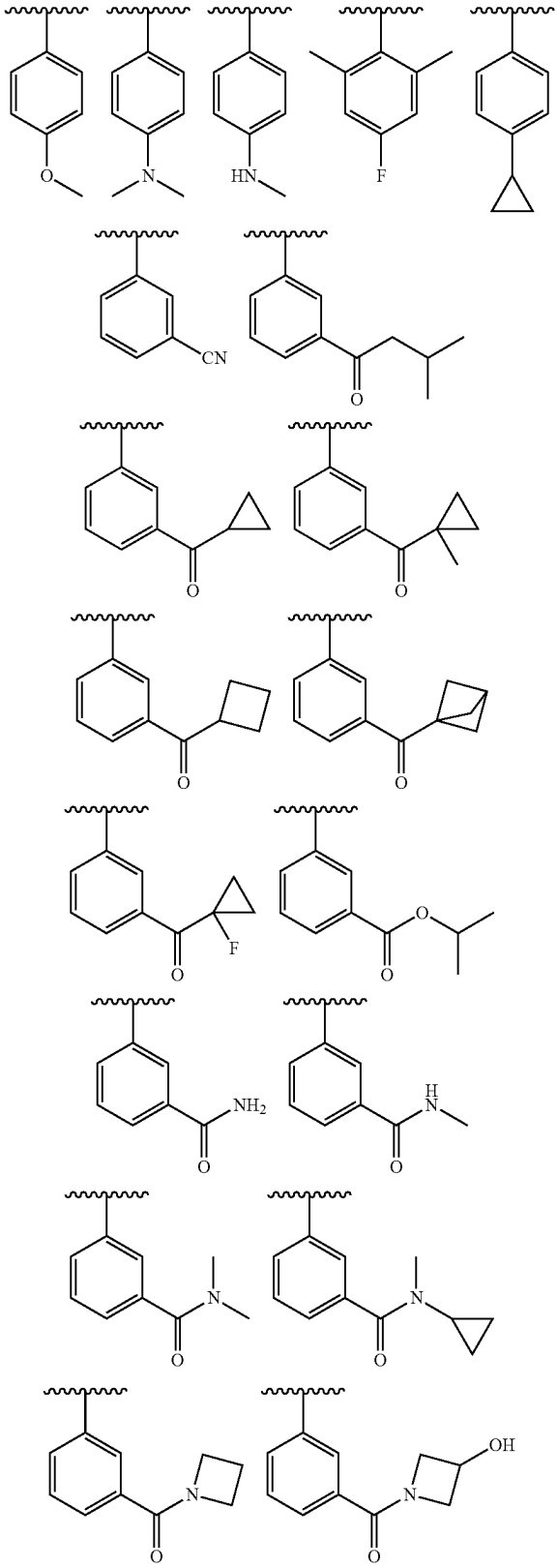

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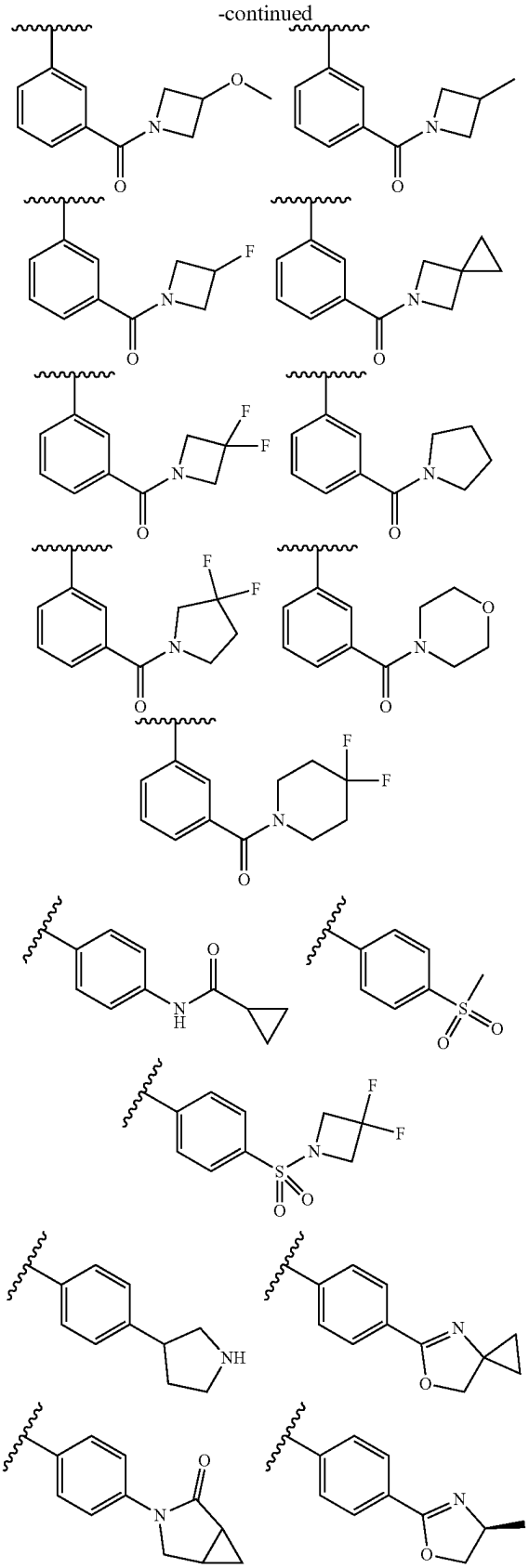

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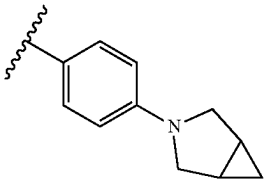

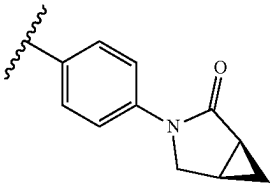

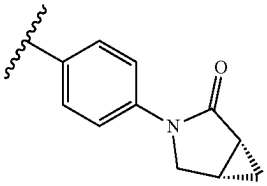

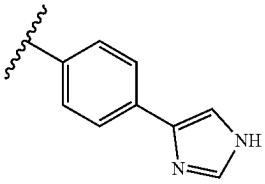

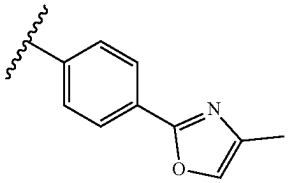

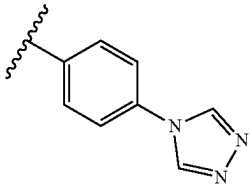

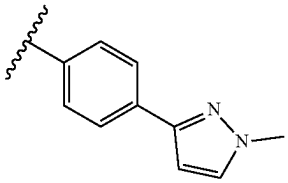

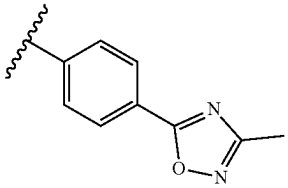

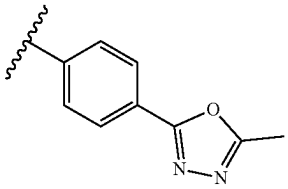

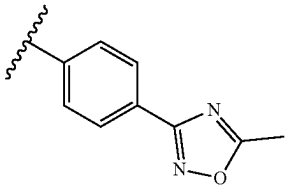

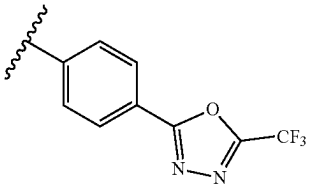

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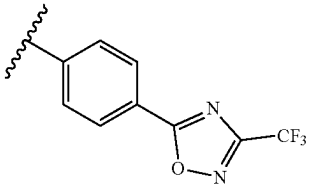

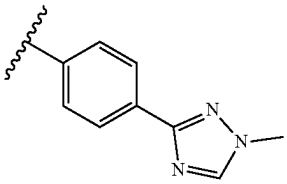

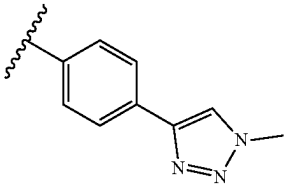

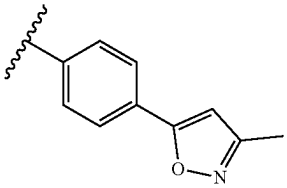

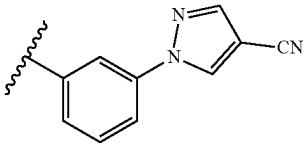

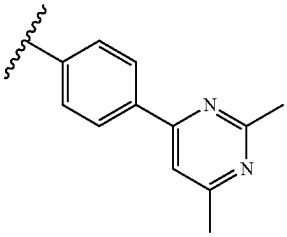

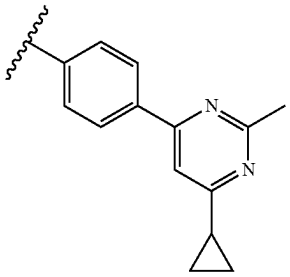

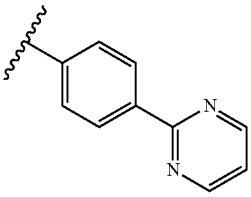

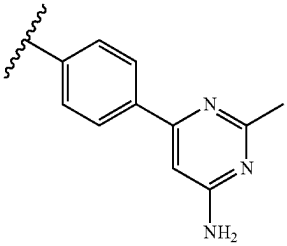

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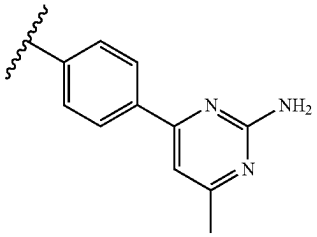

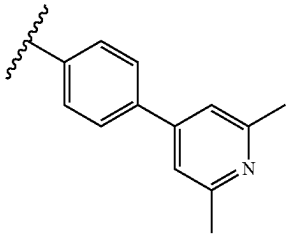

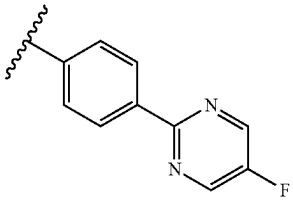

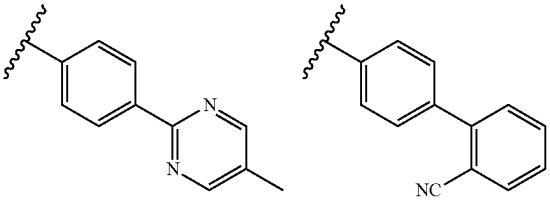

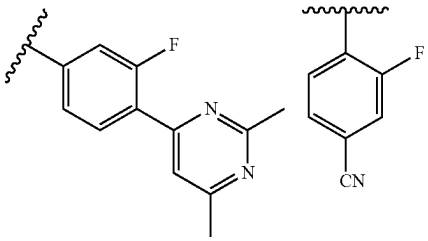

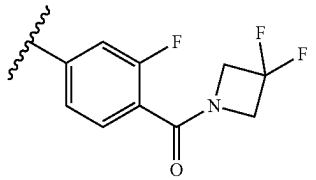

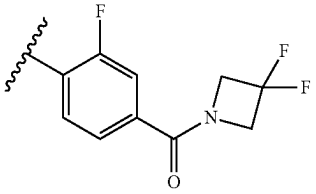

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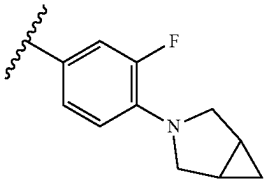
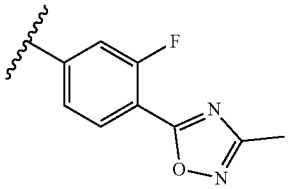
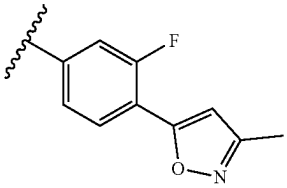
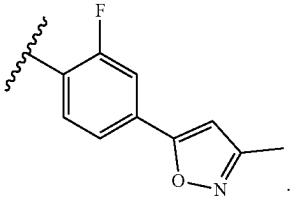
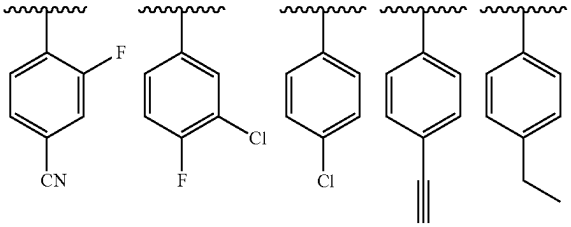


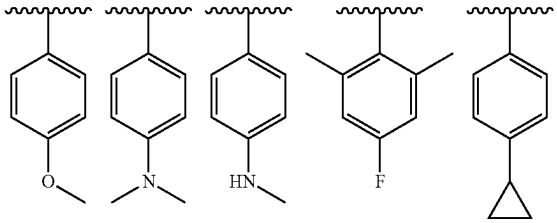


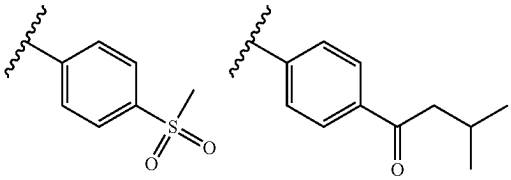


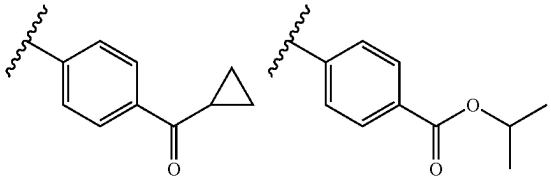


In some embodiments, R^1 can be selected from:









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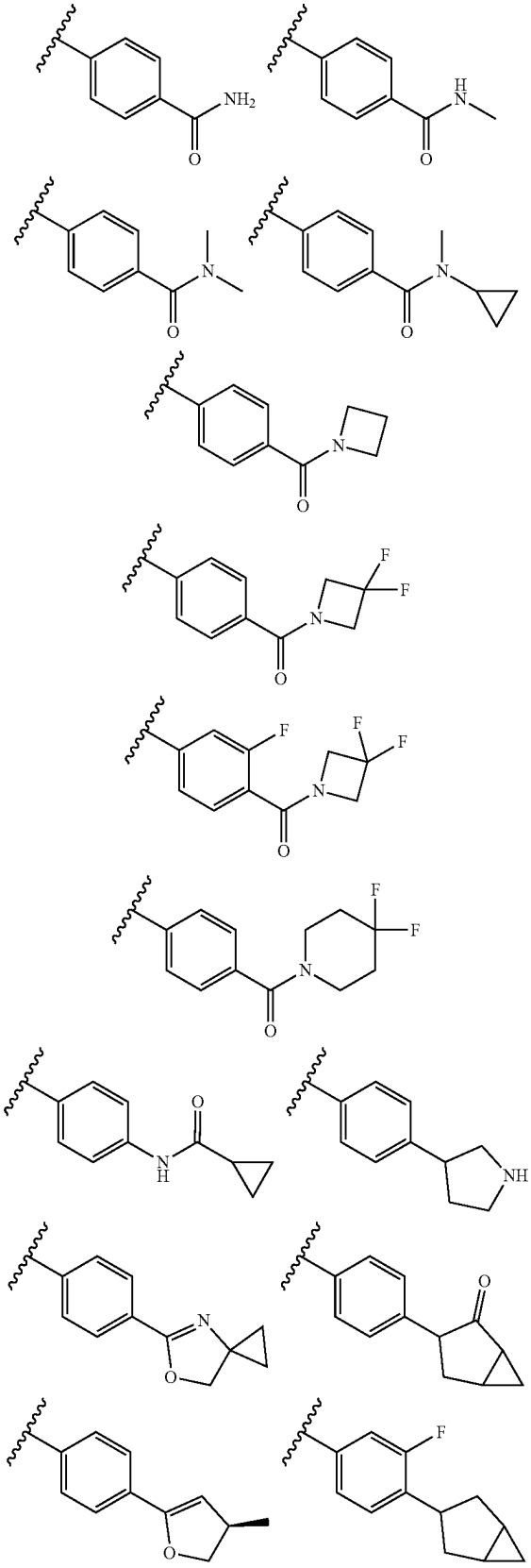

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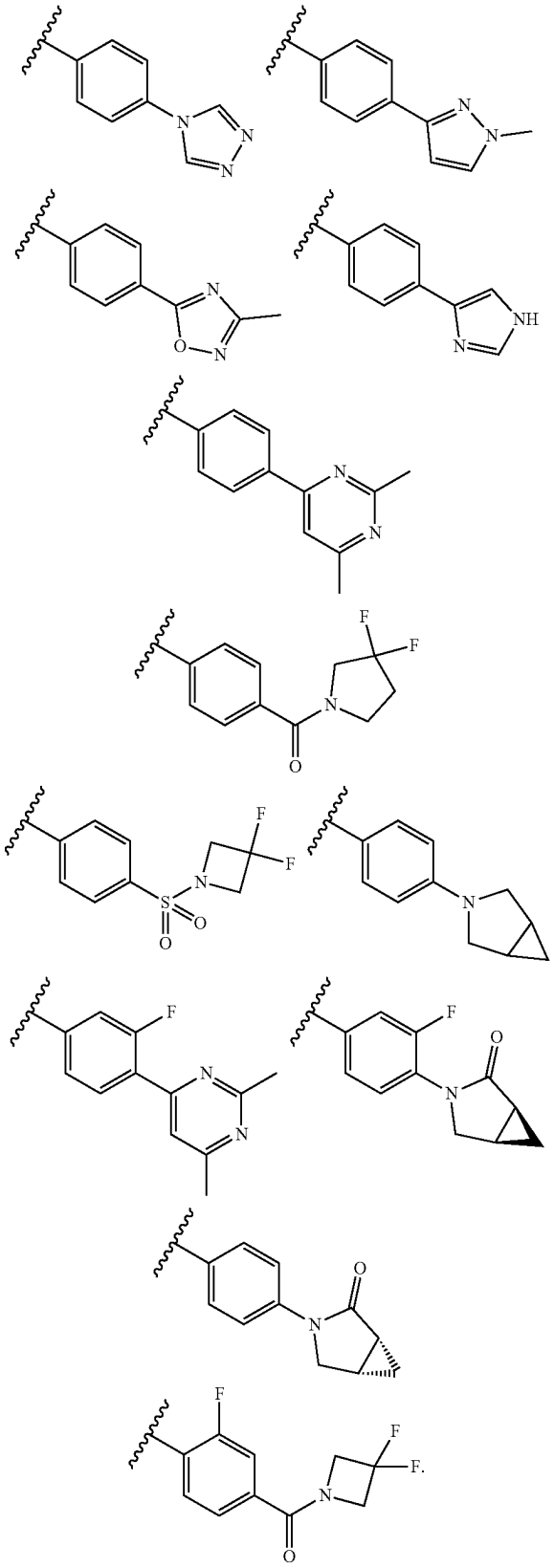
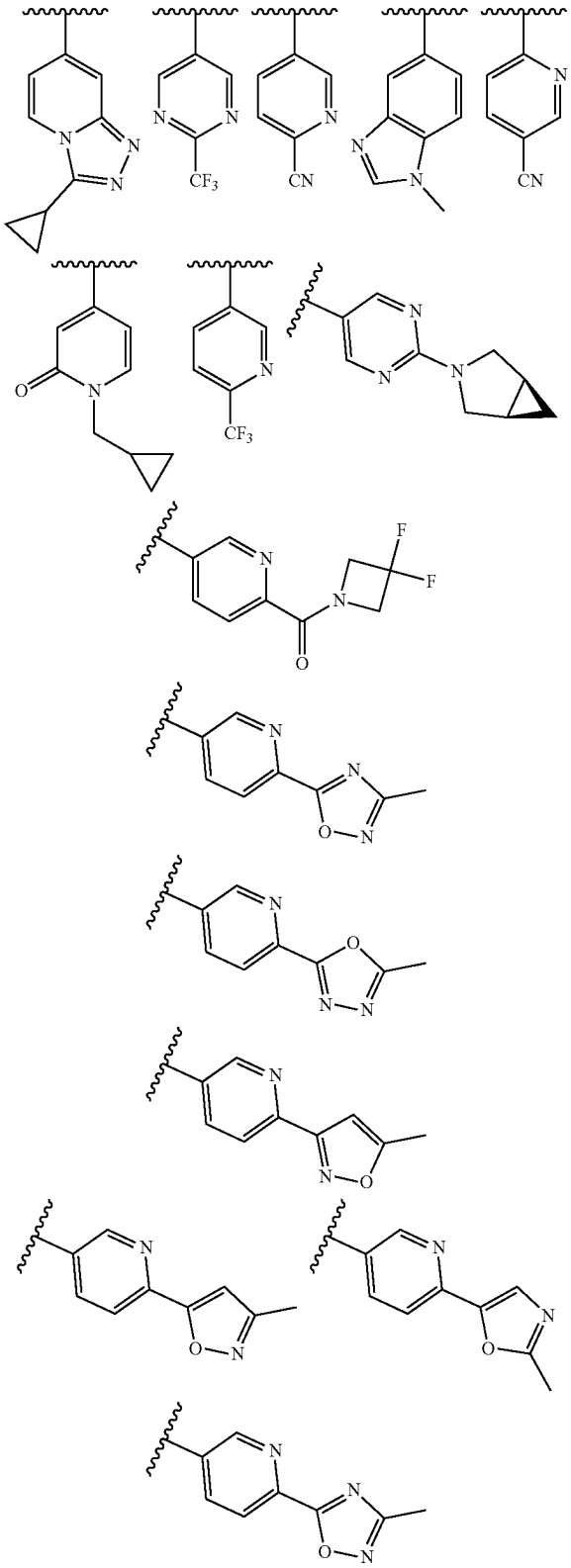


[0319] In some embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be selected from:



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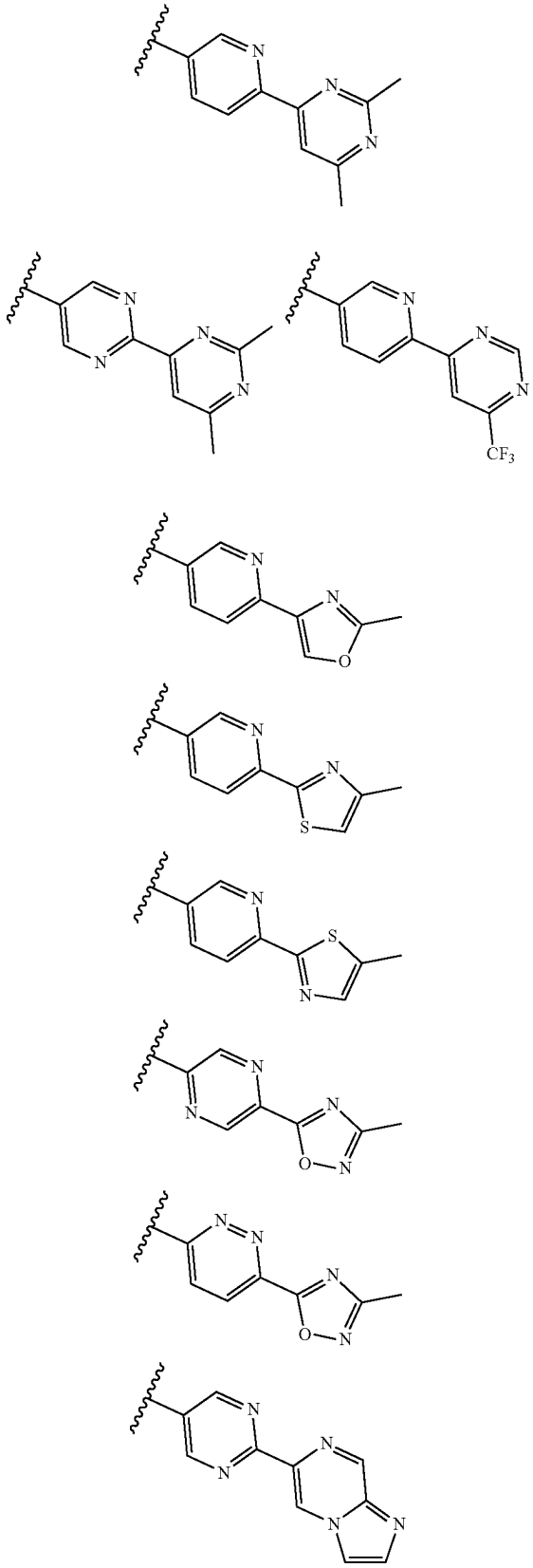

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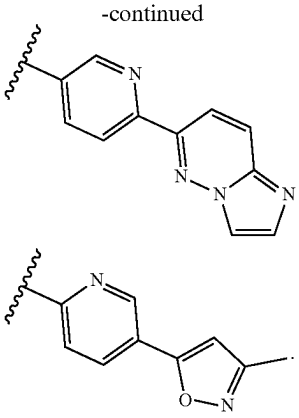
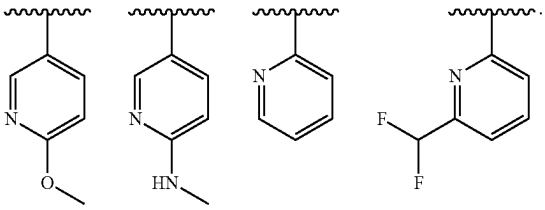
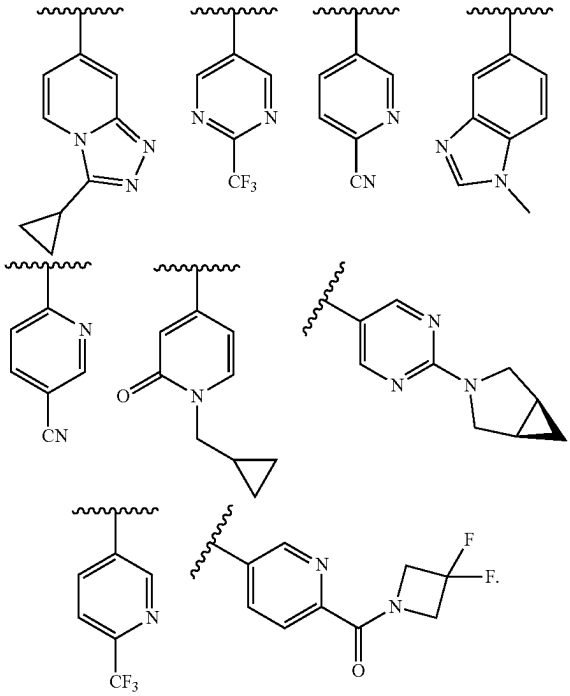


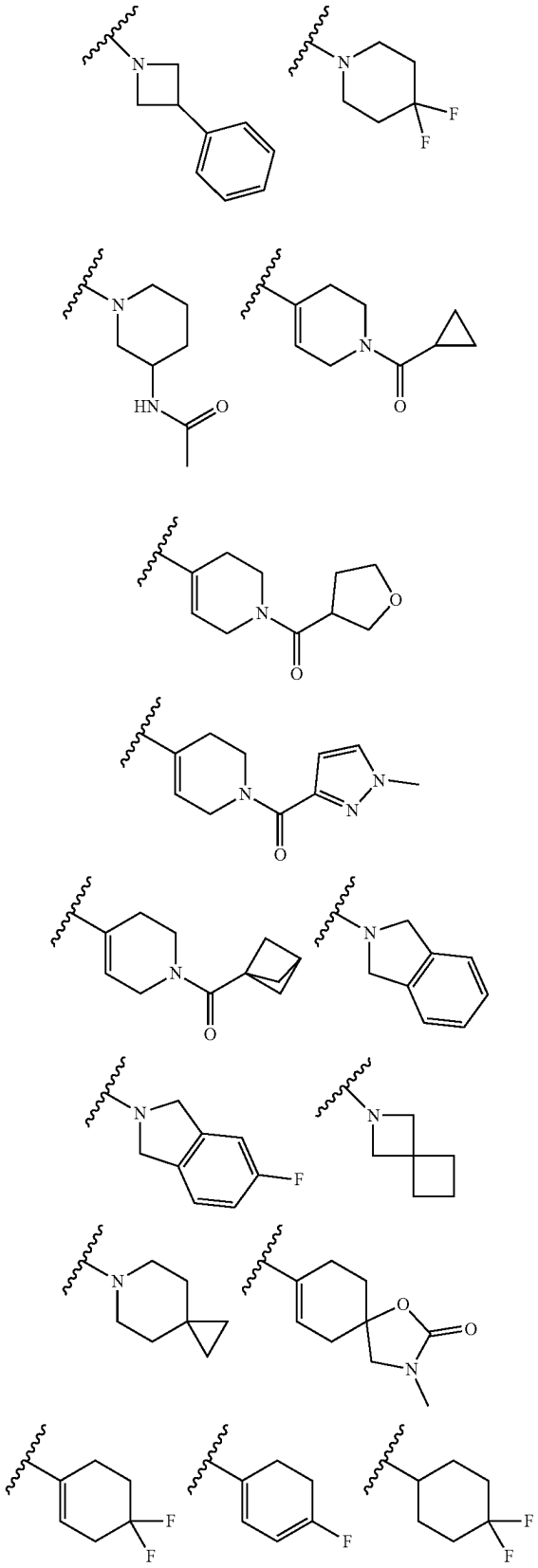
In some embodiments, R^1 can also be selected from:



For example, R^1 can be selected from:



[0320] For example, according to Formula C (such as a subformula, e.g., Formula III or III-1), R^1 can be selected from:



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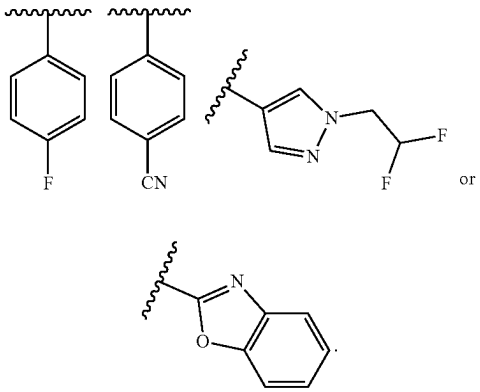
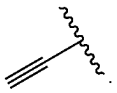


[0321] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), R^2 can be hydrogen or methyl, or R^2 is CD_3 or CF_3.

[0322] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), R^3 can be methyl. In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), R^3 can be hydrogen.

[0323] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), R^4 can be methyl, or R^4 is CD_3 or CF_3.

[0324] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), R^4 can be F, Cl, Br, or



[0325] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), R^5 can be hydrogen.

[0326] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), both R^1 and R^7 can be hydrogen.

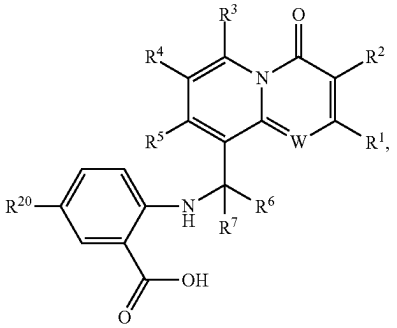
[0327] In some embodiments according to Formula C (such as a subformula, e.g., Formula III or III-1 to III-5), one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is C_{1-4} alkyl, more preferably, one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is methyl.

[0328] In some embodiments, U in Formula C is NR^8, such as in Formula III or III-1 to III-5, R^6 is typically hydrogen.

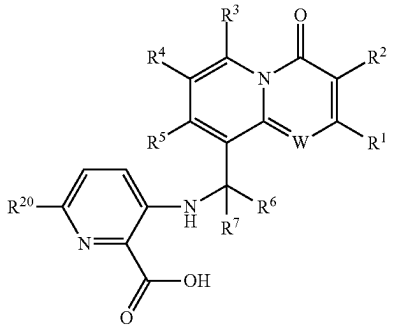
[0329] In some embodiments, R^{100} in Formula C is C(O) R^9, such as in Formula III or III-1 to III-5, R^9 is typically OH.

[0330] In some specific embodiments, the compound of Formula C can be characterized as having a structure according to Formula III-1-a or III-1-b:

Formula III-1-a



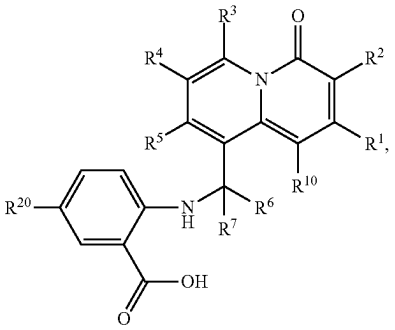
Formula III-1-b



wherein the variables W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined and preferred herein. For example, in some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3. In some embodiments, R^{20} in Formula III-1-a is hydrogen. In some embodiments, R^{20} in Formula III-1-b is Cl.

[0331] In some embodiments, the compound of Formula III-1-a can be characterized as having a structure according to Formula III-1-a-1, or III-1-a-2:

Formula III-1-a-1



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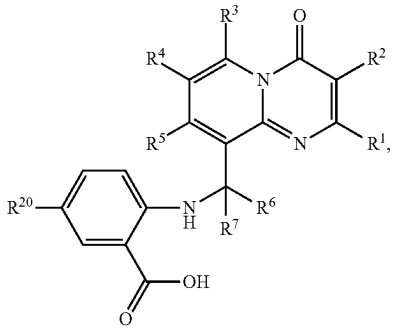
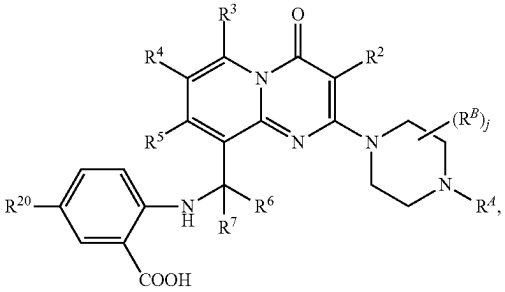
Formula III-1-a-2



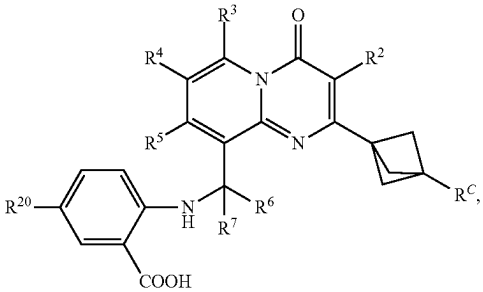
[0332] wherein the variables W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, and R^{20} are defined and preferred herein. For example, in some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3. In some embodiments, R^{20} is hydrogen.

[0333] In some embodiments, the compound of Formula III-1-a-2 can be characterized as having a structure according to Formula III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, or III-1-a-2-d:

Formula III-1-a-2-a



Formula III-1-a-2-b



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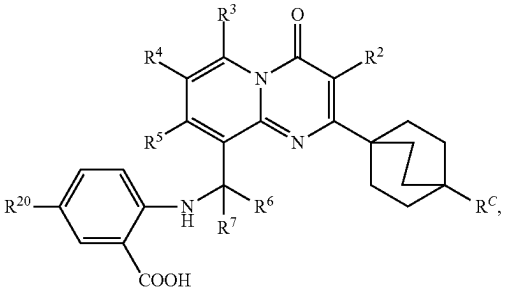
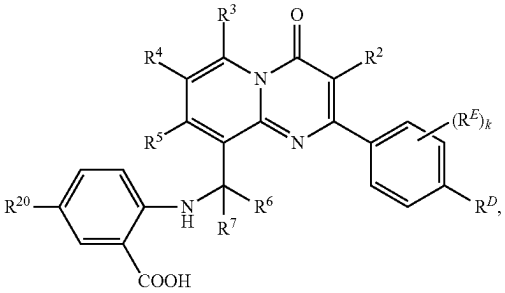
Formula III-1-a-2-c



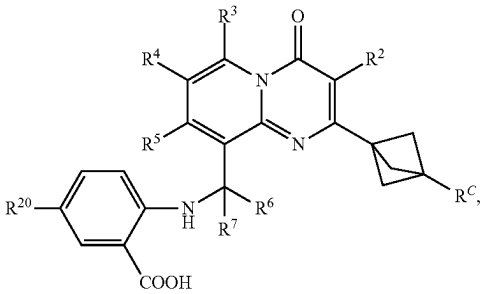
Formula III-1-a-2-d



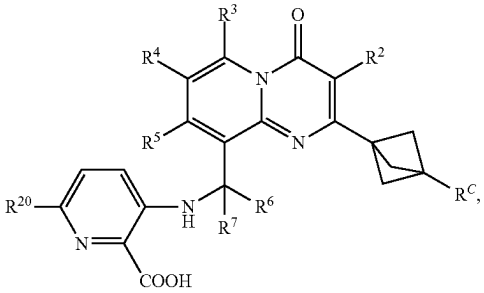
[0334] wherein j, k, R^A, R^C, R^D, R^2, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined herein. In some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3. In some embodiments, R^{20} is hydrogen.

[0335] In some embodiments, the compound of Formula III-1 characterized as having a structure according to III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f:

Formula III-1-a-2-b



Formula III-1-b-2-b



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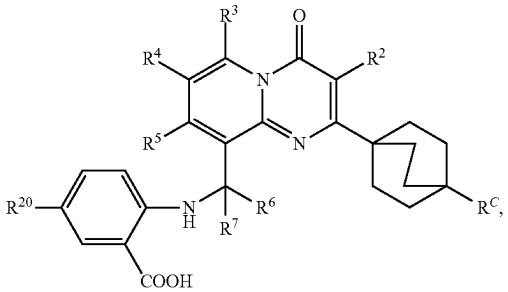
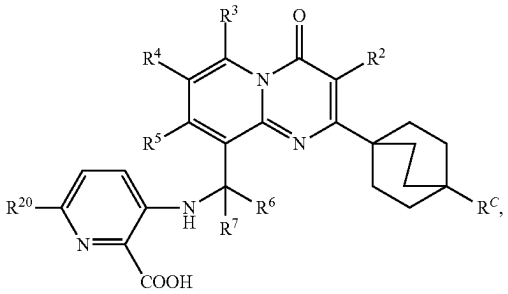
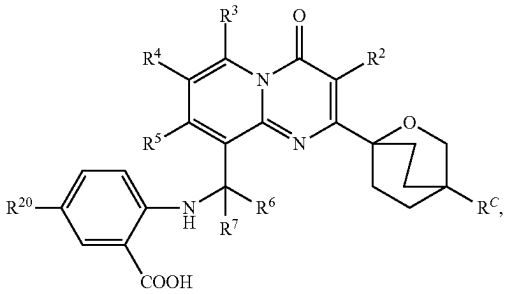
Formula III-1-a-2-c



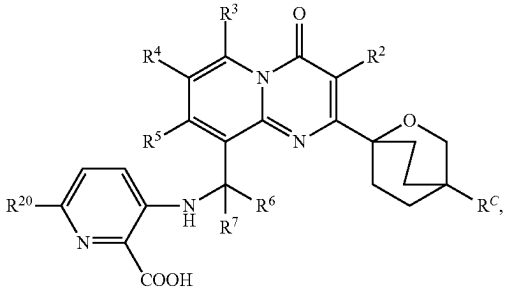
Formula III-1-b-2-c



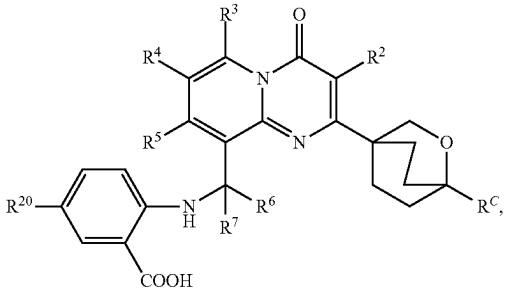
Formula III-1-a-2-e



Formula III-1-b-2-e



Formula III-1-a-2-f



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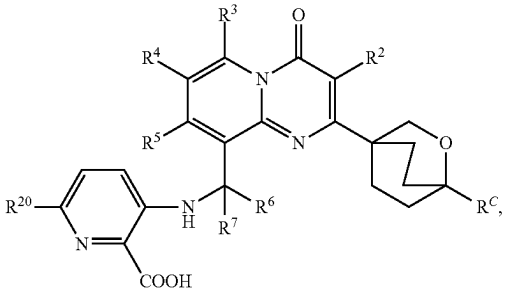
Formula III-1-b-2-f

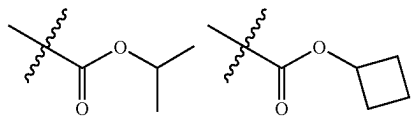


[0336] wherein:

[0337] R^{20} is hydrogen, halogen, CN, OH, COOH, G^1, or OG^1, wherein G^1 is Ct-4 alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F; and

[0338] R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

[0339] In some embodiments, in Formula III-1-a-2-a, R^A can be selected from



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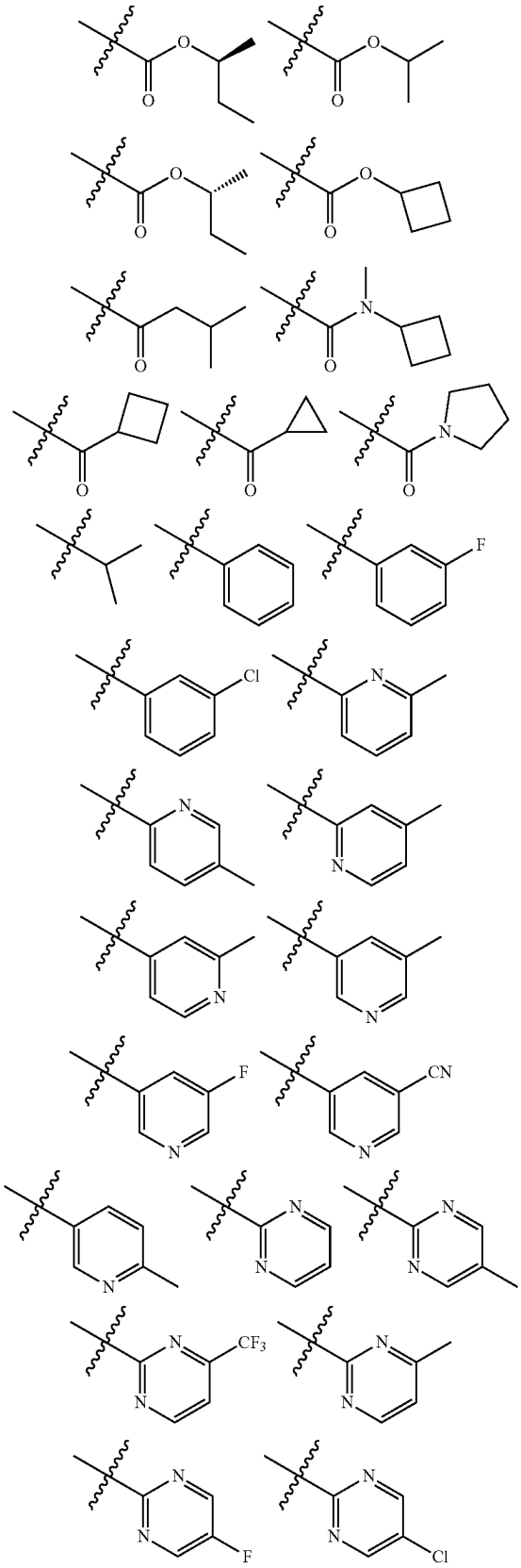

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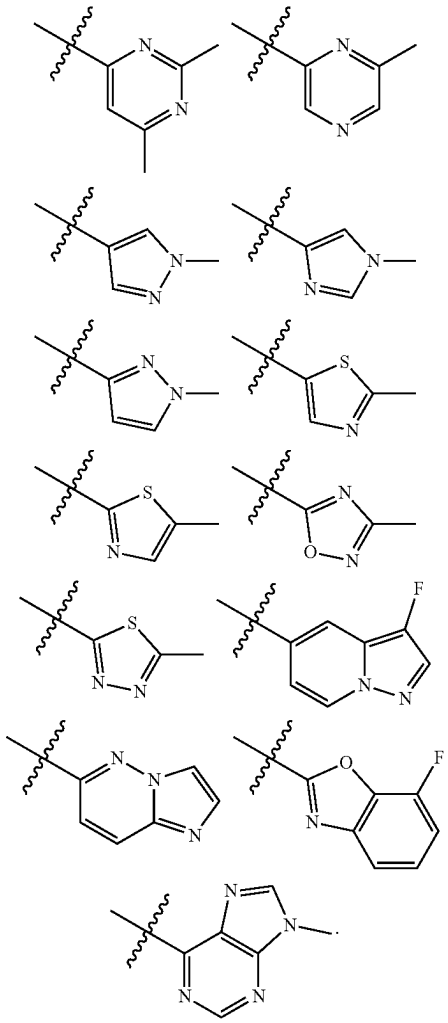
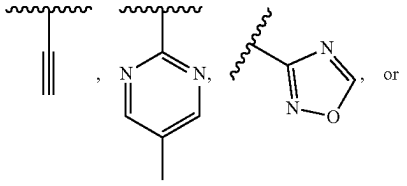


[0340] In some embodiments, in Formula III-1-a-2-a, j can be 0, or R^B is methyl and j can be 1.

[0341] In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, or CH_2OCH_3. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f R^C is



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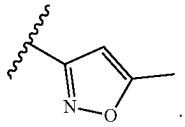
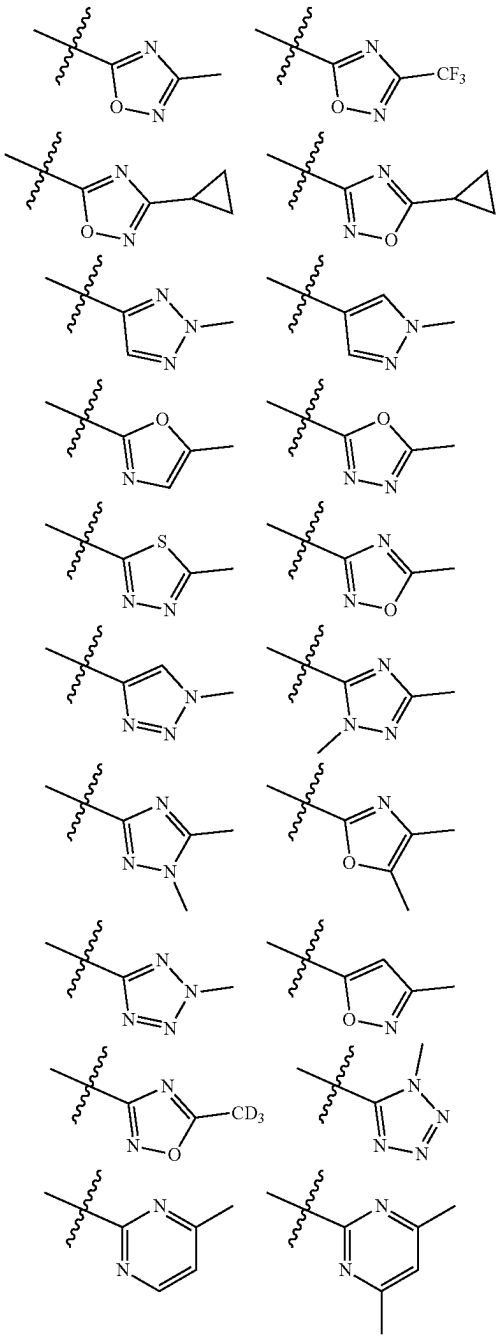


In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is selected from:



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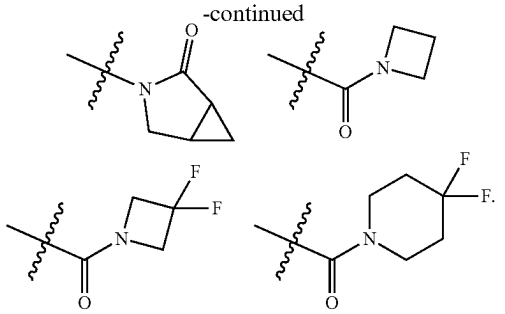
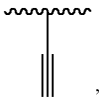
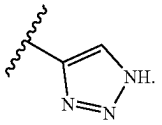


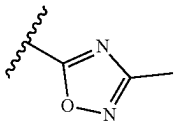
In some preferred embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is H, F, CN,



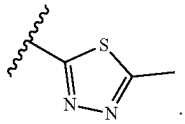
or a 5-membered heteroaryl, such as a triazole, an thiadiazole, or an oxadiazole optionally substituted with methyl, CD_3, CF_3, or cyclopropyl. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is selected from CH_3, CH_2F, CHF_2, CF_3, CH_2OH, CH_2CH_3, or $CH(OH)CH_3$. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is



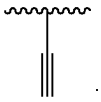
In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is F. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is CHF_2. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is CN. In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is



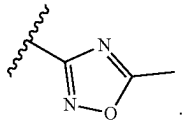
In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is



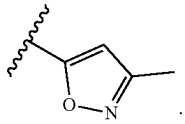
In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is



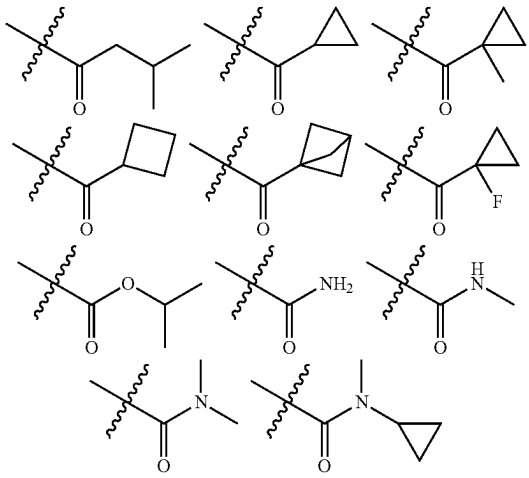
In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is



In some embodiments, in Formula III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f, R^C is



[0342] In some embodiments, in Formula III-1-a-2-d, R^D is H, F, CN, acetenyl, methyl, ethyl, OCH_3, $NHCH_3$, or cyclopropyl. In some embodiments, in Formula III-1-a-2-d, R^D is selected from:



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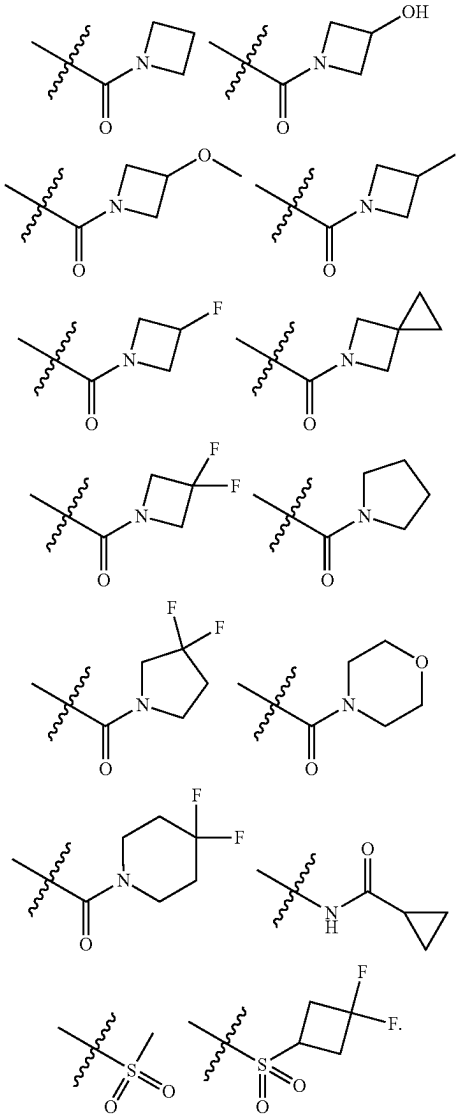
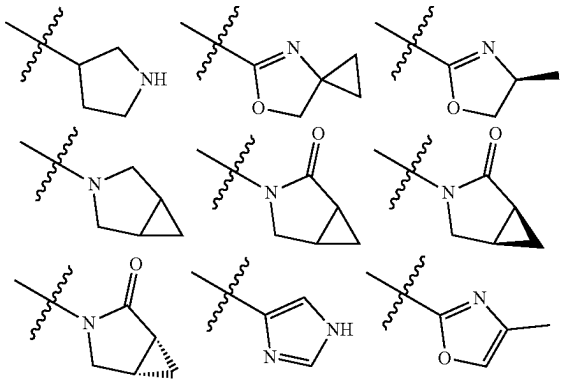


In some embodiments, in Formula III-1-a-2-d, R^D is selected from:



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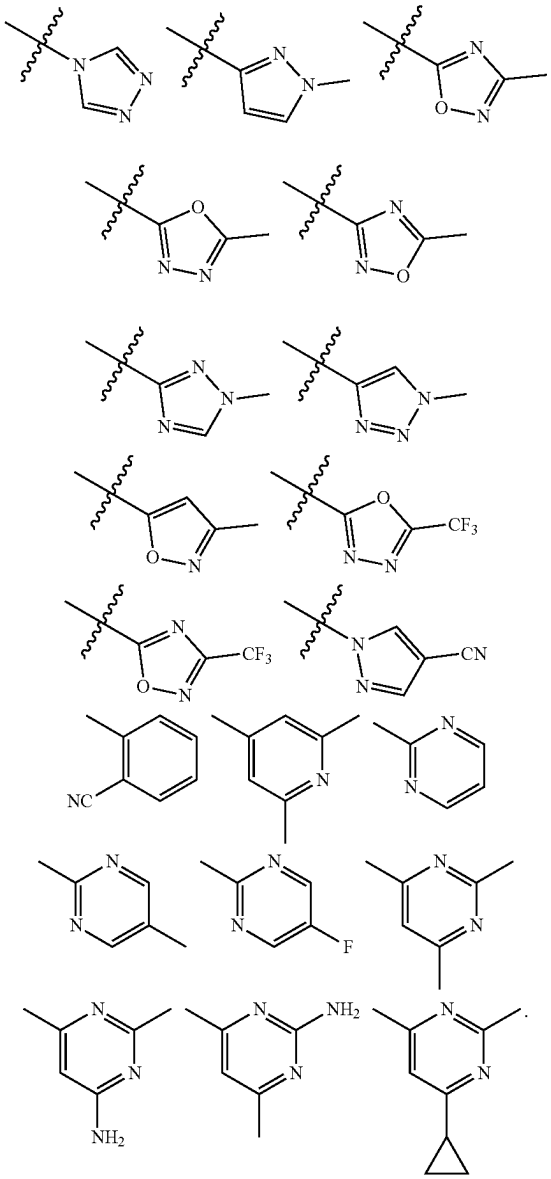


[0343] In some embodiments, in Formula III-1-a-2-d, k is 0, or R^E is F, Cl, CN, methyl and k is 1, or each R^E is independently F or methyl and k is 2.

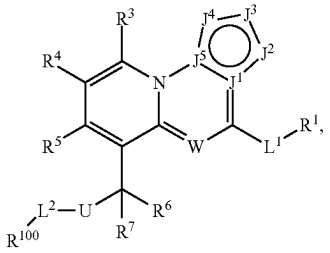
[0344] In some embodiments, in Formula III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, or III-1-a-2-d, R^{20} is H.

[0345] Further specific definitions of the variables for Formula C, such as Formula III or III-1 to III-5, include those respective atom/group/structures shown in the exemplified compounds herein.

Formula D

[0346] In some embodiments, the present disclosure provides a compound of Formula D, or a pharmaceutically acceptable salt thereof:

Formula D



[0347] wherein:

[0348] W is CR^{10} or N, wherein R^{10} is hydrogen, deuterium, halogen, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or C_{1-4} alkoxy optionally substituted with 1-3 fluorine;

[0349] U is null, O, S, S(O), SO_2, or NR^8, wherein R^1 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0350] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0351] R^1 is hydrogen or a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0352] J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5- or 6-membered ring having 2 or 3 ring heteroatoms, preferably, 2 or 3 ring nitrogen atoms, preferably, an optionally substituted 5-membered heteroaryl wherein J^4 is N, and J^5 is C or N;

[0353] R^3, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1,

[0354] R^6 and R^7 are each independently hydrogen, deuterium, halogen, CN, G^2, or OG^2,

[0355] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0356] R^{100} is —R^{102}-R^{103}, wherein R^{102} is null, O, NH, C_{1-4} alkylene or C_{1-4} heteroalkylene having 1 or 2 heteroatoms, and R^{103} is hydrogen, COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, $SO_2NG^3G^3$, or a 5- or 6-membered ring having a hydrogen bond donor, e.g., a tetrazolyl;

[0357] wherein:

[0358] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

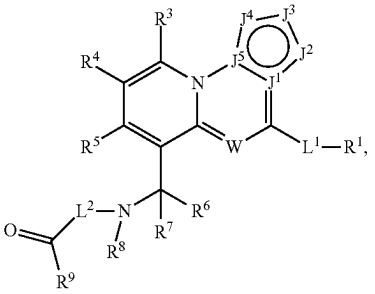
[0359] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0360] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

[0361] Preferably, J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5-membered or 6-membered heteroaryl ring, more preferably, 5-membered heteroaryl, in which J^4 is N, and J^5 is C or N.

[0362] In some embodiments, the compound of Formula D can be characterized as having a structure according to Formula IV:

Formula IV



[0363] wherein:

[0364] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

[0365] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0366] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$,

[0367] wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure,

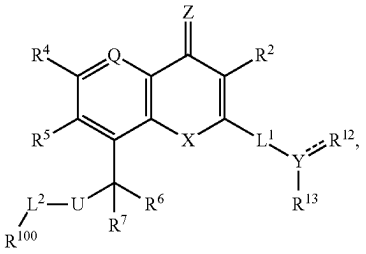
[0368] wherein W, L^1, L^2, J^1, J^2, J^3, J^4, J, R^1, R^3, R^4, and R^5 are defined herein.

[0369] Suitable definitions and preferred definitions of the variables in Formula D (such as those in subformulae, Formula IV) include any of those described for the corresponding variables (i.e., those having the same identifiers, such as U, W, J^1, J^2, J^3, J^4, J^5, L^1, L^2, R^1, R^3, R^4, R^5, R^6, R^7, R^8, and R^9) for Formula A and its subformulae and/or Formula B and its subformulae, as applicable.

Formula E

[0370] In some embodiments, the present disclosure provides a compound of Formula E, or a pharmaceutically acceptable salt thereof:

Formula E



[0371] wherein:

[0372] X is O, NR^{14}, or S, wherein R^{14} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine;

[0373] Q is N or CR^3, wherein R^3 is hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0374] U is null, O, S, S(O), SO_2, or NR^8, wherein R^A is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0375] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0376] R^2, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1,

[0377] R^6 and R^7 are each independently hydrogen, deuterium, halogen, CN, G^2, or OG^2,

[0378] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0379] R^{100} is —R^{102}-R^{103}, wherein R^{102} is null, O, NH, C_{1-4} alkylene or C_{1-4} heteroalkylene having 1 or 2 heteroatoms, and R^{103} is hydrogen, COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, $SO_2NG^3G^3$, or a 5- or 6-membered ring having a hydrogen bond donor, e.g., a tetrazolyl;

[0380] wherein:

[0381] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0382] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0383] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms,

or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure; and wherein:

[0384] (1) Z is NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; or

[0385] (2) Z is O, and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; provided that (a) Y is C when the bond between Y and R^{12} is a double bond; (b) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; or (c) Y is C or N, when Y is included in a heteroaryl, such as a 5-membered heteroaryl;

[0386] (3) Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; R^2 and R^{12}, together with the intervening atoms, are joined together to form a ring structure, wherein (a) Y is N; (b) Y is C when the bond between Y and R^{12} is a double bond; or (c) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and R^{13} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms; or

[0387] (4) Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; either (a) U is null or (b) L^1 is defined above but not null; and

[0388] (i) R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; or

[0389] (ii) R^2 and R^{12}, together with the intervening atoms, are joined together to form a ring structure, wherein (a) Y is N; (b) Y is C when the bond between Y and R^{12} is a double bond; or (c) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and

[0390] R^{13} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms.

[0391] In some embodiments, U in Formula E is NR^1.

[0392] In some embodiments, U in Formula E is O.

[0393] In some embodiments, U in Formula E is null.

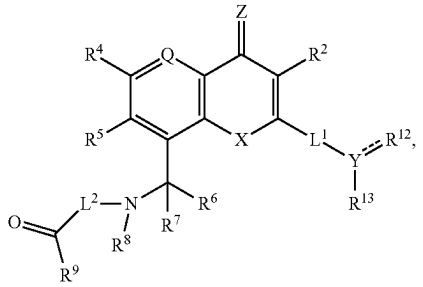
[0394] In some embodiments, U in Formula E is S, S(O), or SO_2.

[0395] In some embodiments, R^{100} in Formula E is R^{103} i.e., R^{102} is null.

[0396] In some embodiments, R^{103} is COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, or $SO_2NG^3G^3$.

[0397] In some embodiments, the compound of Formula E can be characterized as having a structure according to Formula V:

Formula V



[0398] wherein:

[0399] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

[0400] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0401] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$,

[0402] wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure, wherein Q, Z, X, Y, L^1, L^2, R^{12}, R^{13}, R^2, R^4, and R^5, are defined herein.

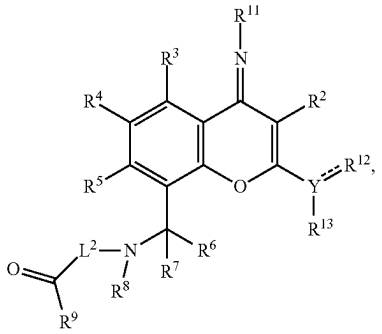
[0403] X in Formula E (e.g., Formula V) is typically O. In some embodiments, X can also be NR^{14}, wherein R^{14} is

defined herein. For example, in some embodiments, X can be NH or N(C_{1-4} alkyl). In some embodiments, X can also be S.

[0404] In some embodiments, Z in Formula E (e.g., Formula V) is NR^{11}, wherein R^{11} is defined herein. For example, in some embodiments, R^{11} can be a C_{1-4} alkoxy, such as methoxy.

[0405] In some embodiments, the compound of Formula E can be characterized as having a structure according to Formula V-1:

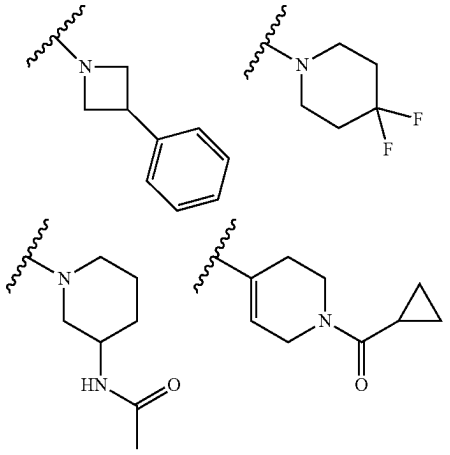
Formula V-1



[0406] wherein: R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S,

[0407] wherein L^2, R^{11}, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

[0408] In some embodiments, R^{12}, R^{13}, and Y in Formula E (e.g., Formula V or V-1) can be joined to form a ring structure as defined herein for R^1 in Formula A and its subformulae. For example, in some embodiments, R^{12}, R^{13}, and Y are joined together to form a moiety selected from:



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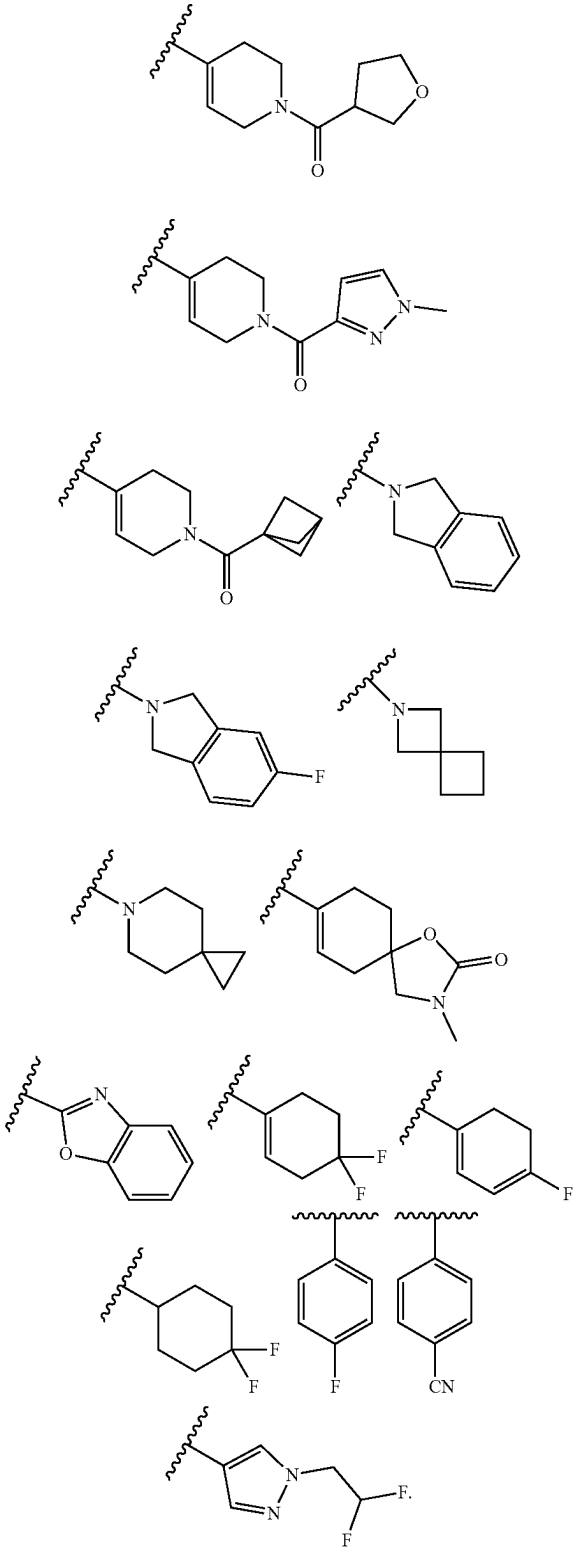
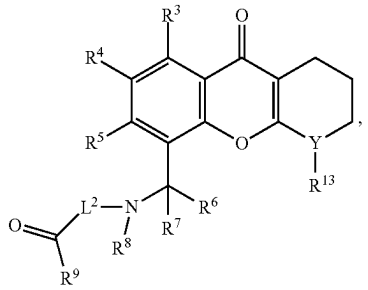


[0409] In some embodiments, the compound of Formula E can be characterized as having a structure according to Formula V-2:

Formula V-2



[0410] wherein: Y is N or CR^{15}, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and

[0411] R^{13} is an optionally substituted C_{1-6} alkyl, such as unsubstituted C_{1-6} alkyl or C_{1-6} alkyl substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or a 3-12 membered ring, such as 3-7 membered ring (e.g., cyclopropyl), wherein the 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F,

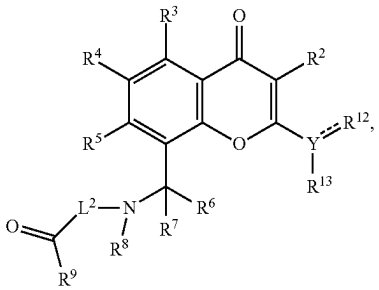
[0412] wherein L^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

[0413] In some embodiments according to Formula V-2, Y is N. In some embodiments, R^{13} is hydrogen or a C_{1-4} alkyl optionally substituted with 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or 3- or 4-membered ring (e.g., cyclopropyl). For example, in some embodiments, R^{13} is —CH_2-cyclopropyl.

[0414] In some embodiments, Y according to Formula V-2, is CR^{15}, wherein R^{15} is defined herein. For example, in some embodiments, R^{15} is hydrogen, deuterium, or a C_{1-4} alkyl.

[0415] In some embodiments, the compound of Formula E can be characterized as having a structure according to Formula V-3:

Formula V-3



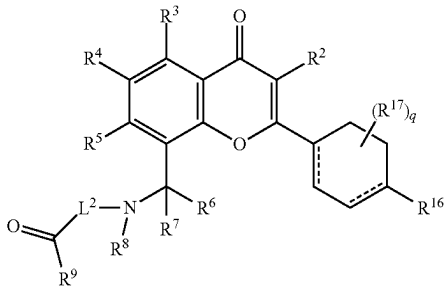
[0416] wherein:

[0417] R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; provided that (a) Y is C when the bond between Y and R^{12} is a double bond; (b) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; or (c) Y is C or N, when Y is included in a heteroaryl, such as a 5-membered heteroaryl, wherein L^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

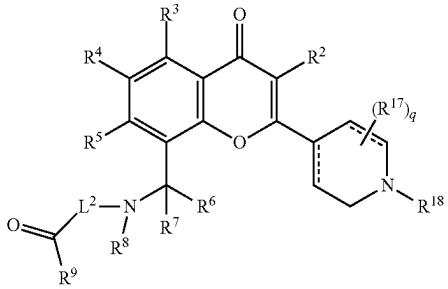
[0418] In some embodiments according to Formula V-3, R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure as defined herein for R^1 in Formula A and its subformulae, which are bounded to Formula V-3 through a ring carbon atom, in other words, Y is C or CR^{15}.

[0419] In some specific embodiments, the compound of Formula E can be characterized as having a structure according to Formula V-4, V-5, V-6, or V-7:

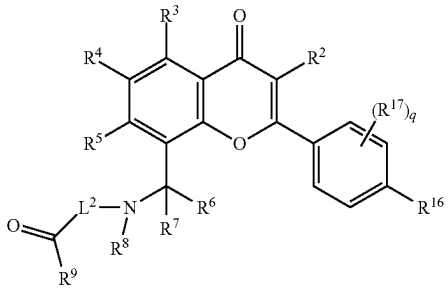
Formula V-4



Formula V-5



Formula V-6



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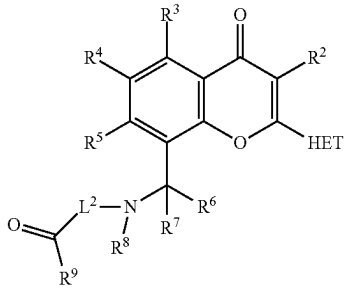
Formula V-7



[0420] wherein:

[0421] R^{16} is hydrogen, deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$;

[0422] R^{18} is hydrogen, $CONH_2$, CN, G^4, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, or $C(O)NG^4G^4$; HET represents (i) a 5 or 6-membered heteroaryl optionally substituted with 1 or 2 instances of R^{17}; or (ii) a 8-10 membered bicyclic heteroaryl optionally substituted with 1-3 instances of R^{17};

[0423] q is 0, 1, or 2;

[0424] R^{17} at each occurrence is independently deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$; and

[0425] G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F;

[0426] or as applicable, R^{16} and one instance of R^{17}, together with the intervening atom(s), are joined to form a 3-12, such as 3-7 membered ring structure, which is optionally substituted;

[0427] or as applicable, R^{18} and one instance of R^{17}, together with the intervening atom(s), are joined to form an 3-7 membered ring structure, which is optionally substituted,

[0428] or R^{16} in Formula V-6 is a structure as defined for R^D herein, and R^{17} at each occurrence is independently F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, C_{1-4} heteroalkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and q is 0, 1, or 2;

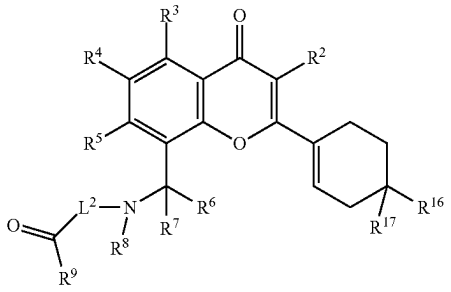
[0429] or R^{18} in Formula V-5 is a structure as defined for R^A herein, and R^{17} at each occurrence is independently F, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and q is 0, 1, or 2;

[0430] or HET in Formula V-7 is an optionally substituted 5- or 6-membered heteroaryl, such as a structure according to M-23, M-24, or M-25 as defined herein;

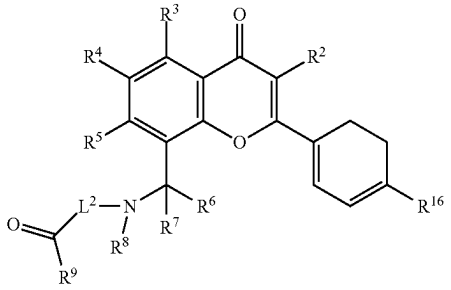
[0431] wherein L^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are defined herein.

[0432] In some more specific embodiments, the compound of Formula V-4, or V-5 can have a structure according to a subformula of Formula V-4-a, V-4-b, V-4-c, or V-5-a,

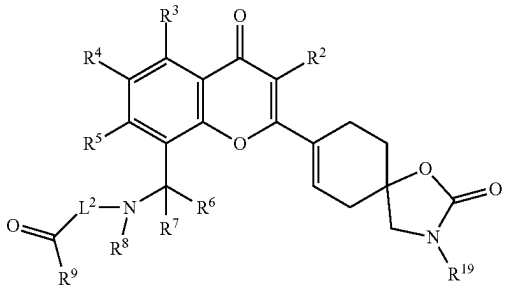
Formula V-4-a



Formula V-4-b



Formula V-4-c



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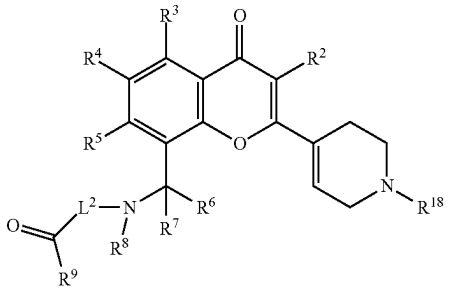
Formula V-5-a



[0433] wherein:

[0434] R^{19} is hydrogen, G^4, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, or $C(O)NG^4G^4$, wherein L^2, G^4, R^2, R^3, R^4, R^5, R^6, R^7, R^1, R^9, R^{16}, R^{17}, and R^{18} are defined herein.

[0435] In some embodiments according to Formula V-4-c, R^{19} is a C_{1-4} alkyl or a 3-12, such as 3-7 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. For example, in some embodiments, R^{19} is a C_{1-4} alkyl, such as methyl.

[0436] In some embodiments according to Formula V-4 or V-6, or an applicable subformula, R^{16} is hydrogen, deuterium, F, or methyl, more preferably, F.

[0437] In some embodiments according to Formula V-4, V-5, or V-6, q is O.

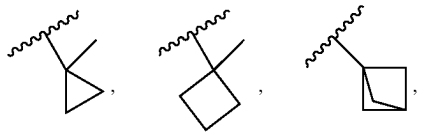
[0438] In some embodiments according to Formula V-4, V-5, or V-6, q is 1, wherein R^{17} is defined herein. For example, in some embodiments, R^{17} is hydrogen, deuterium, F, or methyl, preferably, F.

[0439] In some embodiments according to Formula V-5, or an applicable subformula, R^{15} can be hydrogen, G^5, or $C(O)G^5$, wherein G^5 is C_{1-4} alkyl or a 3-12, such as 3-7 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. For example, in some embodiments, R^{18} can be $C(O)G^5$, wherein G^5 is defined herein. For example, in some embodiments, G^5 is a C_{1-4} alkyl optionally substituted with 1-3F. In some embodiments, G^5 is a 3-12, such as 3-7 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), which is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B is defined herein.

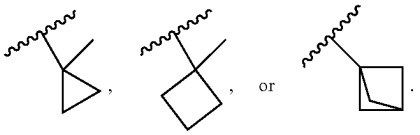
[0440] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)NHG^{5A}$, $C(O)NG^{5A}G^{5A}$, SO_2G^{5A}, SO_2NHG^{5A}, or $SO_2NG^AG^5$, wherein G^{5A} at each occurrence is independently (i) C_{1-4} alkyl; (ii) 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1}, wherein G^{B1} at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or cyclopropyl.

[0441] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some preferred embodiments, R^{18} can be $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_1-4 alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl. In some preferred embodiments, R^{18} can be C_{1-4} alkyl optionally substituted with 1-3F, such as methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, or tert-butyl.

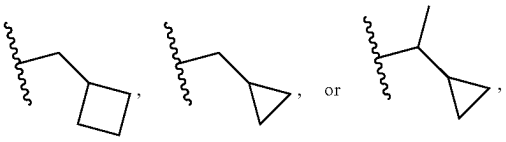
[0442] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



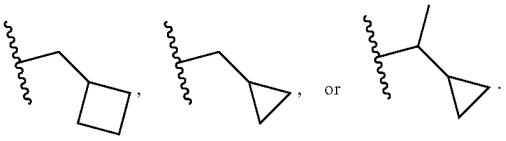
etc. In some preferred embodiments, R^{18} can be $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



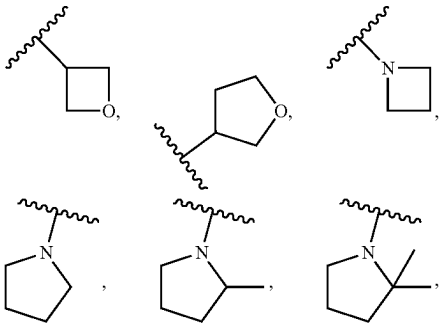
[0443] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



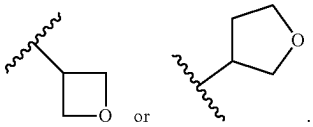
etc. In some preferred embodiments, R^{18} can be $C(O)G^{5A}$ or $C(O)OG^{5A}$, wherein G^{5A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



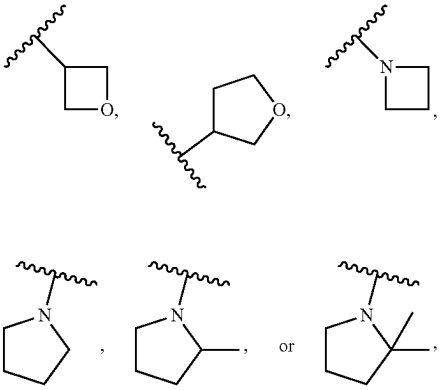
[0444] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



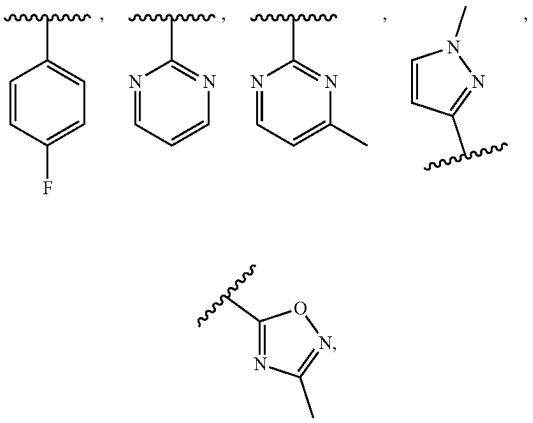
etc. Preferably, the 4-6 membered heterocyclic does not connect to a heteroatom through a ring heteroatom. For example, in some embodiments, R^{18} can be G^{5A}, which can be



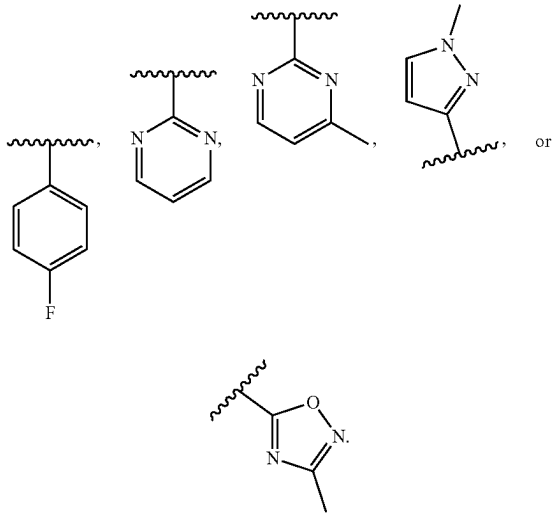
In some preferred embodiments, R^1 can be $C(O)G^{5A}$, wherein G^{5A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as

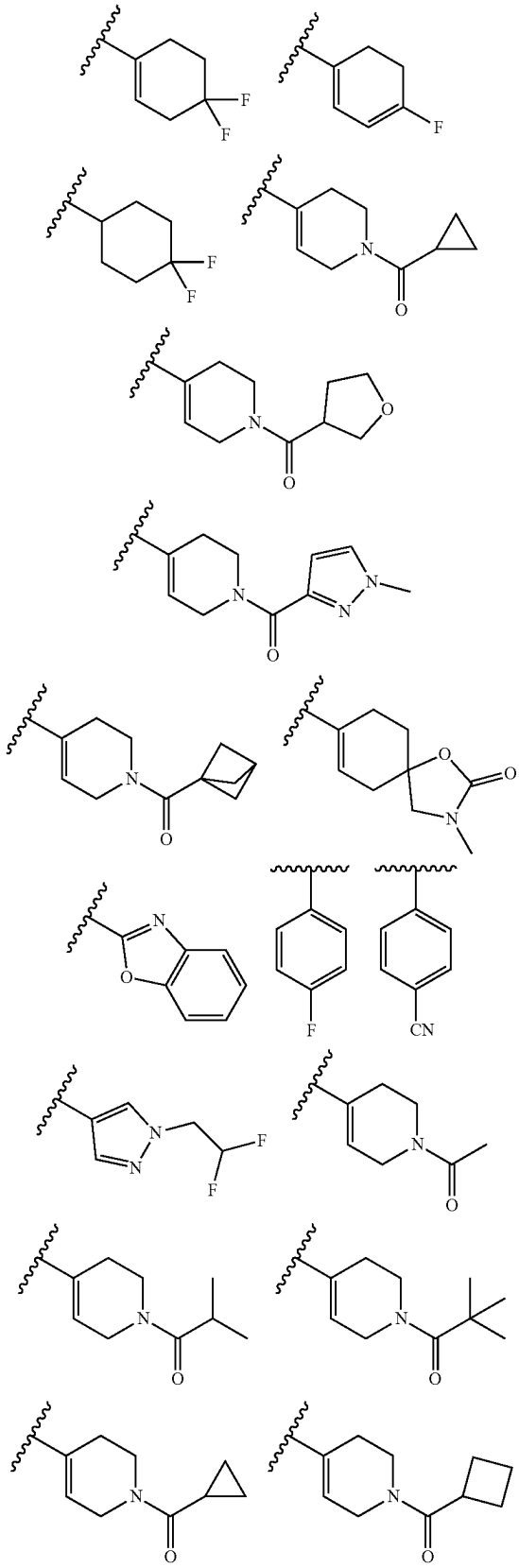


[0445] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be G^{5A}, $C(O)G^{5A}$, or SO_2G^{5A}, wherein G^{5A} is phenyl or 5- or 6-membered heteroaryl (e.g., described herein) optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



etc. In some preferred embodiments, R^{18} can be G^{5A} or $C(O)G^{5A}$, wherein G^{5A} is phenyl or 5- or 6-membered heteroaryl optionally substituted with 1 or 2 substituents each independently F, Cl, CN, or methyl, such as





[0446] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be $C(O)NHG^{5A}$ wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.).

[0447] In some embodiments according to Formula V-5, or an applicable subformula, R^{18} can be $C(O)NG^{5A}G^{5A}$, wherein one instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl.

[0448] In some more particular embodiments according to Formula E (e.g., any of the applicable subformulae, such as Formula V, V-1, V-3, V-4, V-5, V-6, or V-7, etc.), R^{12}, R^{13}, and Y are joined together to form a moiety according to M-1 to M-15 as defined herein in connection with Formula A and its subformulae.

[0449] In some more particular embodiments according to Formula E (e.g., any of the applicable subformulae, such as Formula V, V-1, V-3, V-4, V-5, V-6, or V-7, etc.), R^{12}, R^{13}, and Y are joined together to form a moiety according to M-16 to M-19 as well as M-19' and M-19" as defined herein in connection with Formula A and its subformulae.

[0450] In some more particular embodiments according to Formula E (e.g., any of the applicable subformulae, such as Formula V, V-1, V-3, V-4, V-5, V-6, or V-7, etc.), R^{12}, R^{13}, and Y are joined together to form a moiety according to M-20 to M-25 as defined herein in connection with Formula A and its subformulae.

[0451] In some more particular embodiments according to Formula E (e.g., any of the applicable subformulae, such as Formula V, V-1, V-3, V-4, V-5, V-6, or V-7, etc.), R^{12}, R^{13}, and Y are joined together to form a moiety selected from:

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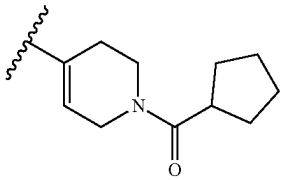

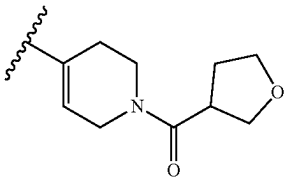

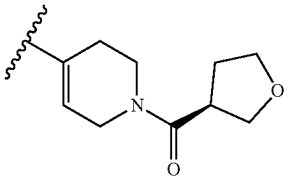

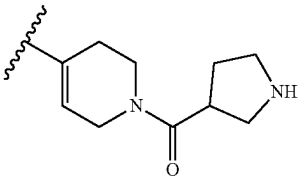

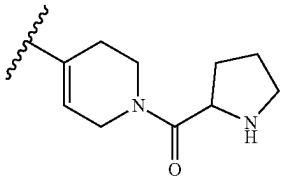

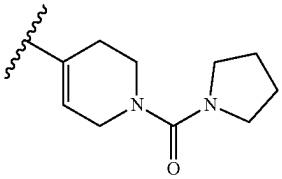

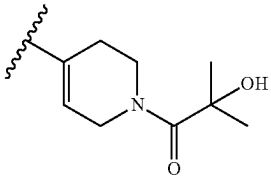

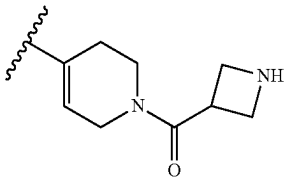

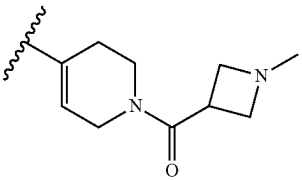

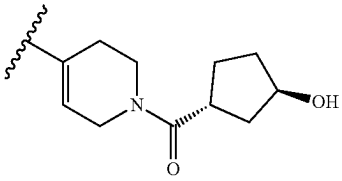

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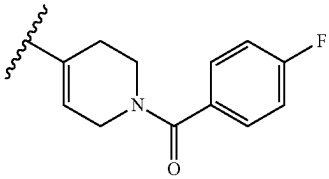

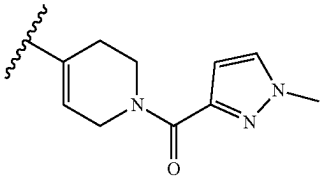

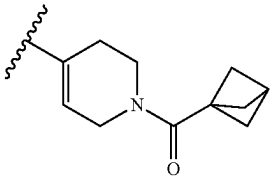

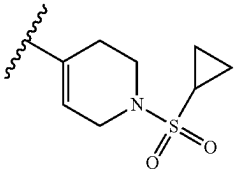

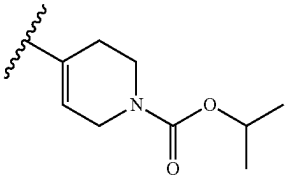

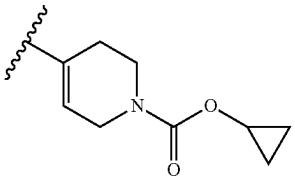

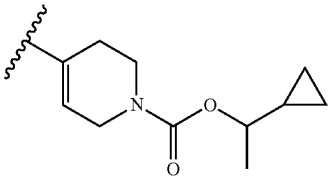

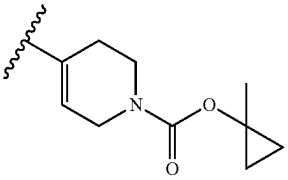

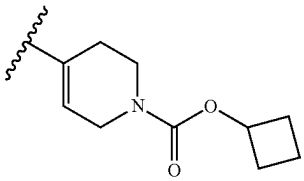

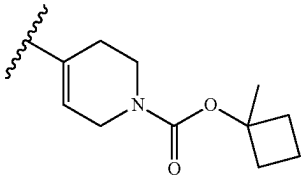

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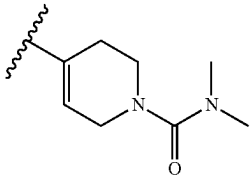

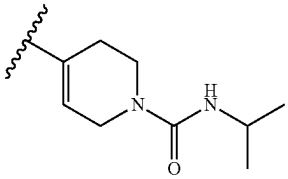

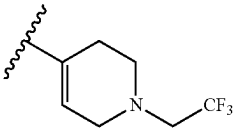

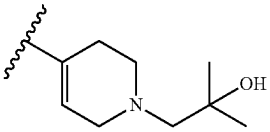

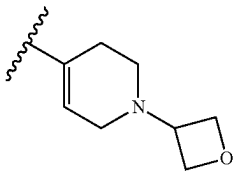

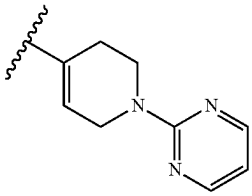

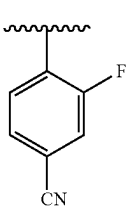

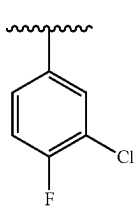

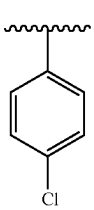

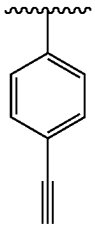

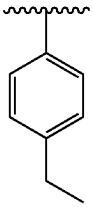

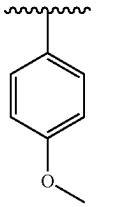

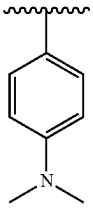

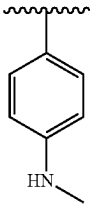

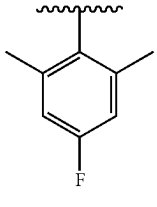

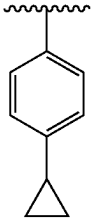

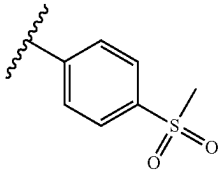

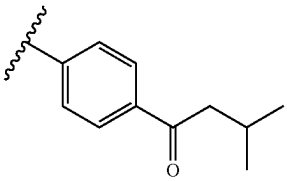

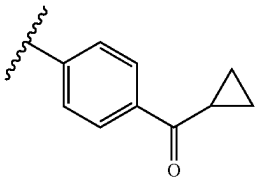

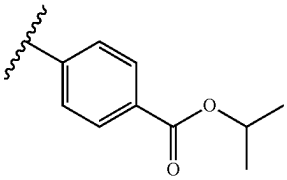

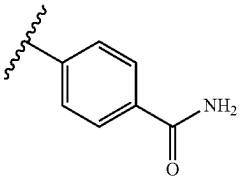

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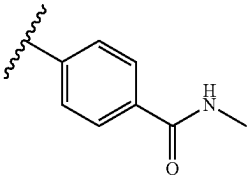

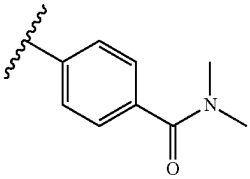

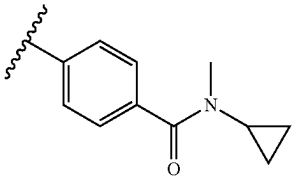

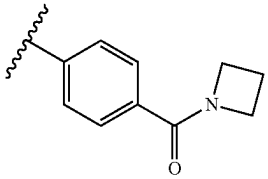

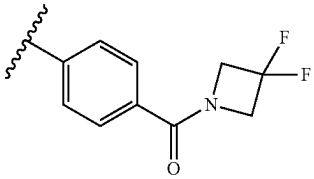

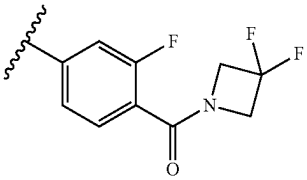

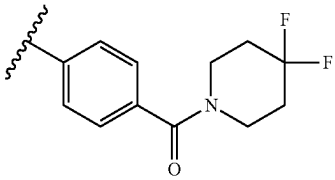

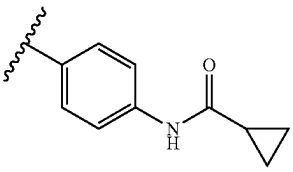

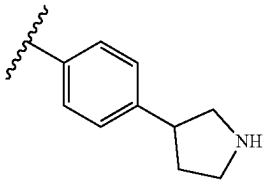

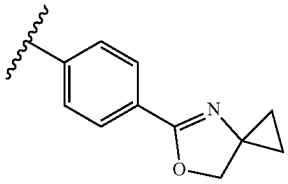

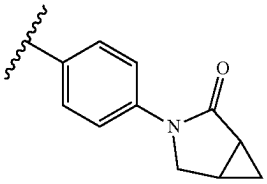

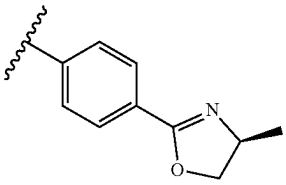

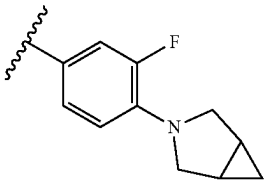

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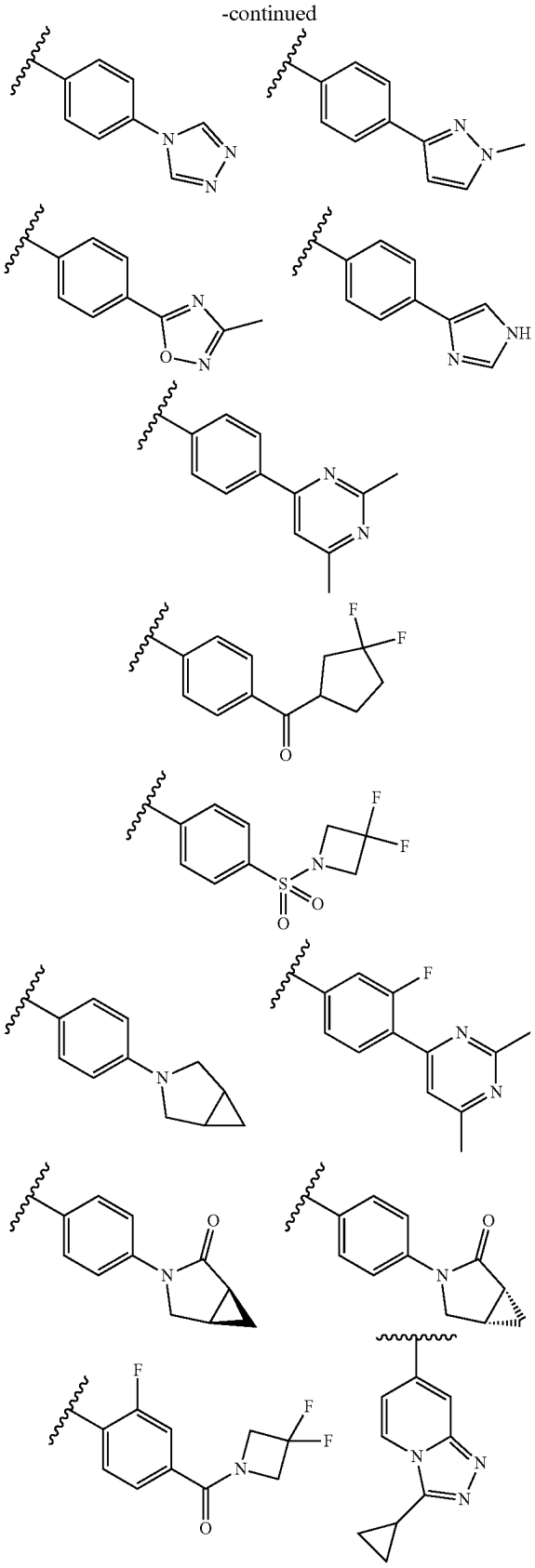

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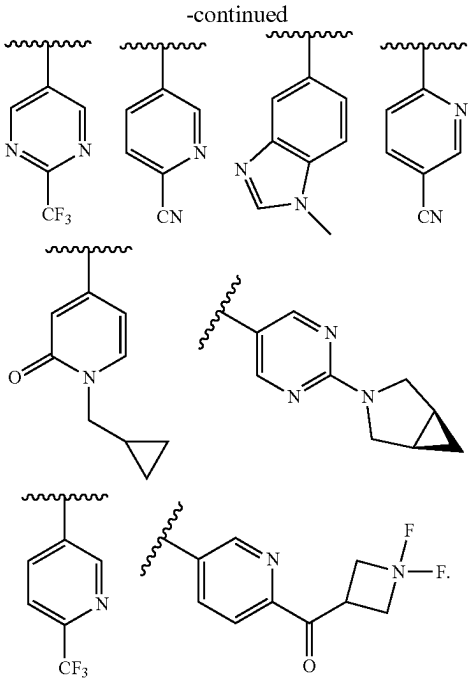
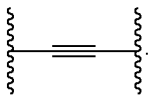


[0452] Suitable definitions and preferred definitions of the variables in Formula E (such as those in subformulae, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7) include any of those described for the corresponding variables (i.e., those having the same identifiers, such as U, Q, R^{100}, L^1, L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9) for Formula A and its subformulae.

[0453] For example, in some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), L^1 is typically absent. In some embodiments, L^1 is O, CH_2, or

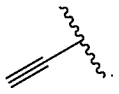


[0454] For example, in some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), R^2 can be hydrogen or methyl.

[0455] In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), Q is CR^3, and R^3 can be methyl. In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), Q is CR^3, and R^3 can be hydrogen.

[0456] In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), R^4 can be methyl.

[0457] In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), R^4 can be F, Cl, Br, or



[0458] In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), R^5 can be hydrogen.

[0459] In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), both R^6 and R^7 can be hydrogen.

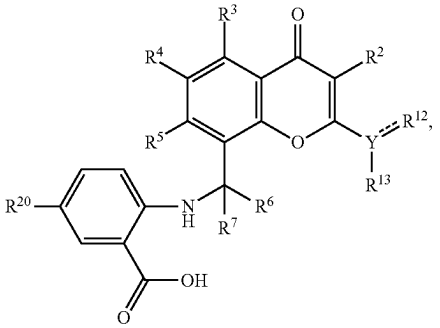
[0460] In some embodiments according to Formula E (such as a subformula, e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7), one of R^6 and R^1 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, more preferably, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl.

[0461] In some embodiments, U in Formula E is NR^8, such as in Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7, R^8 is typically hydrogen.

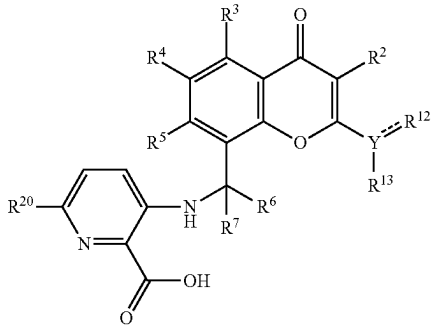
[0462] In some embodiments, R^{100} in Formula E is C(O) R^9, such as in Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7, R^9 is typically OH.

[0463] In some specific embodiments, the compound of Formula E can be characterized as having a structure according to Formula V-3-a or V-3-b:

Formula V-3-a



Formula V-3-b

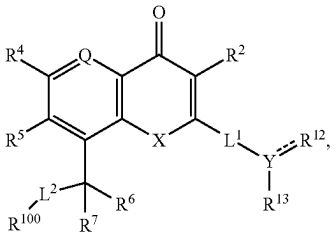


wherein the variables Y, R^{12}, R^{13}, R^2, R^3, R^4, R^5, R^6, R^7, and R^{20} are defined and preferred herein. For example, in some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CF_3. In some preferred embodiments, in Formula V-3-a, R^{20} is hydrogen. In some preferred embodiments, in Formula V-3-b, R^{20} is Cl.

[0464] Further specific definitions of the variables for Formula E, such as Formula V, V-1, V-2, V-3, V-4, V-5, V-6, or V-7, include those respective atom/group/structures shown in the exemplified compounds herein.

[0465] In some embodiments, U is null, and the compound of Formula E can be characterized as having a structure according to Formula VI:

Formula VI



wherein Q, Z, X, Y, L^1, L^2, R^{12}, R^{13}, R^2, R^4, R^5, R^6, R^7, and R^{100}, are defined herein.

[0466] Typically, in Formula VI, L^2 is an optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene). In some embodiments, R^{100} in Formula VI is hydrogen.

[0467] In some embodiments, L^1 in Formula VI is null, and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure as defined herein for R^1 in Formula A and its subformulae.

[0468] In some embodiments, Q in Formula VI is typically CR^3, wherein R^3 is defined herein. For example, R^3 can be hydrogen or methyl.

[0469] X in Formula VI is typically O.

[0470] In some embodiments, Z in Formula VI is O.

[0471] In some embodiments according to Formula VI, R^2 can be hydrogen or methyl.

[0472] In some embodiments according to Formula VI, R^4 can be methyl.

[0473] In some embodiments according to Formula VI, R^4 can be F.

[0474] In some embodiments according to Formula VI, R^5 can be hydrogen.

[0475] In some embodiments according to Formula VI, both R^6 and R^7 can be hydrogen.

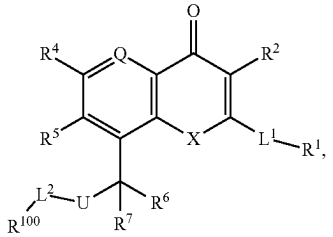
[0476] In some embodiments according to Formula VI, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, more preferably, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl.

[0477] Other definitions for the variables suitable for Formula VI include those defined herein for Formula E and its subformulae.

Formula F

[0478] In some embodiments, the present disclosure provides a compound of Formula F, or a pharmaceutically acceptable salt thereof:

Formula F



[0479] wherein:

[0480] X is O, NR^{14}, or S, wherein R^{14} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine;

[0481] Q is N or CR^3, wherein R^3 is hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0482] U is null, O, S, S(O), SO_2, or NR^8, wherein R^1 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0483] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0484] R^1 is a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0485] R^2, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1,

[0486] R^6 and R^7 are each independently hydrogen, deuterium, halogen, CN, G^2, or OG^2,

[0487] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0488] R^{100} is —R^{102}-R^{103}, wherein R^{102} is null, O, NH, C_{1-4} alkylene or C_{1-4} heteroalkylene having 1 or 2 heteroatoms, and R^{103} is hydrogen, COOH, $CONH_2$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $CONHSO_2G^3$, SO_3H, SO_2NH_2, SO_2NHG^3, $SO_2NG^3G^3$, or a 5- or 6-membered ring having a hydrogen bond donor, e.g., a tetrazolyl;

[0489] wherein:

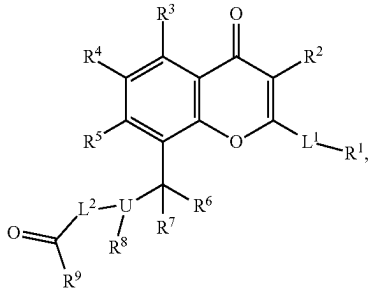
[0490] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0491] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0492] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

[0493] In some embodiments, the compound of Formula F can be characterized as having a structure according to Formula VII:

Formula VII



[0494] wherein:

[0495] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

[0496] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

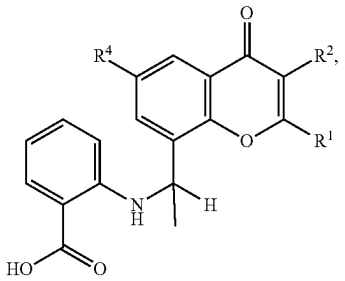
[0497] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$,

[0498] wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure,

[0499] wherein L^1, L^2, R^1, R^2, R^3, R^4, and R^5, are defined herein.

[0500] In some embodiments, the compound of Formula F can be characterized as having a structure according to Formula VII-1 or VII-2:

Formula VII-1



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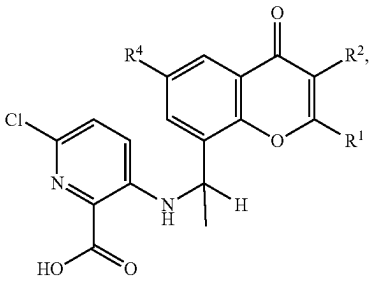
Formula VII-2

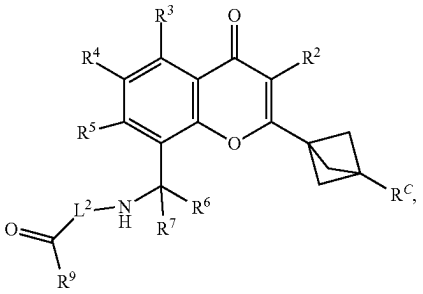


[0501] wherein:

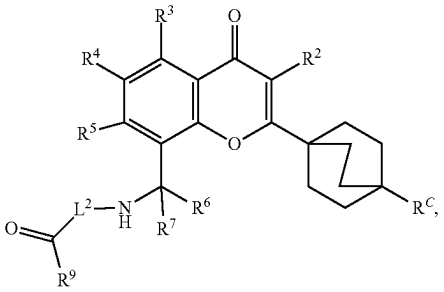
[0502] R^1, R^2, and R^4, are defined herein.

[0503] In some embodiments, the compound of Formula F can be characterized as having a structure according to Formula VII-3 or VII-4:

Formula VII-3



Formula VII-4



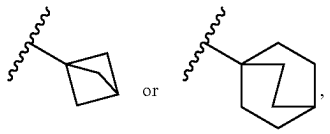
[0504] wherein:

[0505] the variables L^2, R^2, R^3, R^4, R^5, R^6, R^7, R^9, and R^C are defined herein.

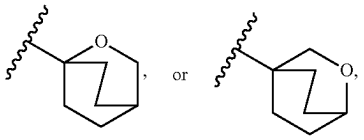
[0506] Suitable definitions and preferred definitions of the variables in Formula F (such as those in subformulae, e.g., Formula VII, VII-1 to VII-4) include any of those described for the corresponding variables (i.e., those having the same identifiers, such as U, R^C, L^1, L^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9) for Formula A and its subformulae.

[0507] For example, in some embodiments according to Formula F (e.g., Formula VII, VII-1 or VII-2), R^1 can have a structure according to any of M-1 to M-25 as described herein in connection with Formula A and its subformulae.

[0508] In some embodiments, R^1 in Formula F (e.g., Formula VII, VII-1 or VII-2) can be a bridged 5-12 membered ring structure, which is optionally substituted, wherein the bridged ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S. For example, in some embodiments, R^1 in Formula F (e.g., Formula VII, VII-1 or VII-2) can be a 5-12 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted. For example, in some embodiments, R^1 is a 5-8 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted. In some embodiments, R^1 in Formula F (e.g., Formula VII, VII-1 or VII-2) can be a 5-12 membered (preferably, 7-10 membered, e.g., 7 or 8 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one ring heteroatom which is a ring oxygen. In some embodiments, R^1 in Formula F (e.g., Formula VII, VII-1 or VII-2) can be a 5-12 membered (preferably, 8-10 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one or two ring heteroatoms independently selected from S, O, and N. In some preferred embodiments, R^1 in Formula F (e.g., Formula VII, VII-1 or VII-2) can be



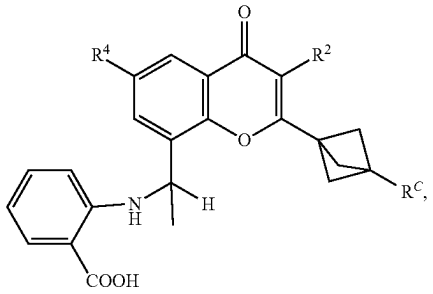
each of which is optionally substituted, e.g., as described herein. In some preferred embodiments, R^1 in Formula C (such as a subformula, e.g., Formula III or III-1) can be



each of which is optionally substituted, e.g., as described herein.

[0509] In some embodiments, the compound of Formula F can be characterized as having a structure according to Formula VII-1-a or VII-1-b:

Formula VII-1-a



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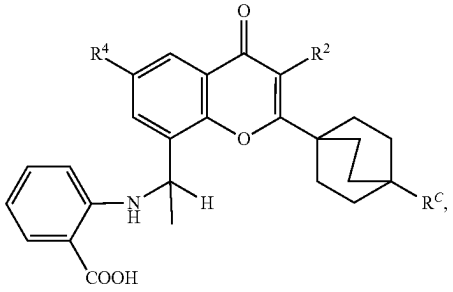
Formula VII-1-b

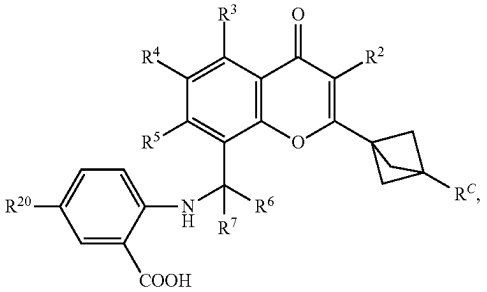


[0510] wherein:

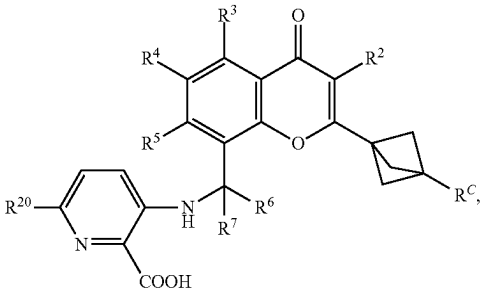
[0511] R^C, R^2, and R^4, are defined herein.

[0512] In some embodiments, the compound of Formula F can be characterized as having a structure according to Formula VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b:

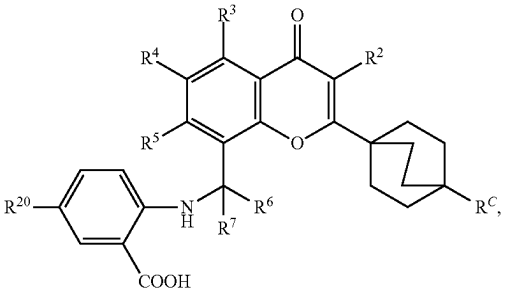
Formula VII-3-a



Formula VII-3-b



Formula VII-4-a



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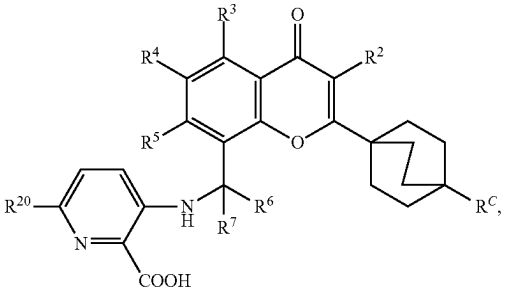
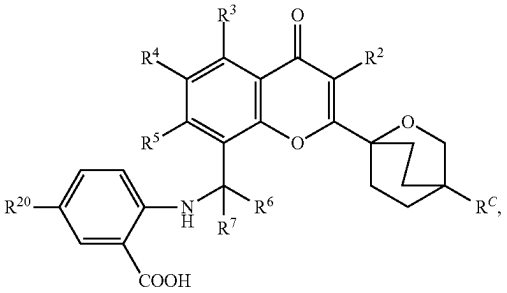
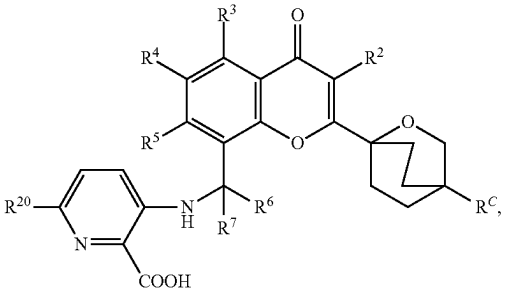
Formula VII-4-b



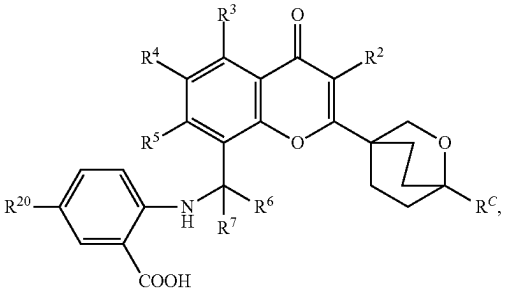
Formula VII-5-a



Formula VII-5-b



Formula VII-6-a



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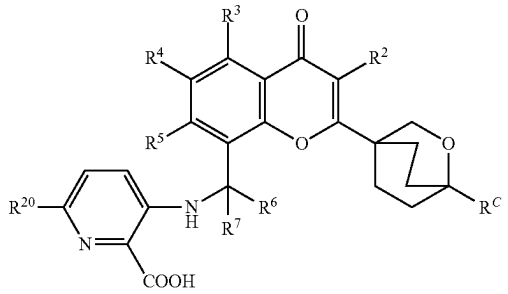
Formula VII-6-b



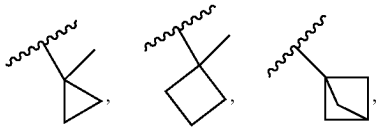
[0513] wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F; and

[0514] R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. In some preferred embodiments, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3.

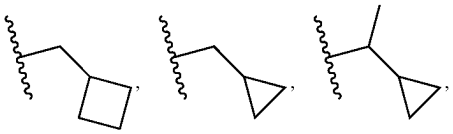
[0515] For example, in some embodiments according to Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is H, halogen, such as F, Cl, or Br, OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, CH_2OCH_3, CHF_2, CH_3, or OCH_3. In some embodiments according to Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is CN, COOH, $CONH_2$, G^{4A}, OG^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, $NHC(O)NHG^{4A}$ $NHC(O)NG^{4A}G^{4A}$, $NG^{4A}C(O)G^{4A}$, $NG^{4A}C(O)OG^{4A}$, $NG^{4A}C(O)NHG^{4A}$, $NG^{4A}C(O)NG^{4A}G^{4A}$ SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl. The C_{1-4} alkylene in (iii) can be straight chain or branched alkylene, for example, in some embodiments, the C_{1-4} alkylene is CH_2 or $CH(CH_3)$. In some embodiments, the C_{1-4} heteroalkylene in (iv) contains one or two heteroatoms, such as one oxygen, one nitrogen, two oxygen, two nitrogen, or one oxygen and one nitrogen atoms. Similarly, the C_{1-4} heteroalkylene can be straight chained or branched, for example, in some embodiments, the C_{1-4} heteroalkylene can be O—CH_2, or $CH(OCH_3)$, etc. The 3-12 membered ring typically can include 0-3 ring heteroatoms. For example, in some embodiments, the 3-12 membered ring is a C_{3-7} cycloalkyl. In some embodiments, the 3-12 membered ring is a 4-7 membered heterocyclyl having 1-2 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is phenyl. In some embodiments, the 3-7 membered ring is a 5-membered heteroaryl having 1-4, such as 1-3 ring heteroatoms each independently O, S, or N. In some embodiments, the 3-12 membered ring is a 6-membered heteroaryl having 1-2 ring nitrogens. In some embodiments, the 3-12 membered ring is cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, or phenyl.

[0516] In some embodiments, in some embodiments according to Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is CN. In some embodiments, R^C is H. In some embodiments, R^C is CH_2OCH_3. In some embodiments, R^C is G^{4A}. In some embodiments, R^C is $C(O)G^{4A}$. In some embodiments, R^C is $C(O)NHG^{4A}$ or $C(O)NG^{4A}G^{4A}$. In some embodiments, R^C is $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, $NHC(O)NHG^{4A}$ or $NHC(O)NG^{4A}G^{4A}$. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.). In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, NHC(O)

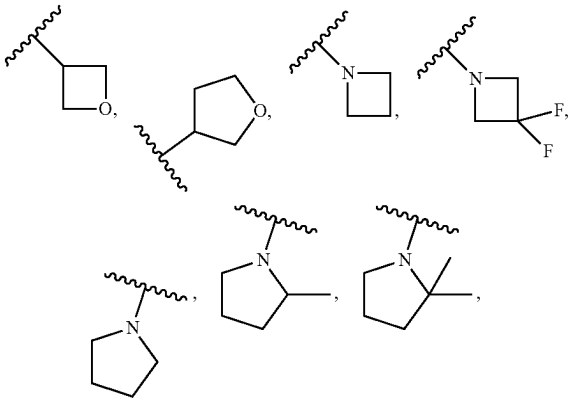
OG^{4A}, or $NHC(O)NHG^{4A}$, wherein G^{4A} is C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



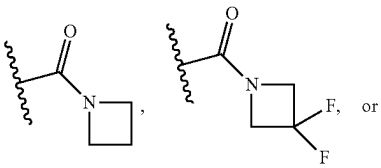
etc. In some embodiments, R^C is G^4, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



etc. In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



etc., typically, when the 4-6 membered heterocyclic attaches through a ring nitrogen, R^C is $C(O)G^{4A}$, for example, in some embodiments, R^C is



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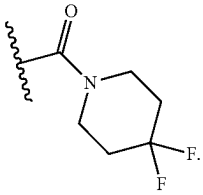
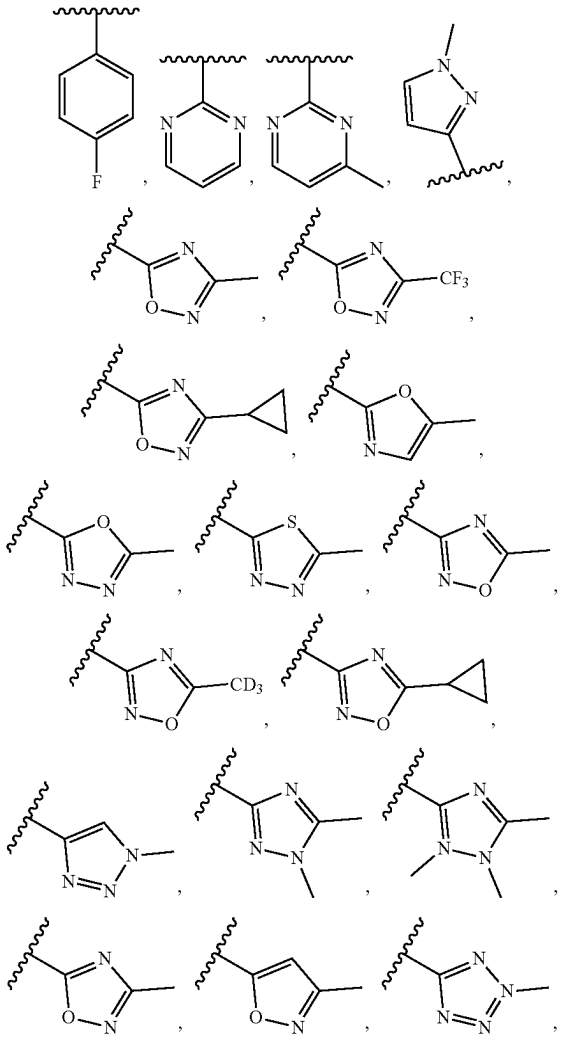


In some embodiments, R^C is G^{4A}, $C(O)G^{4A}$, $C(O)NHG^{4A}$, $NHC(O)G^{4A}$, $NHC(O)OG^{4A}$, or $NHC(O)NHG^{4A}$, wherein G^{4A} is phenyl or 5- or 6-membered heteroaryl (e.g., pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, etc.), optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



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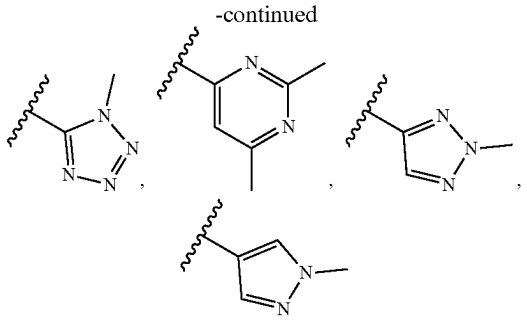
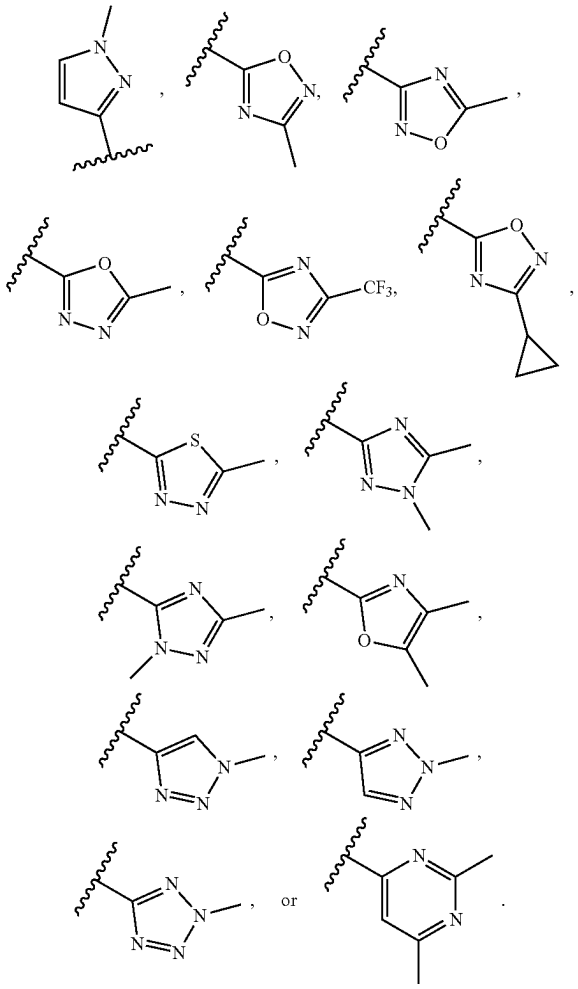
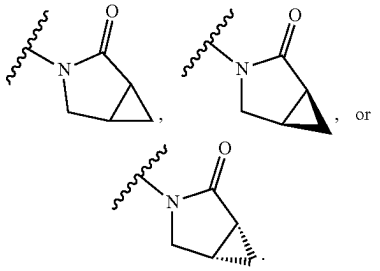


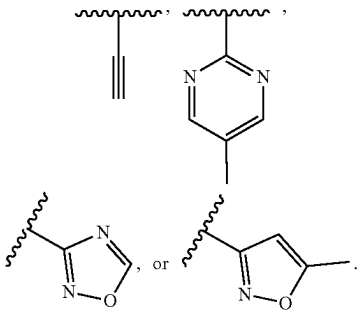
etc. In some embodiments, R^C is $C(O)NG^{4A}G^{4A}$ or $NHC(O)NG^{4A}G^{4A}$, wherein one instance of G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{4A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl. In some embodiments, R^C is



[0517] In some embodiments, R^C is

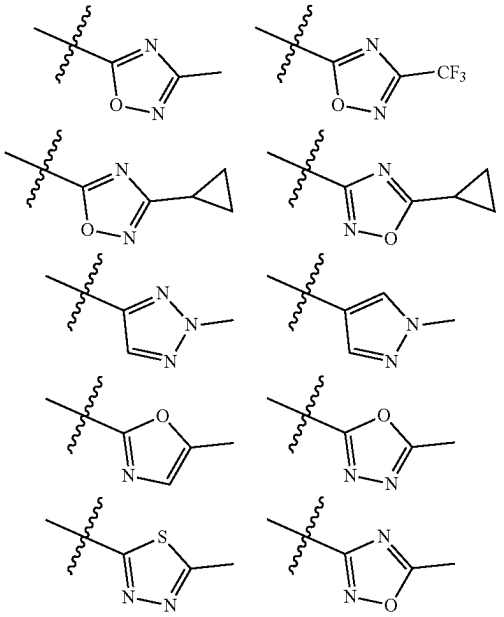


In some embodiments, R^C is



[0518] In some embodiments, in some embodiments according to Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3.

[0519] In some embodiments, in some embodiments according to Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is selected from:



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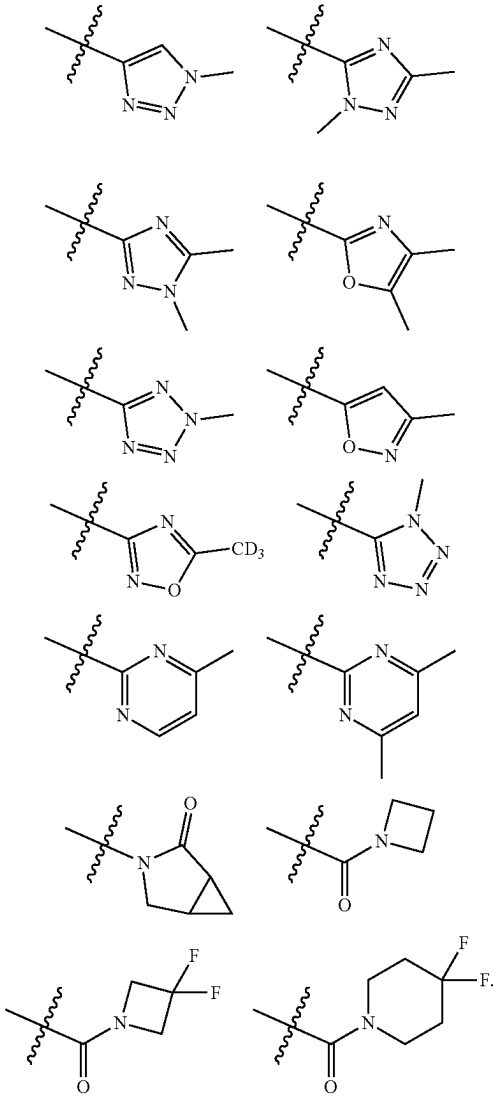
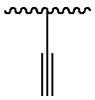
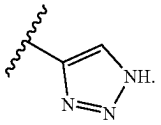


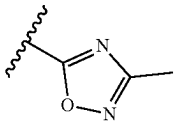
In some preferred embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is H, F, CN,



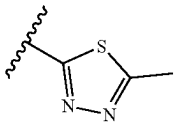
or a 5-membered heteroaryl, such as a triazole, an thiadiazole, or an oxadiazole optionally substituted with methyl, CD_3, CF_3, or cyclopropyl. In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is selected from CH_3, CH_2F, CHF_2, CF_3, CH_2OH, CH_2CH_3, or CH(OH)CH_3. In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is



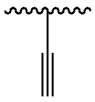
In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is F. In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is CHF_2. In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is CN. In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is



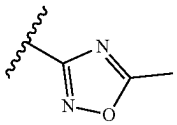
In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is



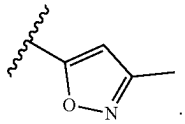
In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is



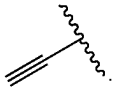
In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is



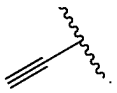
In some embodiments, in Formula VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, R^C is



[0520] In some embodiments according to Formula F (such as a subformula, e.g., Formula VII, VII-1, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, or VII-2), R^2 is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. In some preferred embodiments, R^2 is methyl. In some preferred embodiments, R^2 is H, F, Cl, CF_3, or CD_3. In some preferred embodiments, R^2 is



[0521] In some embodiments according to Formula F (such as a subformula, e.g., Formula VII, VII-1, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, or VII-2), R^3, R^4, and R^5 are each independently hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F. In some preferred embodiments, R^4 is methyl, or R^4 is F, Cl, Br, or



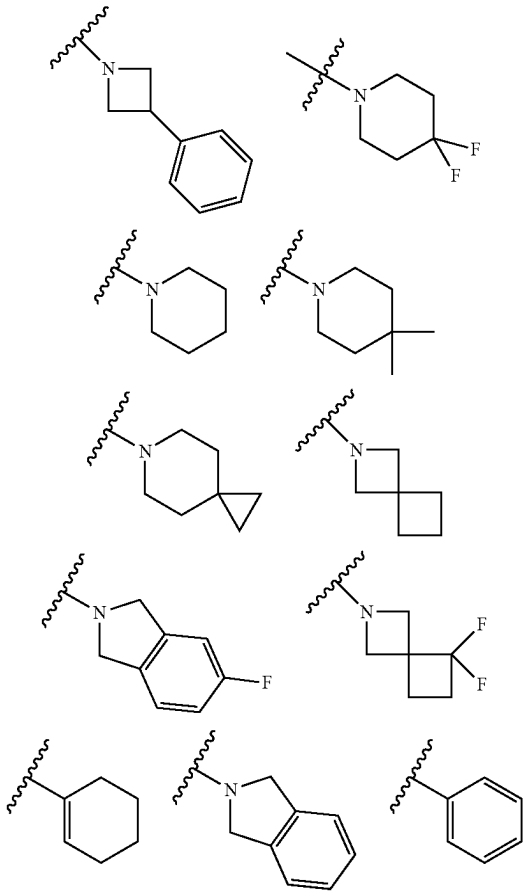
In some preferred embodiments, R^4 is CF_3 or CD_3. In some preferred embodiments, R^3 is hydrogen. In some preferred embodiments, R^5 is hydrogen.

[0522] In some preferred embodiments according to Formula F (such as a subformula, e.g., Formula VII, VII-1, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, or VII-2), one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is C_{1-4} alkyl optionally substituted with 1-3F, more preferably, one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is methyl.

[0523] Further specific definitions of the variables for Formula F, such as a subformula, e.g., Formula VII, VII-1, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, or VII-2, include those respective atom/group/structures shown in the exemplified compounds herein, see e.g., those shown in Table A and Examples section.

[0524] In some embodiments, the compound of Formula A, B, C, D, E, or F (including any of the applicable sub-formulae as described herein) can have stereoisomer(s). In such embodiments, the compound of Formula A, B, C, D, E, or F (including any of the applicable sub-formulae as described herein) can exist in the form of an individual enantiomer, diastereomer, atropisomer, and/or geometric isomer, as applicable, or a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomers. In some embodiments, when applicable, the compound of Formula A, B, C, D, E, or F (including any of the applicable sub-formulae as described herein) can exist as a mixture of a pair of enantiomers in any ratio, including a racemic mixture with a ratio of 1:1. In some embodiments, when applicable, the compound of Formula A, B, C, D, E, or F (including any of the applicable sub-formulae as described herein) can exist as an isolated or enriched individual enantiomer substantially free (e.g., with less than 20%, less than 10%, less than 5%, less than 1%, by weight, by HPLC or SFC area, or both, or with a non-detectable amount) of the other enantiomer, such as having an enantiomeric excess ("ee") of greater than 50%, such as 80% ee or higher, 90% ee or higher, 95% ee or higher, 98% ee or higher, 99% ee or higher.

[0525] In some embodiments, R^1 in Formula I (e.g., I-1) is not selected from any of the following:



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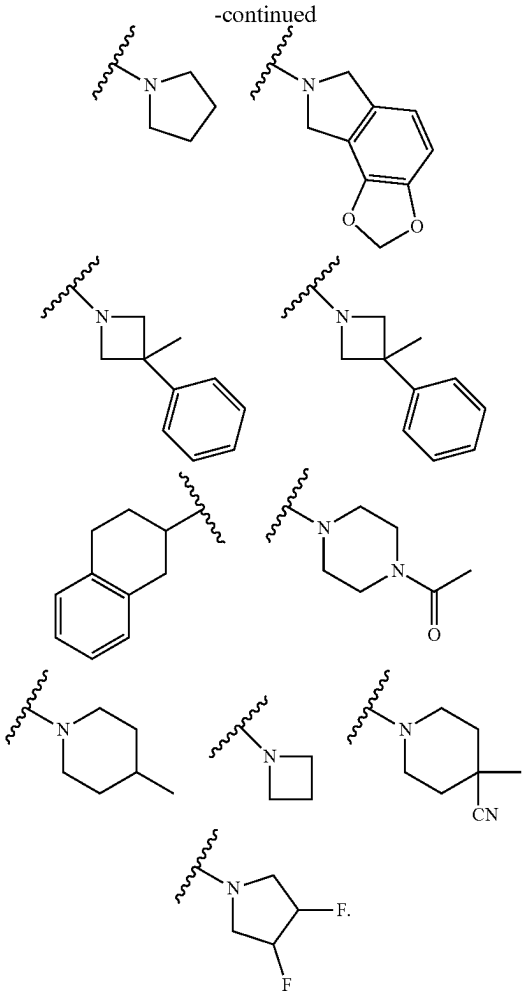


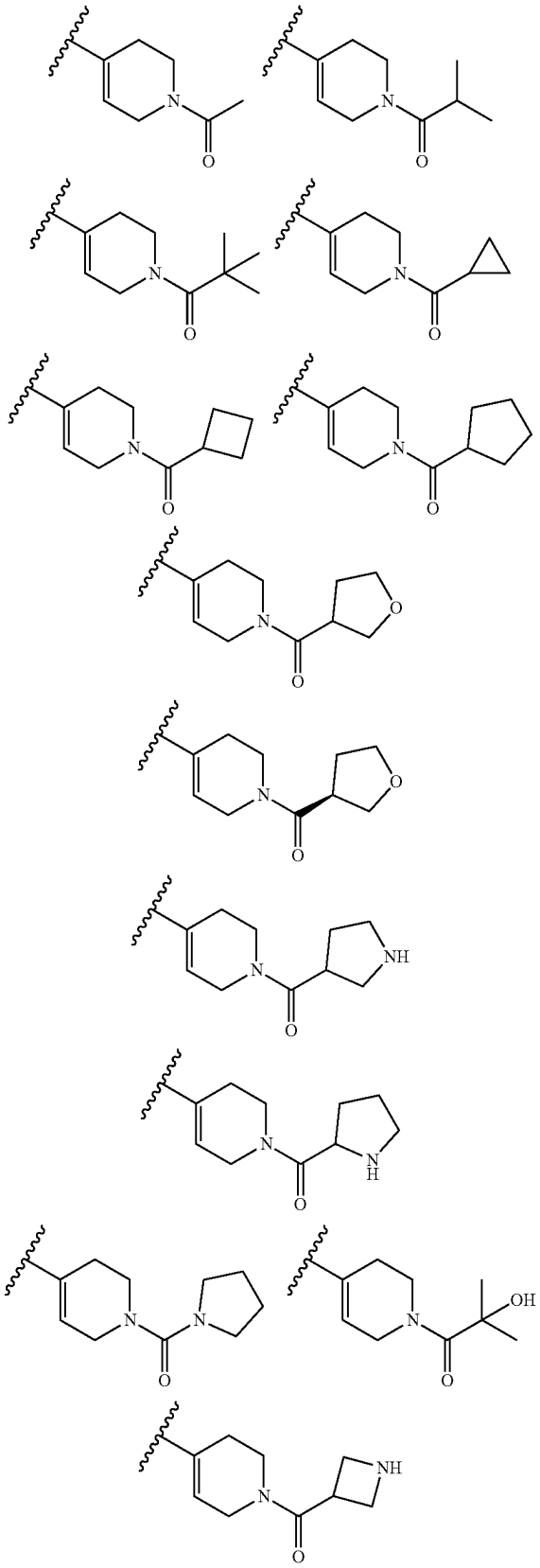
In some embodiments, R^1 in Formula III (e.g., III-1) or VII is not selected from any of the above groups.

[0526] In some embodiments, the present disclosure also provides the following exemplary embodiments 1-38:

[0527] Embodiment 1. A compound of Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, I-1-a-5, II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, II-3-b, III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-x, III-y, III-4, III-5, IV, VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b, as defined herein, or a pharmaceutically acceptable salt thereof.

[0528] Embodiment 2. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^1 has a structure according to any of M-1 to M-25 as defined herein.

[0529] Embodiment 3. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^1 is selected from:



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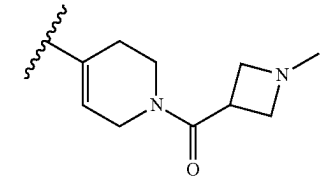

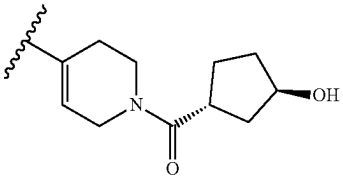

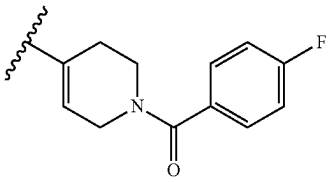

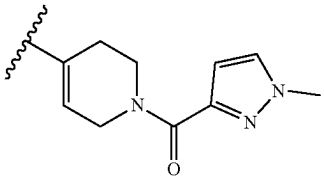

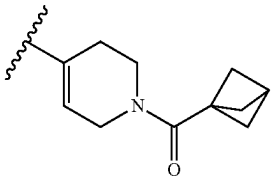

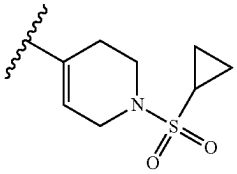

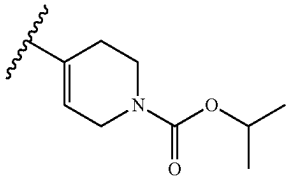

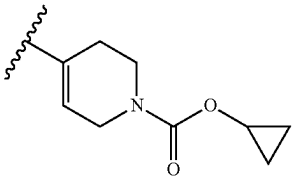

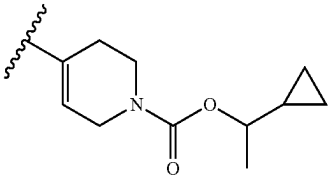

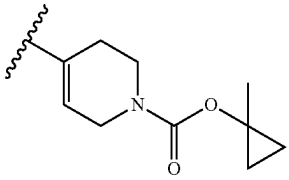

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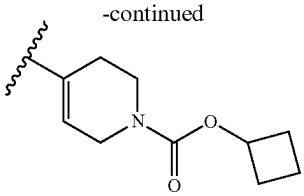
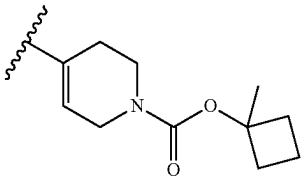
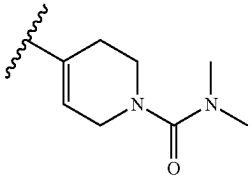
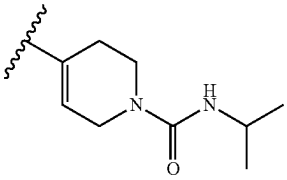
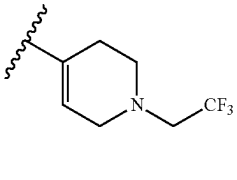
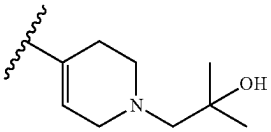


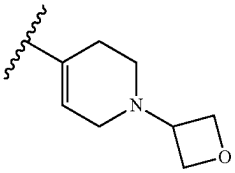


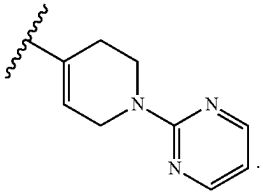




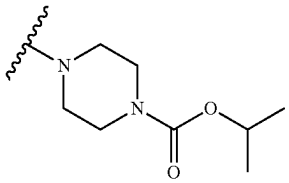


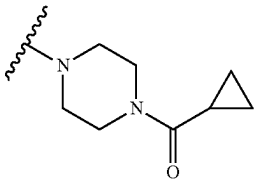


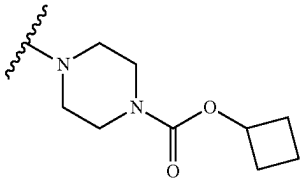




[0530] Embodiment 4. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^1 is selected from:







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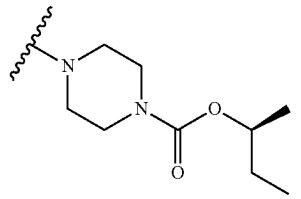

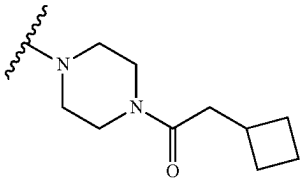

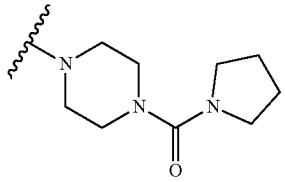

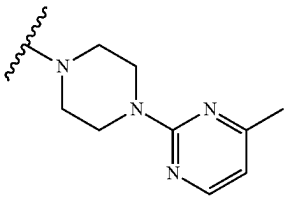

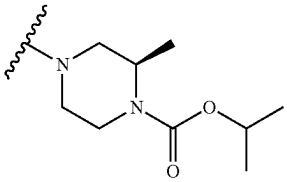

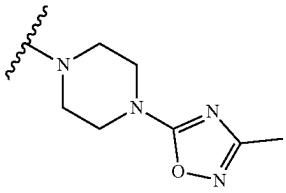

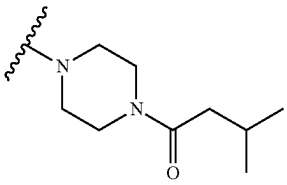

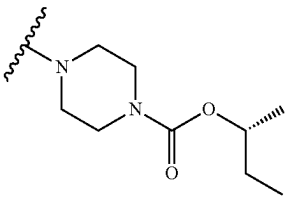

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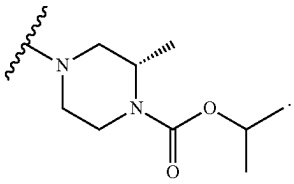
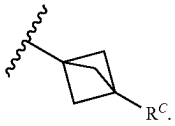
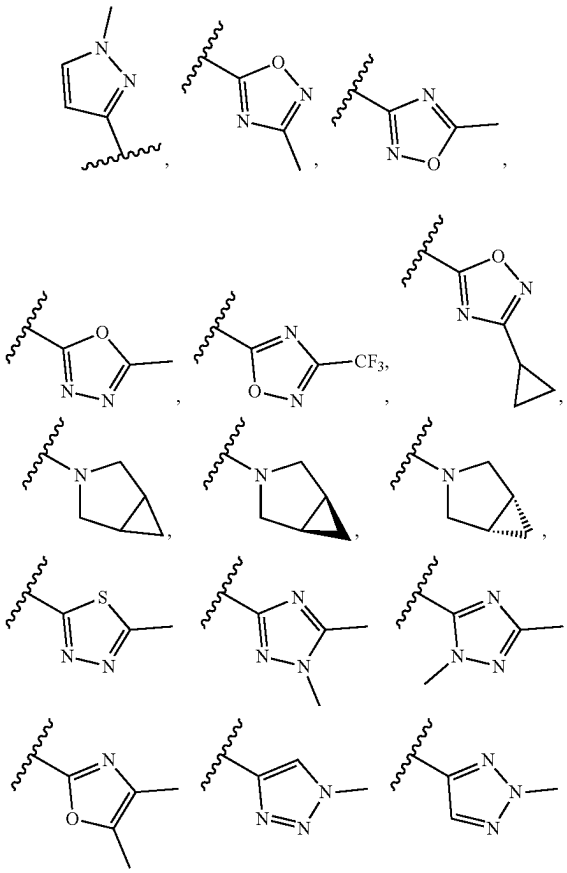


[0531] Embodiment 5. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^1 has a structure of M-17,

(M-17)



[0532] Embodiment 6. The compound of Embodiment 1 or 5, or a pharmaceutically acceptable salt thereof, wherein R^C is



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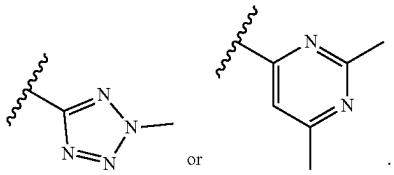
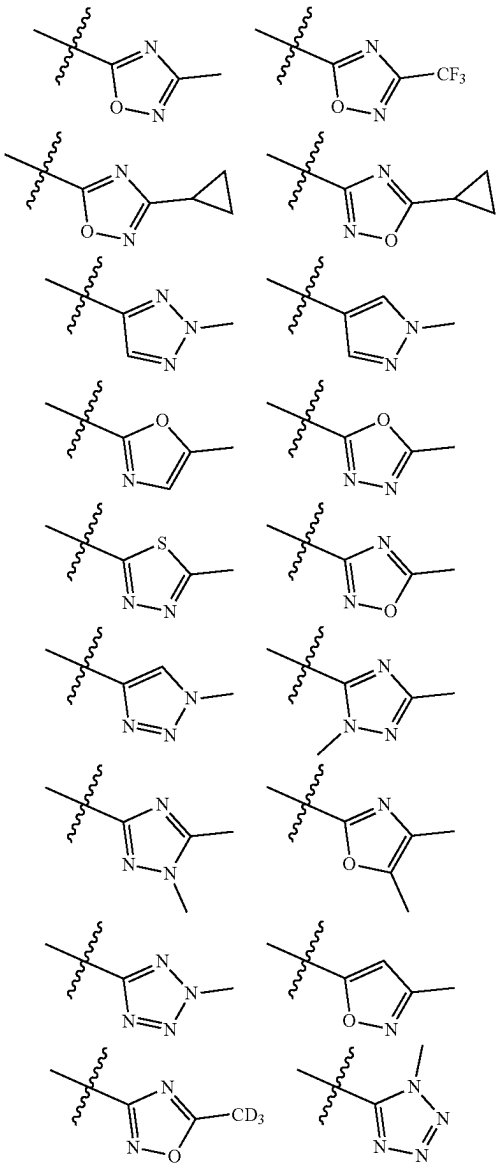


[0533] Embodiment 7. The compound of Embodiment 1 or 5, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3.

[0534] Embodiment 8. The compound of Embodiment 1 or 5, or a pharmaceutically acceptable salt thereof, wherein R^C is



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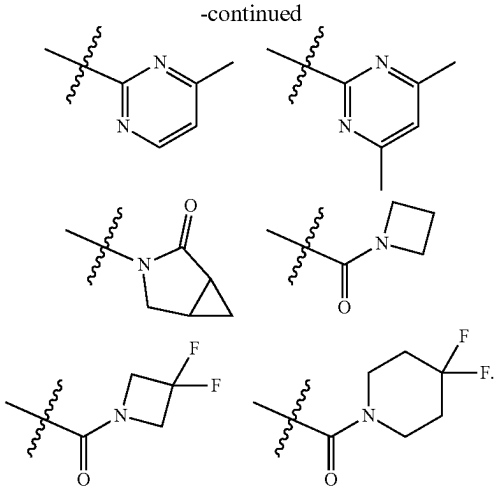
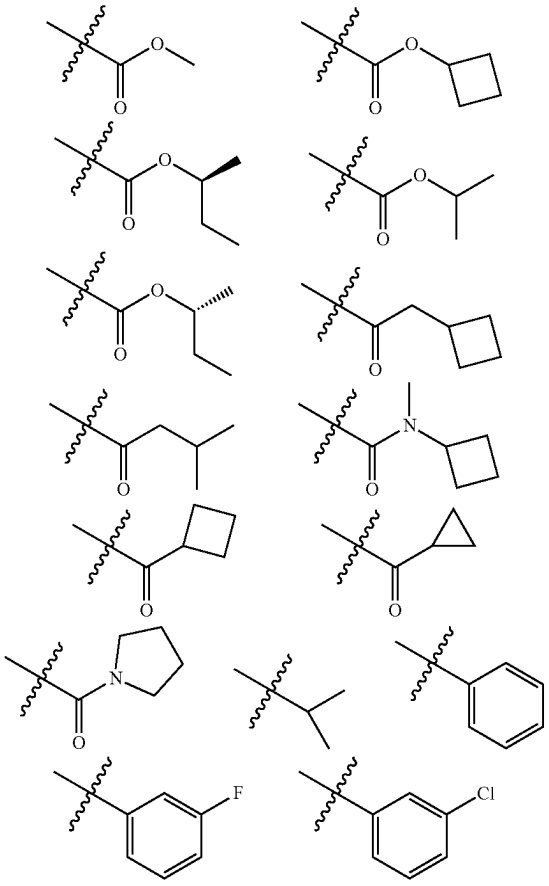


[0535] Embodiment 9. The compound of Embodiment 1 or 5, or a pharmaceutically acceptable salt thereof, wherein R^C is any of those shown in the exemplified compounds in Table A herein.

[0536] Embodiment 10. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^A is selected from:



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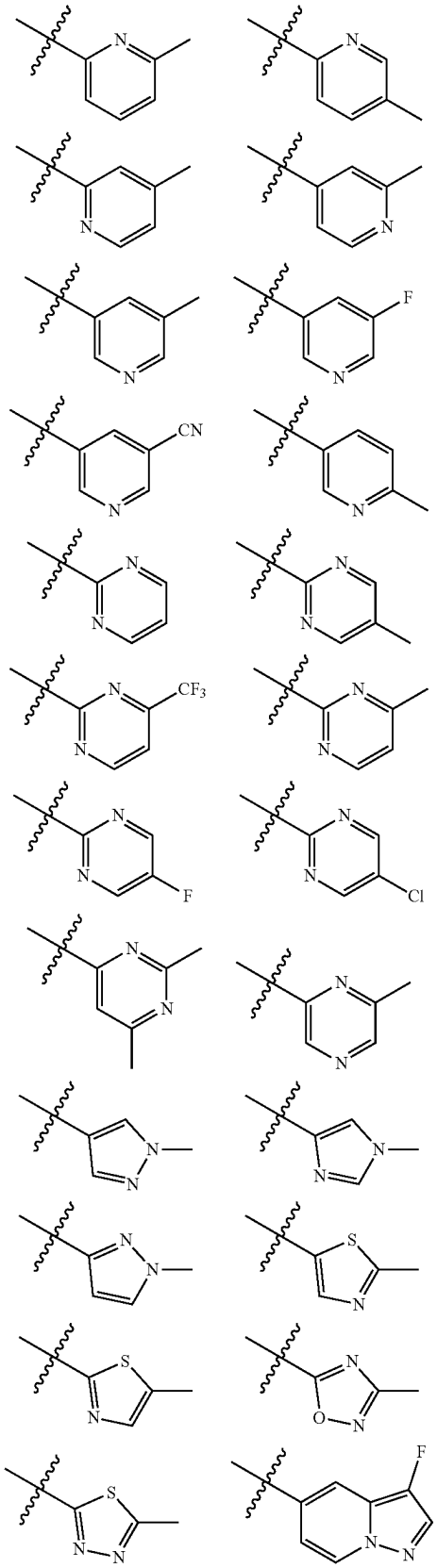

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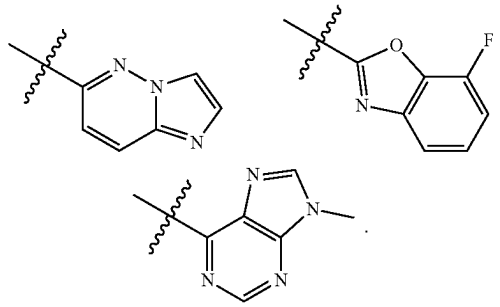
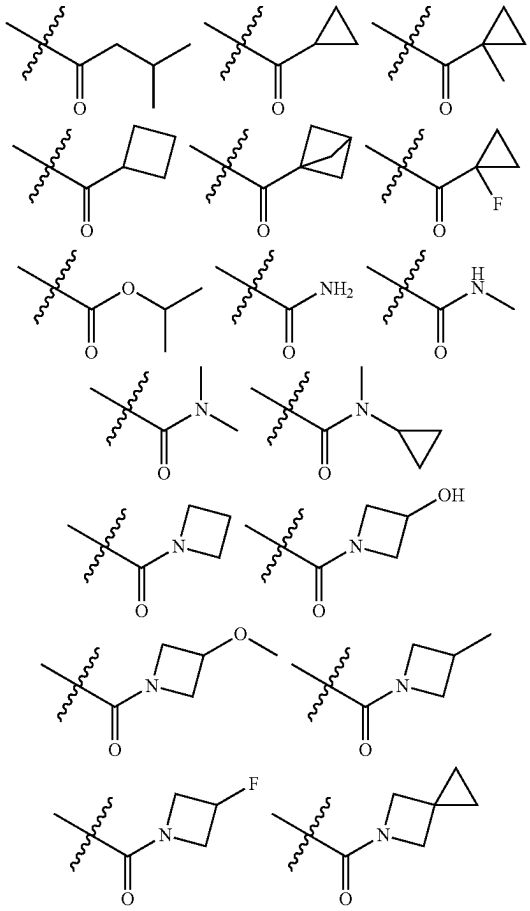


[0537] Embodiment 11. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^A is any of those shown in the exemplified compounds in Table A herein.

[0538] Embodiment 12. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^D is H, F, CN, acetenyl, methyl, ethyl, OCH_3, $NHCH_3$, or cyclopropyl.

[0539] Embodiment 13. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^D is selected from:



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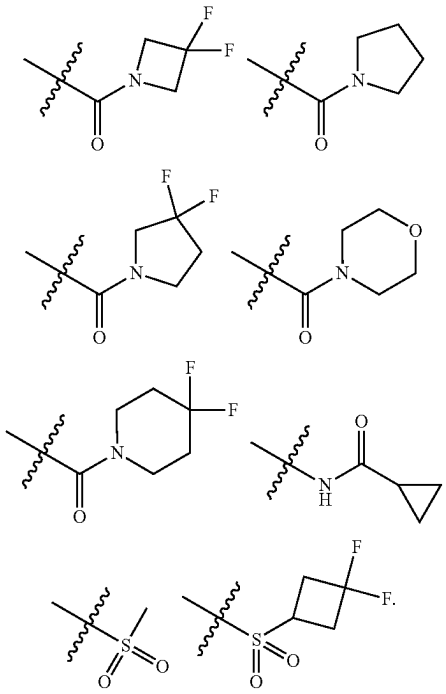
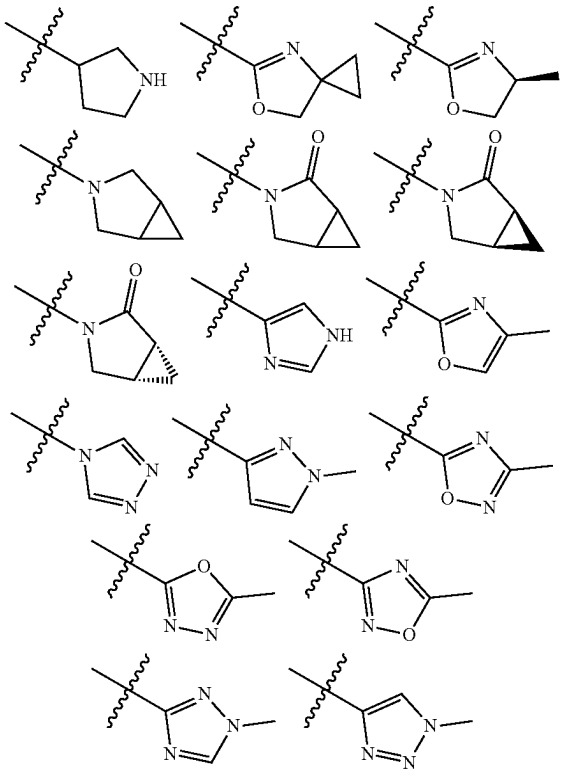


[0540] Embodiment 14. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^D is selected from:



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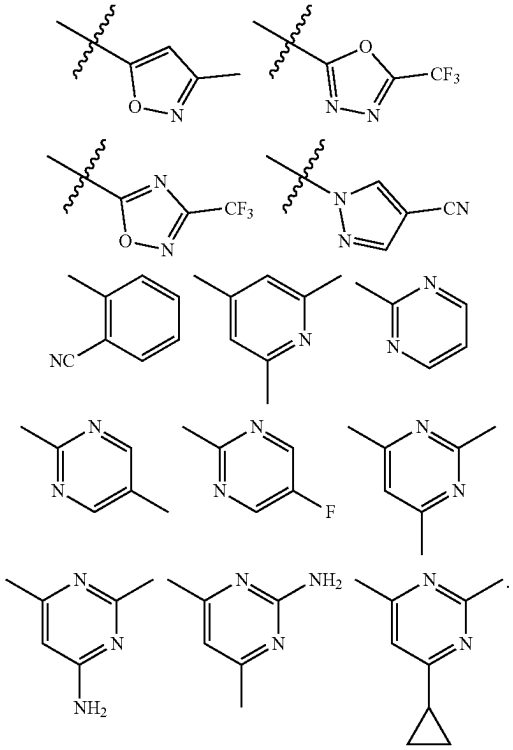
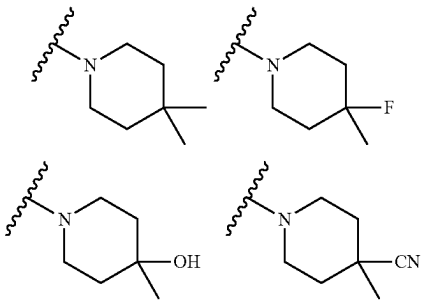


[0541] Embodiment 15. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^D is any of those shown in the exemplified compounds in Table A herein.

[0542] Embodiment 16. The compound of Embodiment 1, 10, or 11, or a pharmaceutically acceptable salt thereof, wherein as applicable, j is 0, or R^B is methyl and j is 1.

[0543] Embodiment 17. The compound of Embodiment 1, 12, 13, 14, or 15, or a pharmaceutically acceptable salt thereof, wherein as applicable, k is 0, or R^E is F, Cl, CN, or methyl and k is 1, or each R^E is independently F or methyl and k is 2.

[0544] Embodiment 18. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



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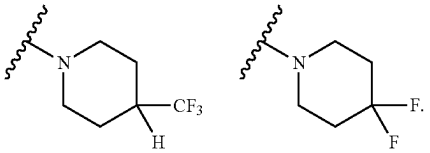
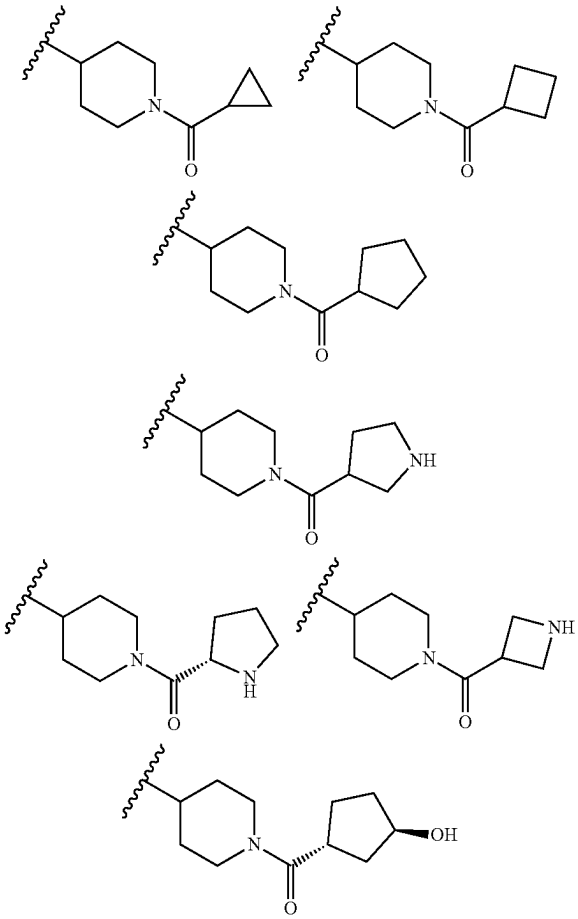


[0545] Embodiment 19. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



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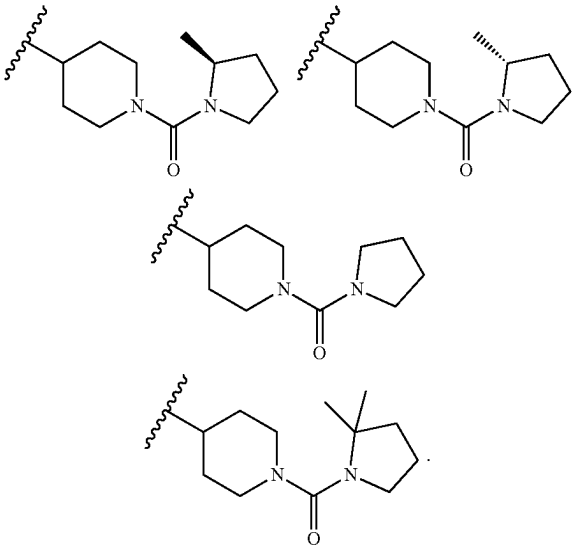
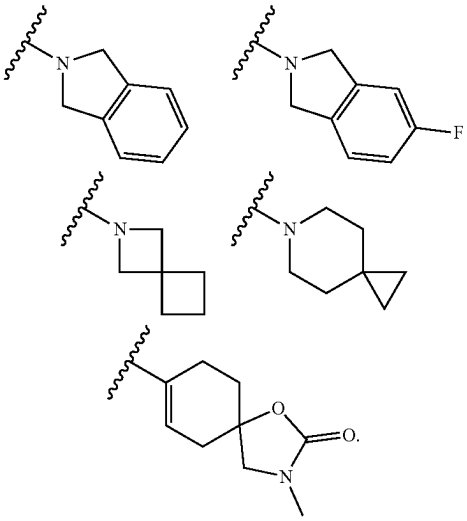
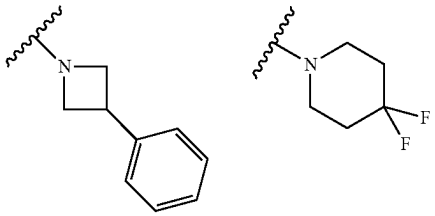


[0546] Embodiment 20. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



[0547] Embodiment 21. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



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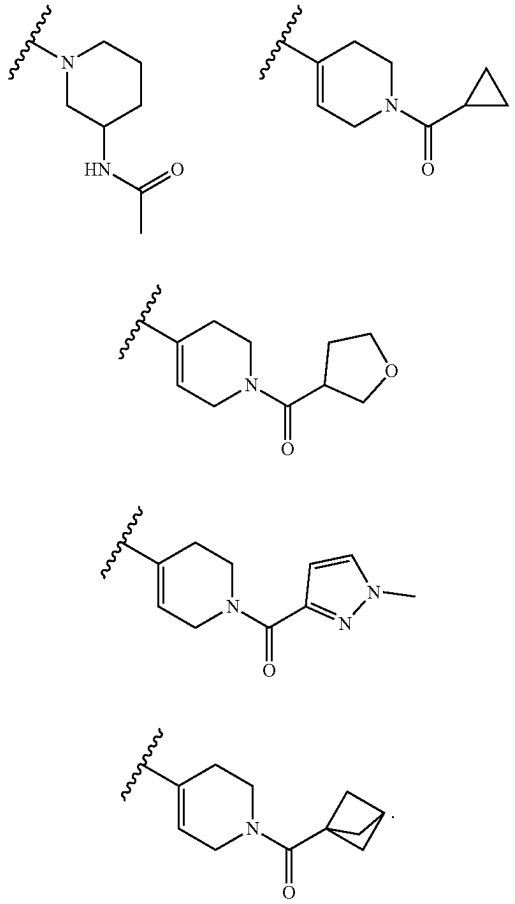

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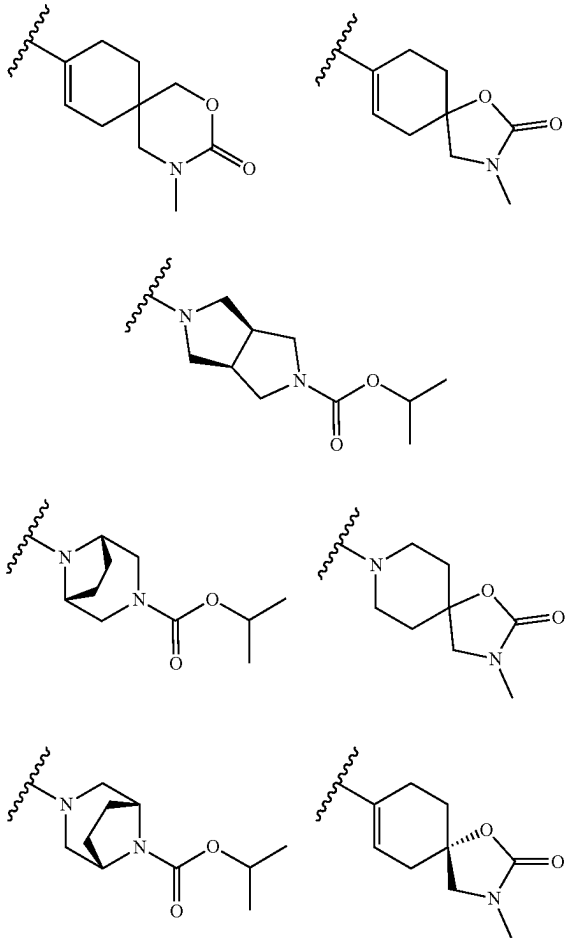
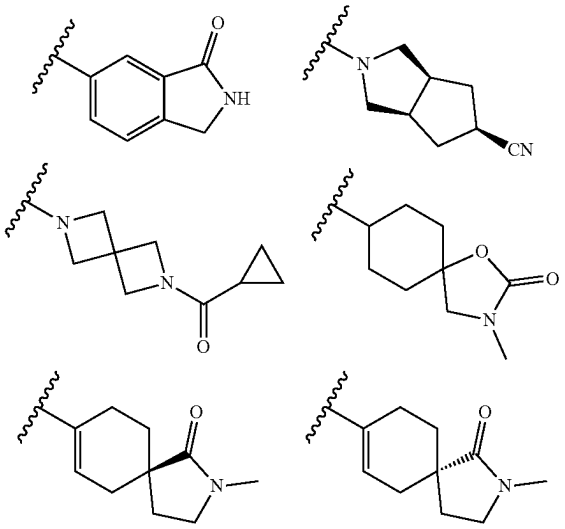
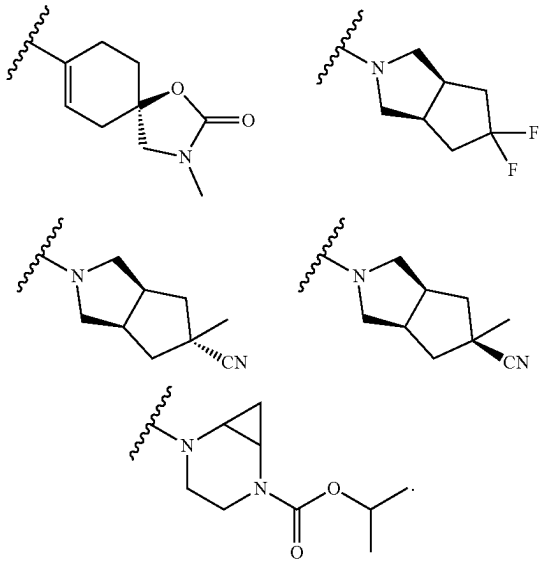
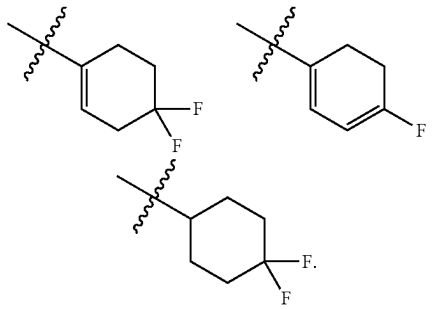


[0548] Embodiment 22. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:

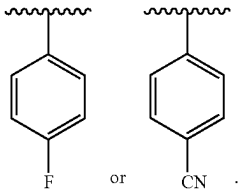




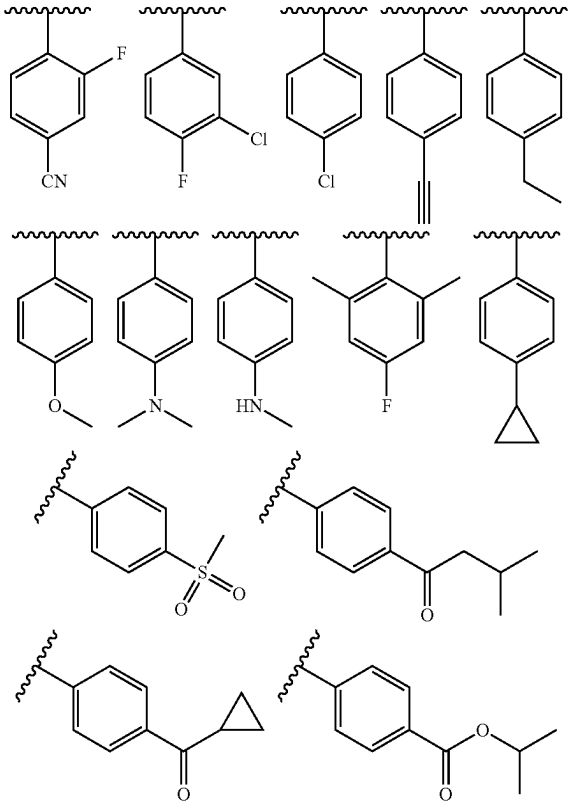
[0549] Embodiment 23. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



[0550] Embodiment 24. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



[0551] Embodiment 25. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



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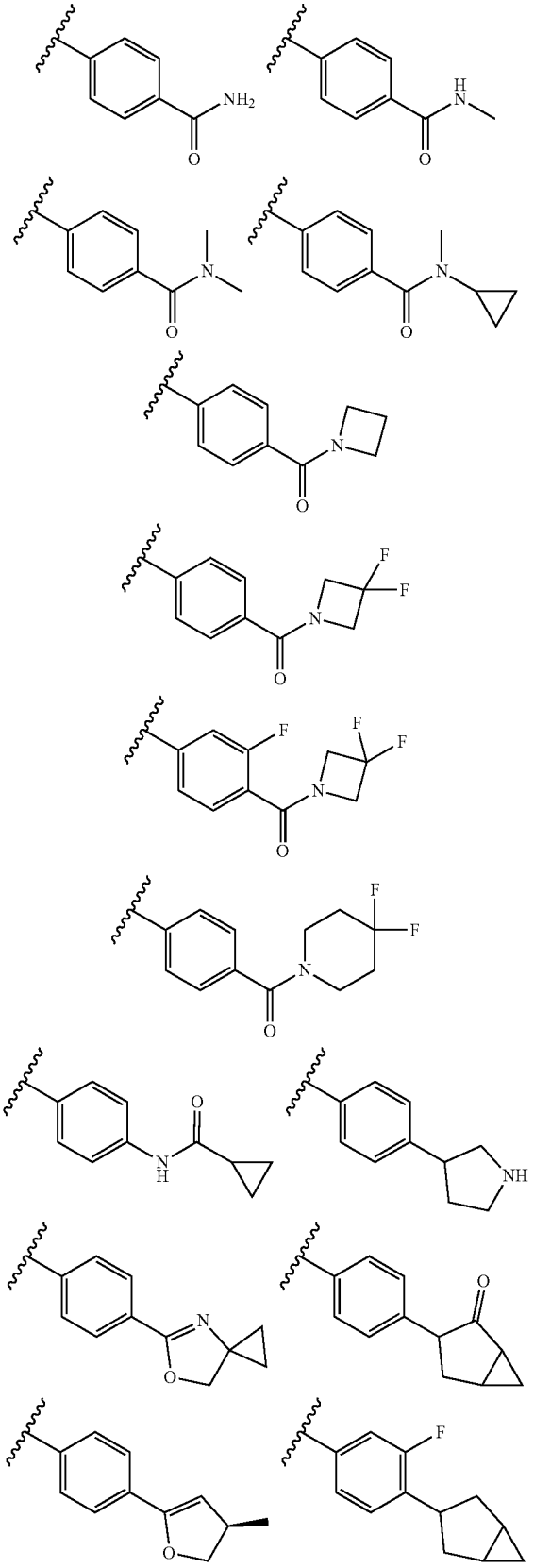

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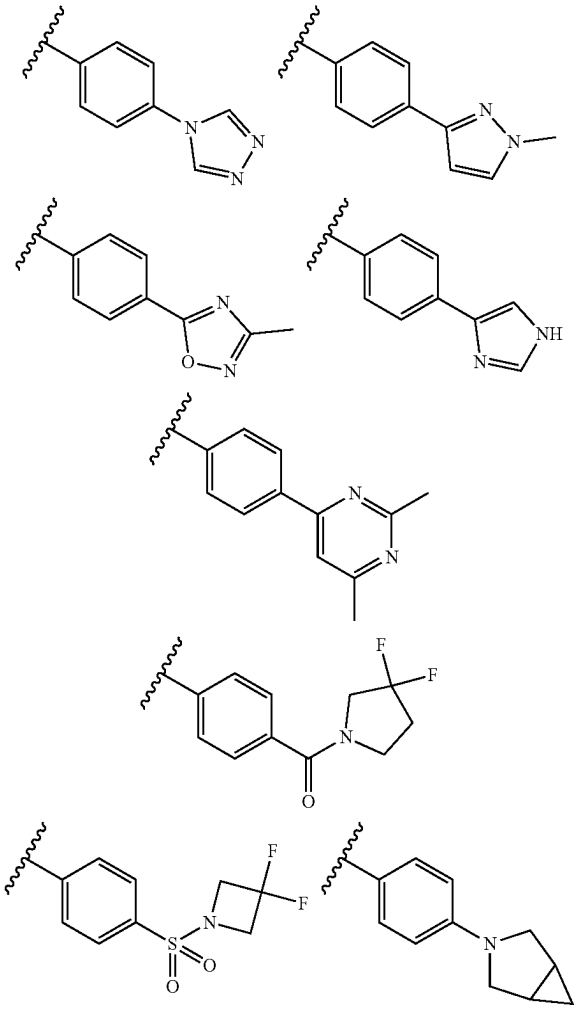
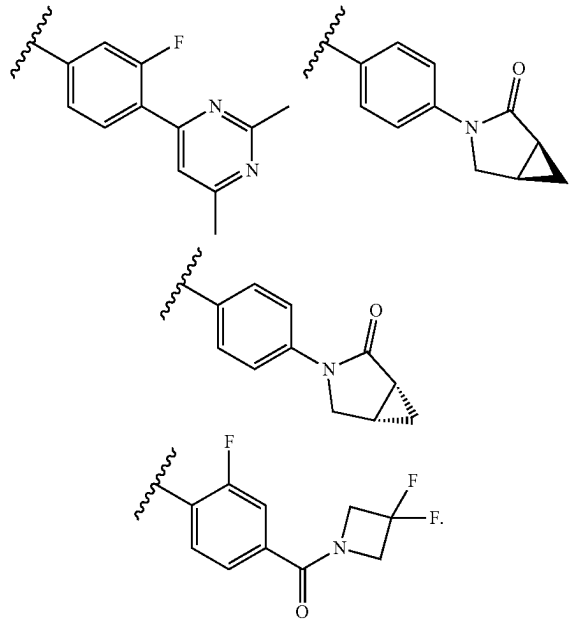
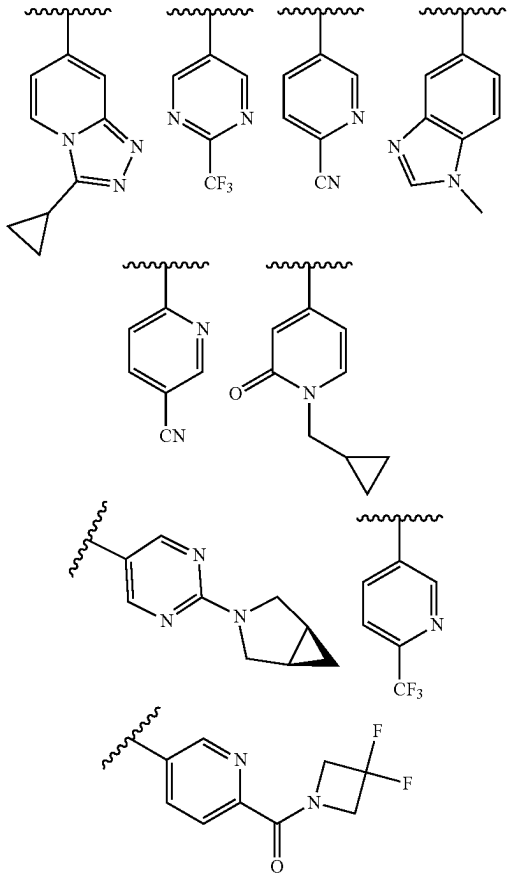
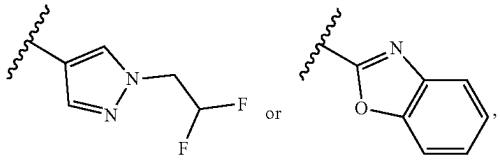




[0552] Embodiment 26. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



[0553] Embodiment 27. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



[0554] Embodiment 28. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^1 is any of those shown in the exemplified compounds in Table A herein.

[0555] Embodiment 29. The compound of any of Embodiments 1-28, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^{20} is hydrogen, or R^{20} is any of those shown in the exemplified compounds in Table A herein.

[0556] Embodiment 30. The compound of any of Embodiments 1-29, or a pharmaceutically acceptable

salt thereof, wherein as applicable, R^2 is any of those shown in the exemplified compounds in Table A herein.

[0557] Embodiment 31. The compound of any of Embodiments 1-30, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^3 is any of those shown in the exemplified compounds in Table A herein.

[0558] Embodiment 32. The compound of any of Embodiments 1-31, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^4 is any of those shown in the exemplified compounds in Table A herein.

[0559] Embodiment 33. The compound of any of Embodiments 1-32, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^5 is any of those shown in the exemplified compounds in Table A herein.

[0560] Embodiment 34. The compound of any of Embodiments 1-33, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^6 and R^7 are any of those shown in the exemplified compounds in Table A herein.

[0561] Embodiment 35. The compound of any of Embodiments 1-34, or a pharmaceutically acceptable salt thereof, wherein as applicable, one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl, and (i) the carbon attached to R^6 and R^7 has a S-configuration, e.g., have an enantiomeric excess (ee) of greater than 50%, such as greater than 80%, greater than 90%, greater than 95%, greater than 98%, greater than 99%, etc.; or (ii) the carbon attached to R^6 and R^7 has an R-configuration, e.g., have an enantiomeric excess (ee) of greater than 50%, such as greater than 80%, greater than 90%, greater than 95%, greater than 98%, greater than 99%, etc.

[0562] Embodiment 36. The compound of any of Embodiments 1-35, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^5 is any of those shown in the exemplified compounds in Table A herein.

[0563] Embodiment 37. The compound of any of Embodiments 1-36, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^9 is any of those shown in the exemplified compounds in Table A herein.

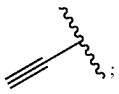
[0564] Embodiment 38. The compound of any of Embodiments 1-37, or a pharmaceutically acceptable salt thereof, characterized by one or more (e.g., 3 or more, 5 or more, or 7, 8, or 9) of the following:

[0565] 1) R^2 is methyl;

[0566] 2) R^3 is hydrogen;

[0567] 3) R^4 is methyl;

[0568] 4) R^4 is F, Cl, Br, or



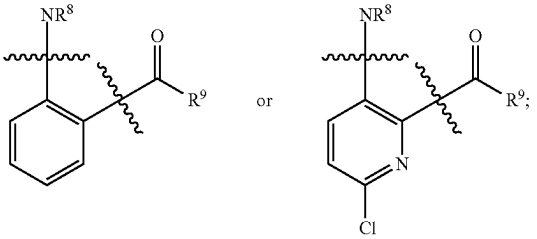
[0569] 5) R^5 is hydrogen;

[0570] 6) one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is methyl;

[0571] 7) R^8 is hydrogen;

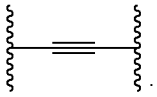
[0572] 8) R^9 is OH;

[0573] 9) L^2 is



[0574] 10) L^1 is absent; and

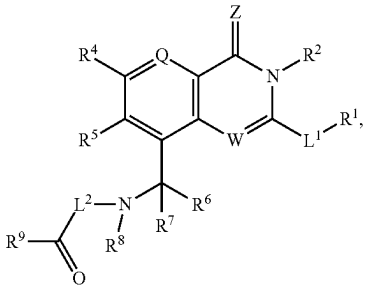
[0575] 11) L^1 is O, CH_2, or



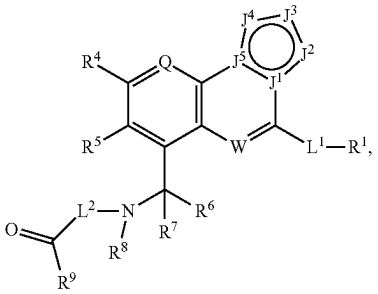
[0576] In some embodiments, the present disclosure also provides the following exemplary embodiments B1-87:

[0577] Embodiment B1. A compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof:

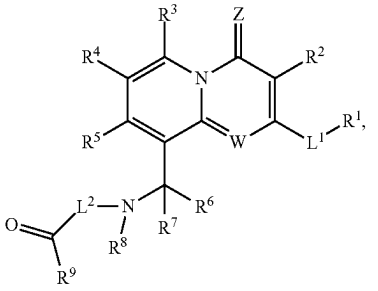
Formula I



Formula II



Formula III



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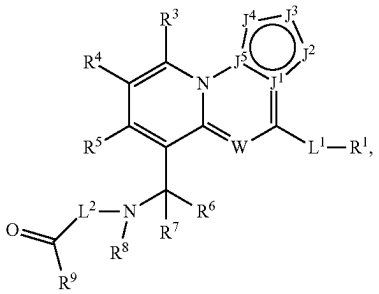
Formula IV



[0578] wherein:

[0579] W is CR^{10} or N, wherein R^{10} is hydrogen, deuterium, halogen, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or C_{1-4} alkoxy optionally substituted with 1-3 fluorine;

[0580] Q is N or CR^3; Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy;

[0581] J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5- or 6-membered ring having 2 or 3 ring heteroatoms, preferably, 2 or 3 ring nitrogen atoms, preferably, an optionally substituted 5-membered heteroaryl wherein J^4 is N, and J^5 is C or N;

[0582] L^1 is null, O, C(O), S, S(O), SO_2, NR^1, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein

[0583] R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0584] R^1 is a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0585] R^2, R^3, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1; preferably, in Formula I, R^2 is not halogen, CN, OH, or OG^1;

[0586] R^6 and R^1 are each independently hydrogen, deuterium, CN, or G^2

[0587] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0588] L^2 is optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0589] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$;

[0590] wherein:

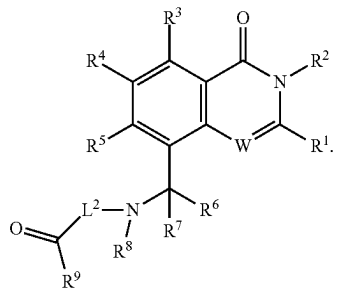
[0591] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0592] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

[0593] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

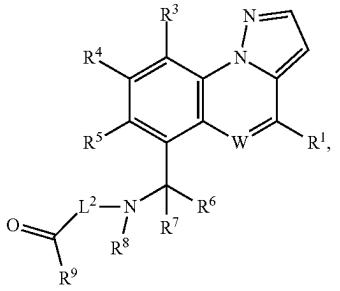
[0594] Embodiment B2. The compound of Embodiment B1, or a pharmaceutically acceptable salt thereof, having a structure according to Formula I-1:

Formula I-1

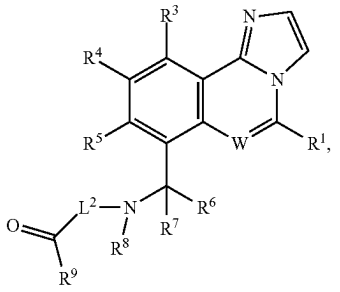


[0595] Embodiment B3. The compound of Embodiment B1, or a pharmaceutically acceptable salt thereof, having a structure according to Formula II-1, II-2, or II-3:

Formula II-1



Formula II-2



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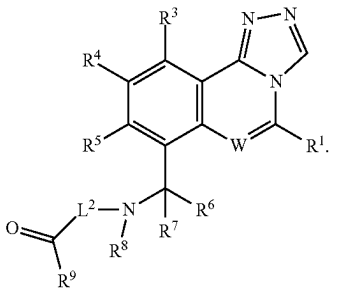
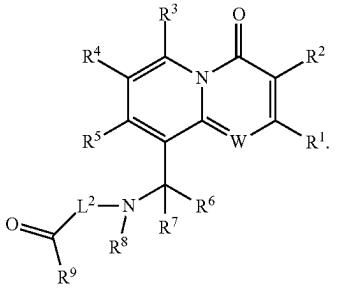
Formula II-3



[0596] Embodiment B4. The compound of Embodiment B1, or a pharmaceutically acceptable salt thereof, having a structure according to Formula III-1:

Formula III-1

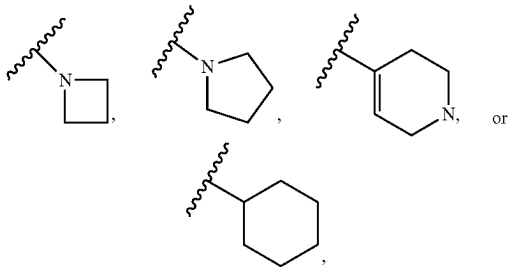


[0597] Embodiment B5. The compound of any one of Embodiments B1-4, or a pharmaceutically acceptable salt thereof, wherein W is N.

[0598] Embodiment B6. The compound of any one of Embodiments B1-4, or a pharmaceutically acceptable salt thereof, wherein W is CH.

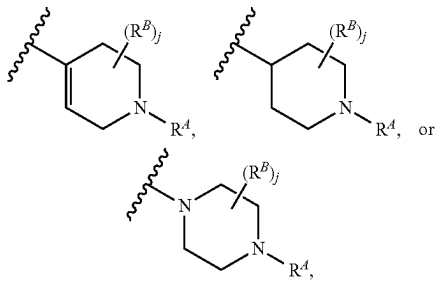
[0599] Embodiment B7. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-12 membered heterocyclyl having 1 or 2 ring heteroatoms each independently O, N, or S, wherein the heterocyclyl is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, oxo, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0600] Embodiment B8. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-7 membered monocyclic heterocyclyl having 1 or 2 ring heteroatoms each independently O, N, or S, such as



wherein the 4-7 membered monocyclic heterocyclyl is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, oxo, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or

[0601] R^1 is

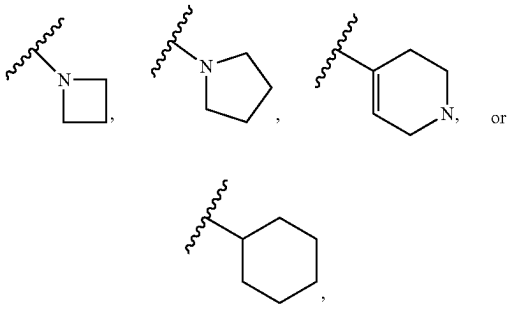


wherein R^A is G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$,

[0602] wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl; (ii) a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl,

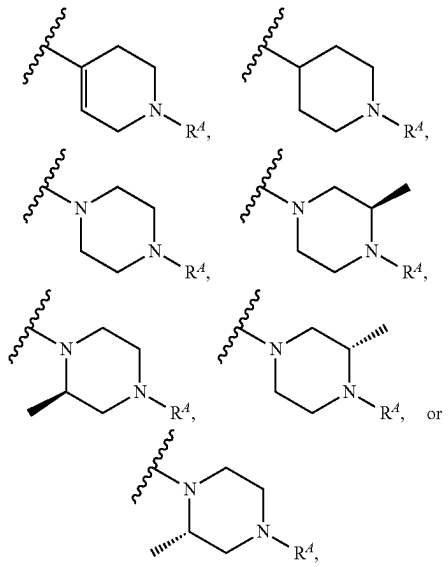
pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A1, wherein G^A1 at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; wherein R^B at each occurrence is independently F, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and j is 0, 1, or 2.

[0603] Embodiment B9. The compound of Embodiment B8, or a pharmaceutically acceptable salt thereof, wherein R^1 is

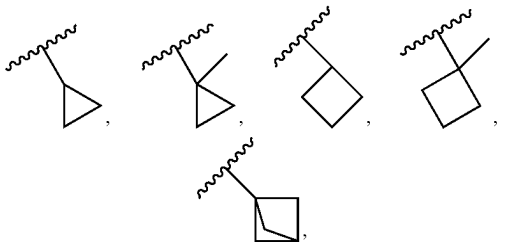


which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, NH—C(O)G^5, or C(O)G^5, wherein G^5 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or

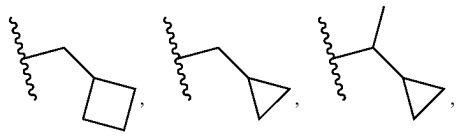
[0604] R^1 is



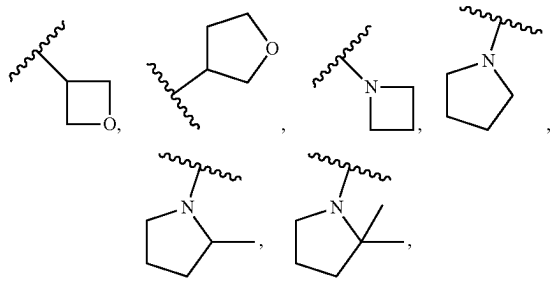
wherein R^A is G^{5A}, C(O)G^{5A}, C(O)OG^{5A}, C(O)NHG^{5A}, C(O)N$G^{5A}G^{5A}$, SO_2G^{5A}, SO_2NHG^{5A}, or $SO_2NG^{5A}G^{5A}$, wherein G^{5A} at each occurrence is independently (i) C_{1-4} alkyl; (ii) 3-12 membered ring, such as a 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1}, wherein G^{B1} at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3 F, C_{1-4} alkyl optionally substituted with 1-3F, or cyclopropyl; preferably, R^A is G^{5A}, C(O)G^{5A}, C(O)OG^{5A}, or SO_2G^5, wherein G^{5A} is (i) C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.); (ii) C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



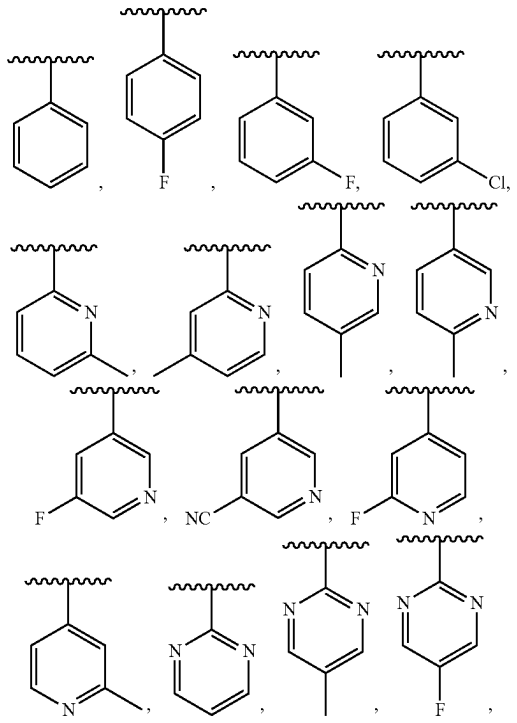
etc.; (iii) —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as



etc.; (iv) 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



etc.; (v) phenyl or 5- or 6-membered heteroaryl optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



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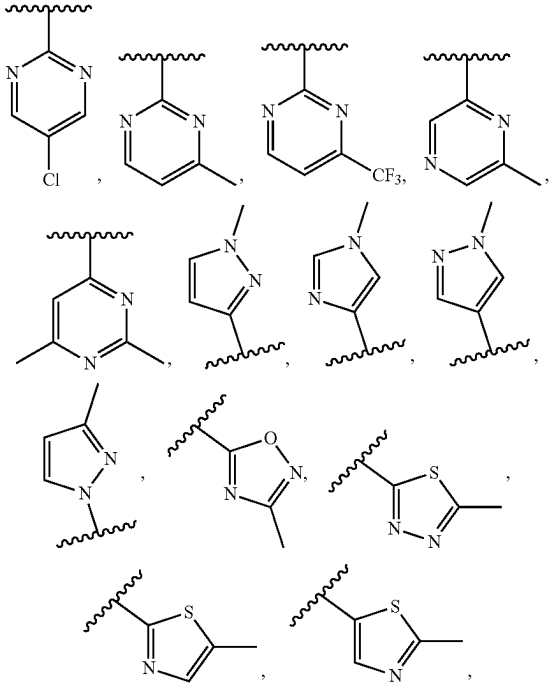
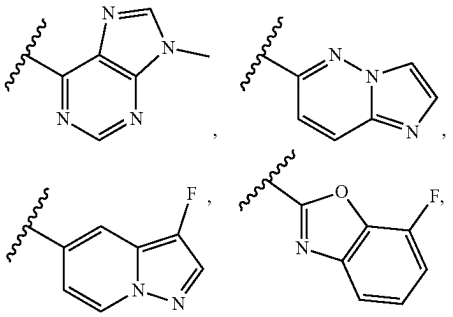


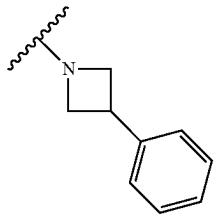
etc.; or (vi) bicyclic heteroaryl optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as

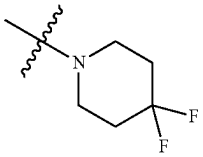


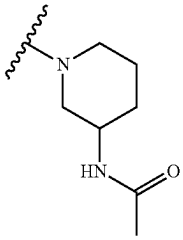
etc., or preferably, R^A is C(O)NHG^{5A} wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.),

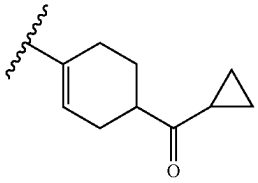
[0605] or R^A is C(O)N$G^{5A}G^{5A}$, wherein one instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl.

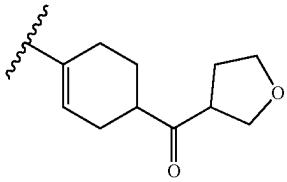
[0606] Embodiment B10. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from

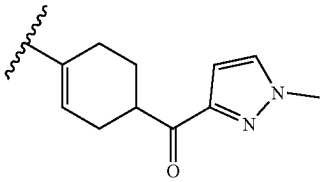


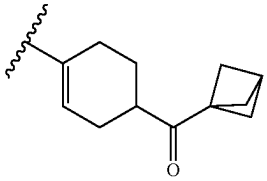






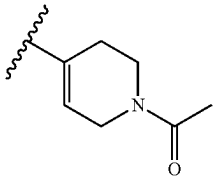


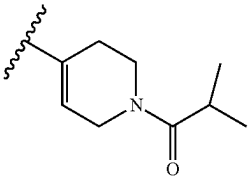


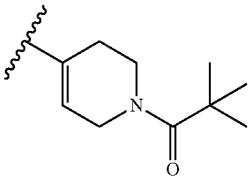


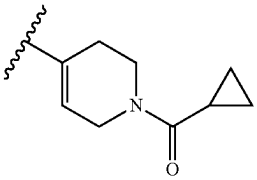
or

[0607] R^1 is selected from









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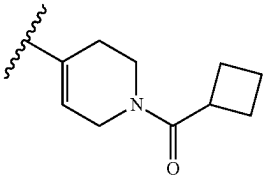

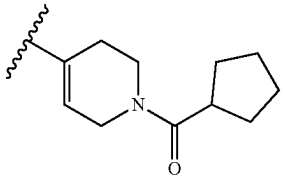

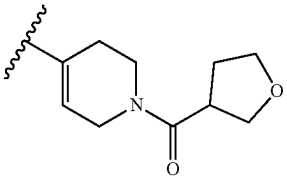

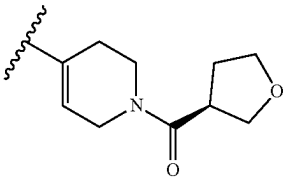

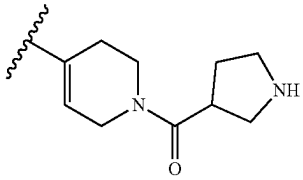

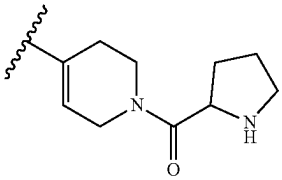

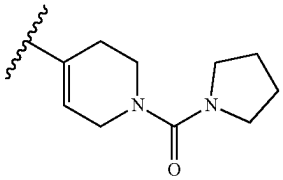

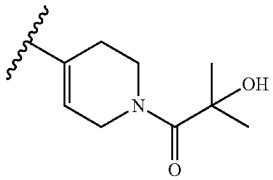

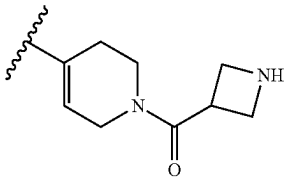

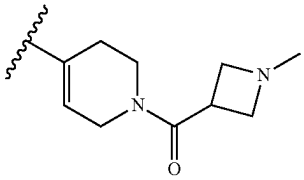

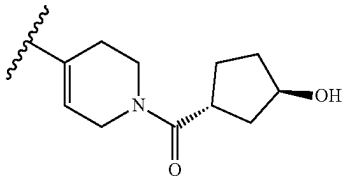

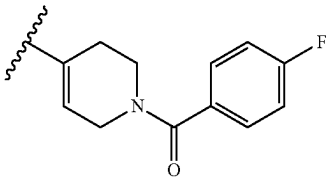

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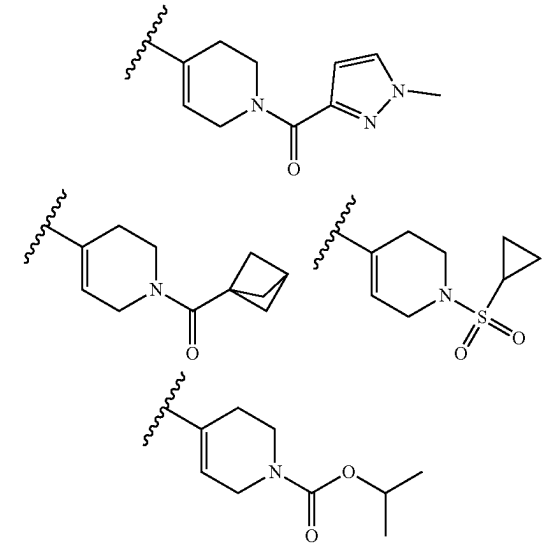

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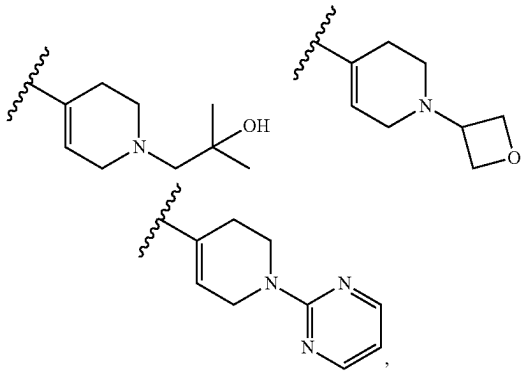

or

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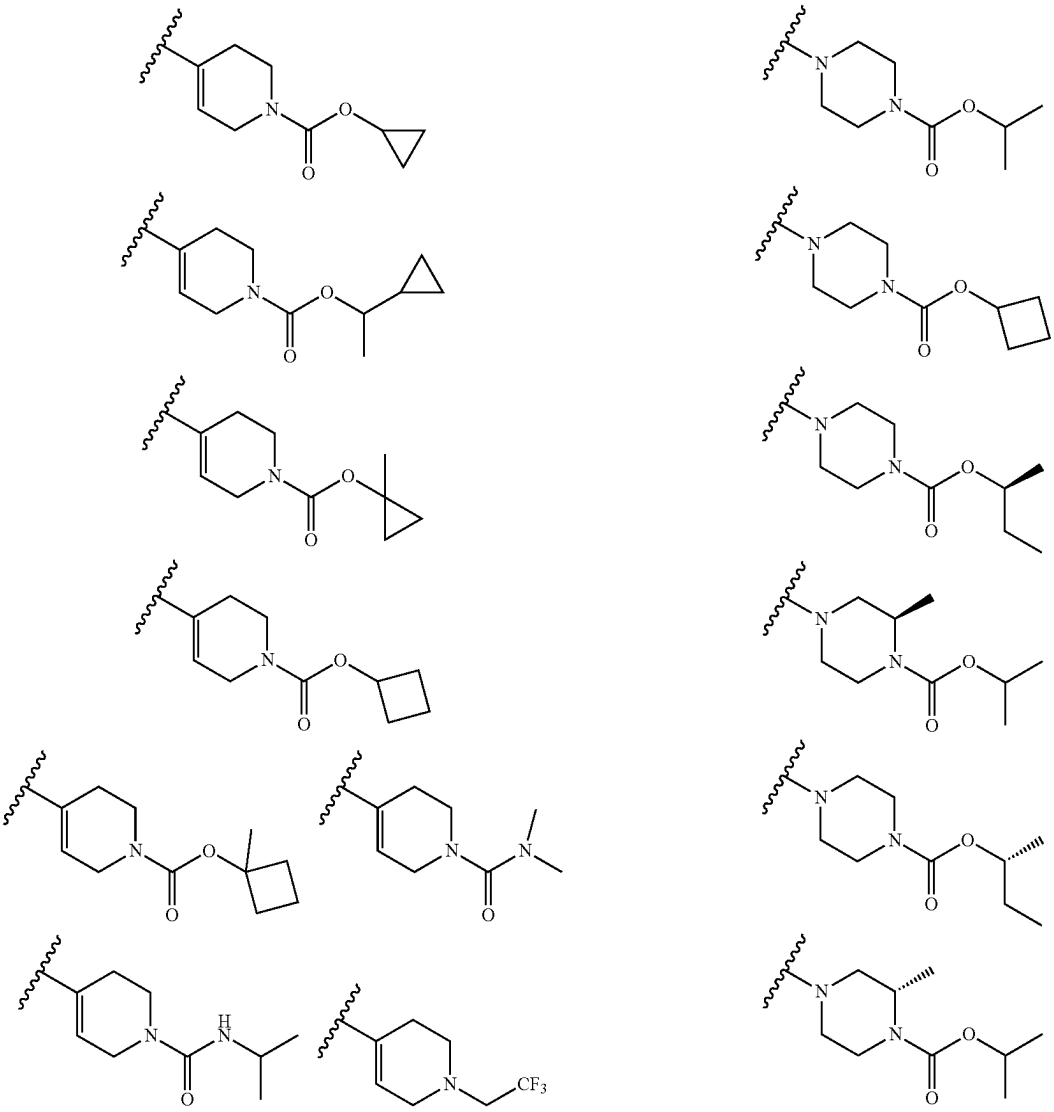

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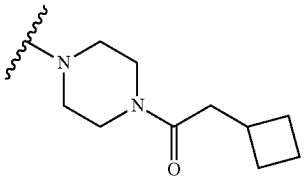

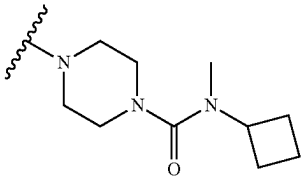

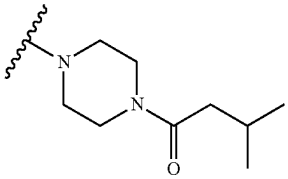

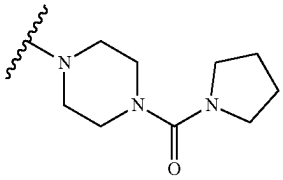

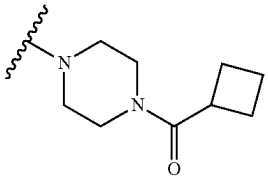

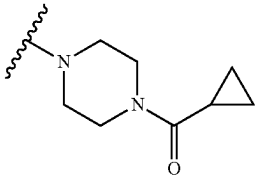

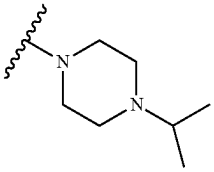

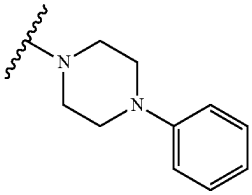

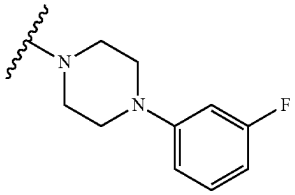

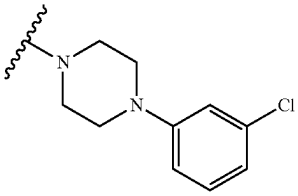

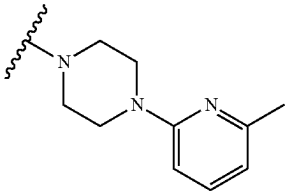

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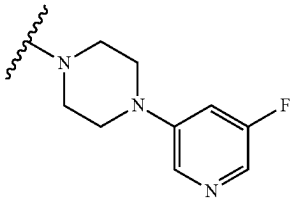

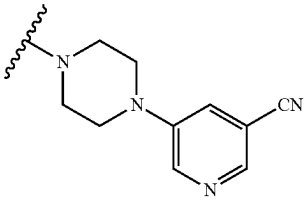

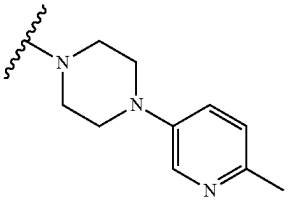

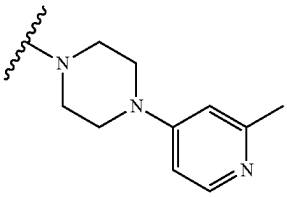

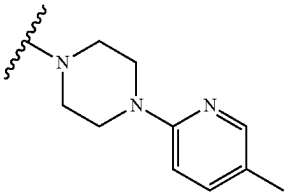

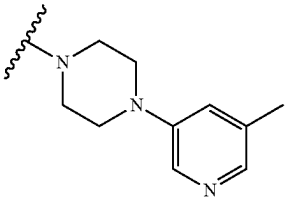

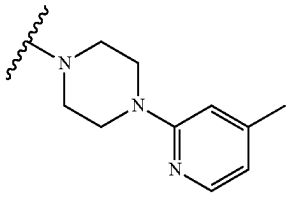

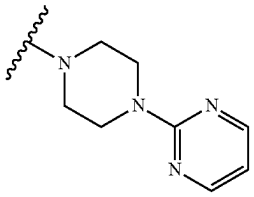

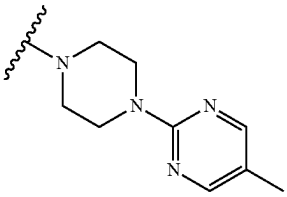

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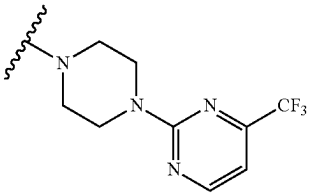

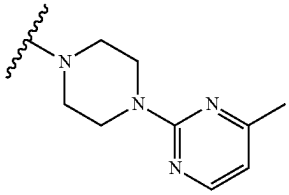

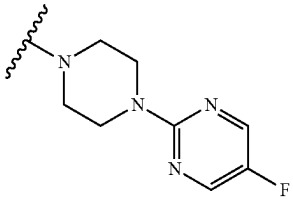

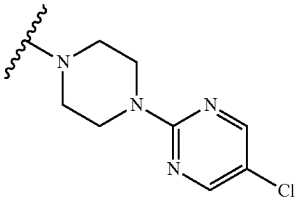

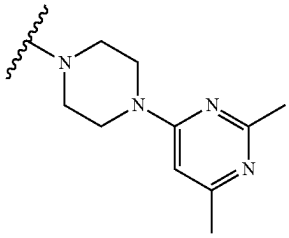

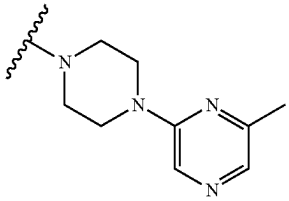

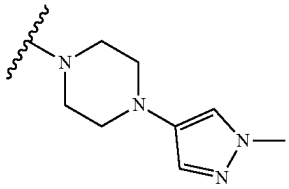

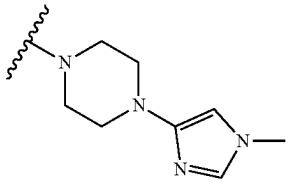

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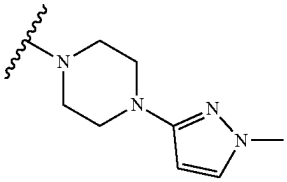

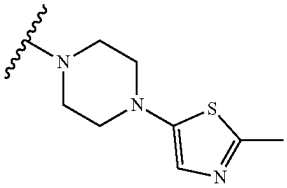

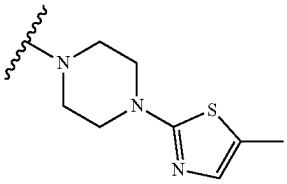

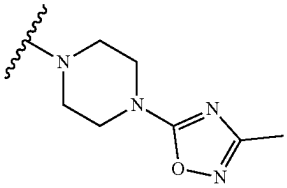

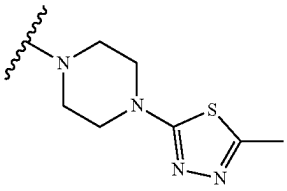

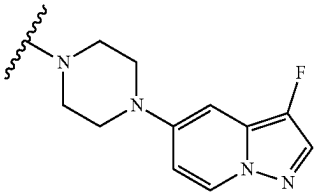

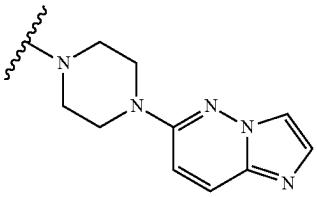

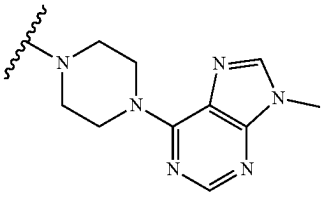

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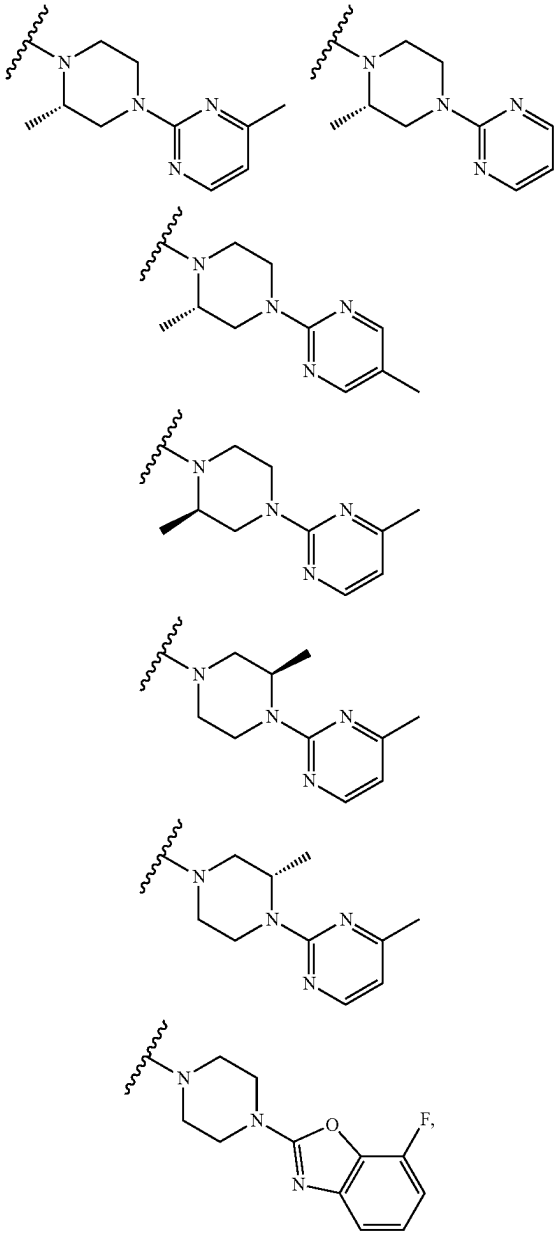
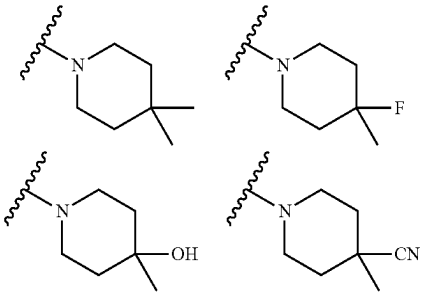


[0609] or R^1 is selected from



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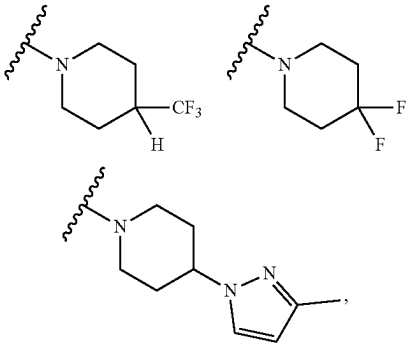
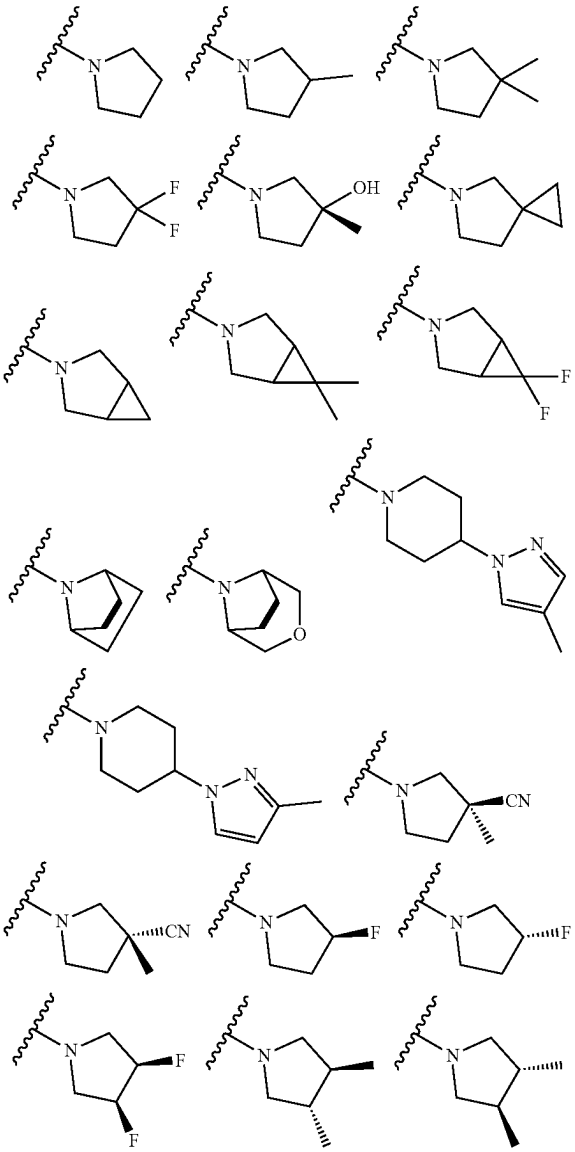


[0610] or R^1 is selected from



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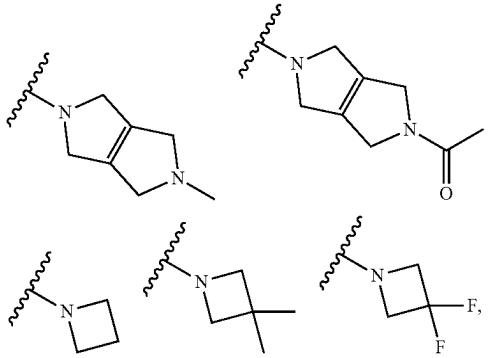
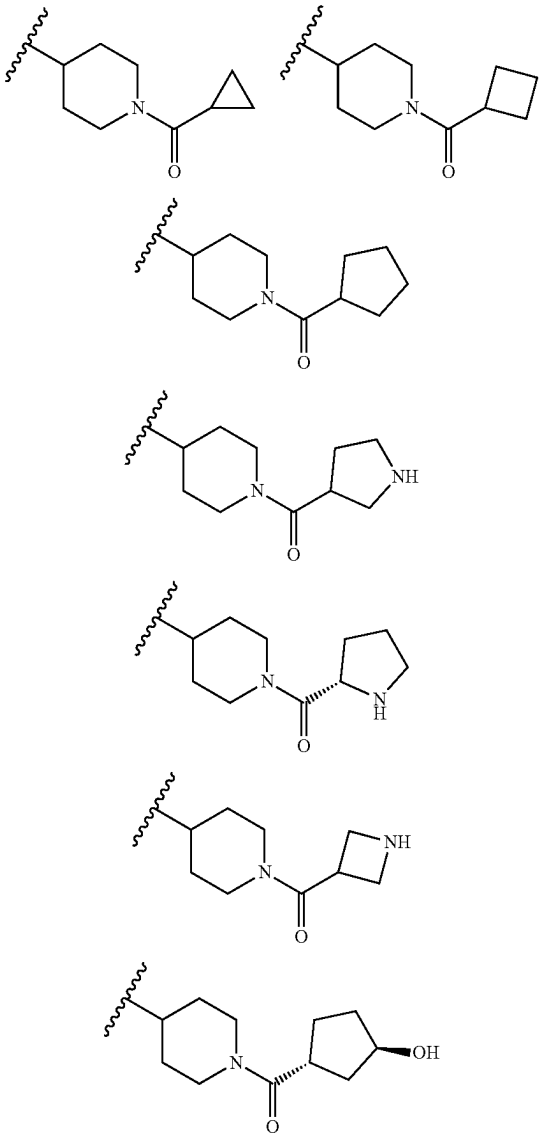


[0611] or R^1 is selected from



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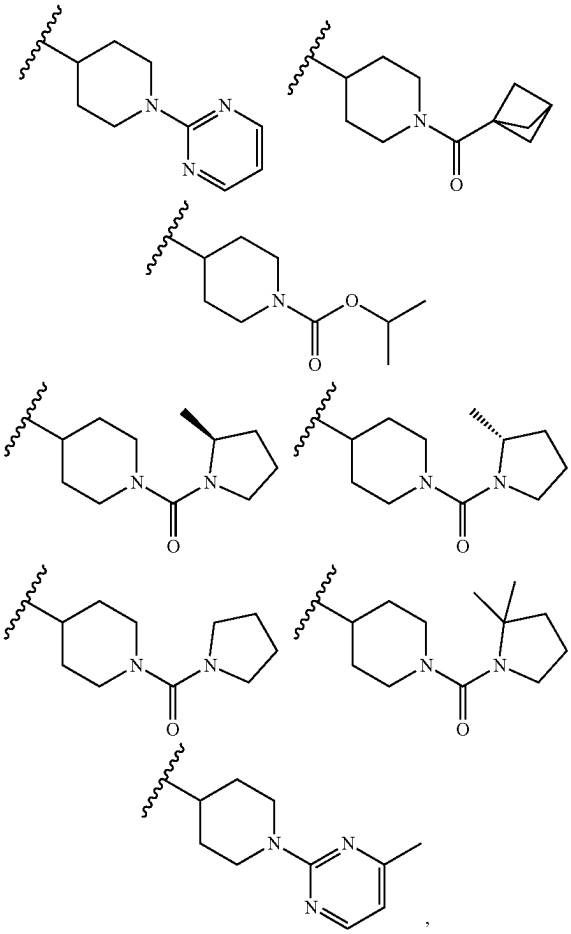
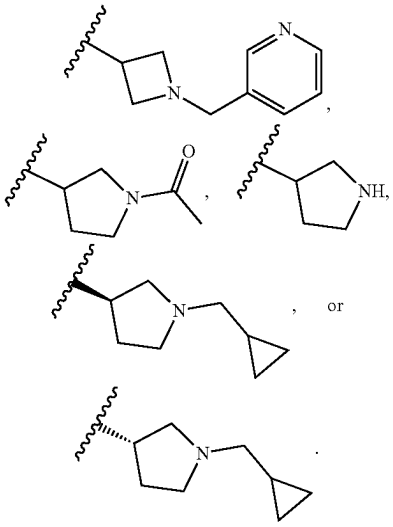
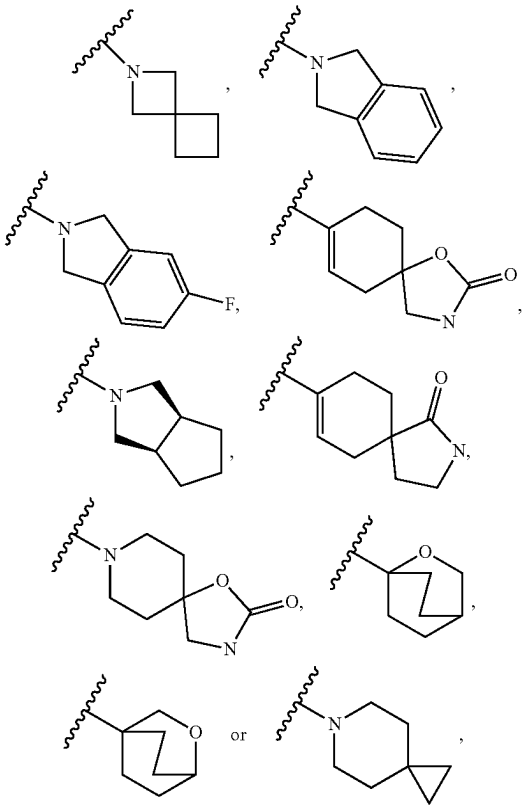


[0612] or R^1 is selected from



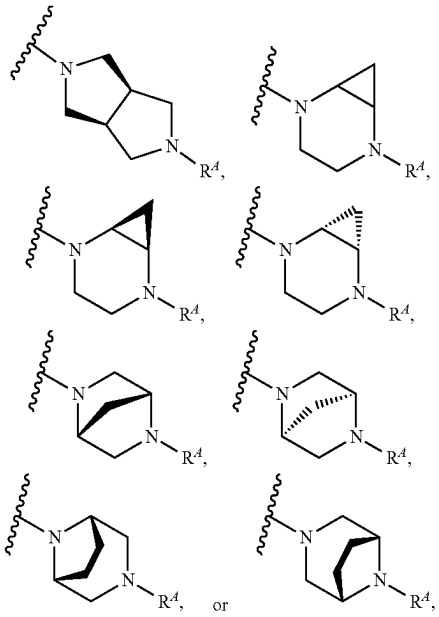
[0613] Embodiment B11. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable

salt thereof, wherein R^1 is a 6-12 membered (preferably 7-11 membered, such as 8, 9, or 10-membered) polycyclic heterocyclyl (such as spiro, fused, or bridged bicyclic heterocyclyl) having 1-3, such as 1 or 2, ring heteroatoms each independently O, N, or S, such as,



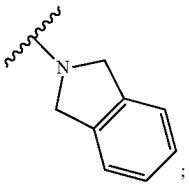
wherein each ring of the 6-12 membered polycyclic heterocyclyl is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, oxo, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, for example, the substituents can be independently selected from F, CN, methyl, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, or $C(O)NG^4G^4$, wherein G^4 is defined above; or

[0614] R^1 is

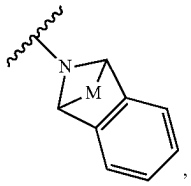


wherein R^A is G^4, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-7 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

[0615] Embodiment B12. The compound of Embodiment B11, or a pharmaceutically acceptable salt thereof, wherein R^1 is a)



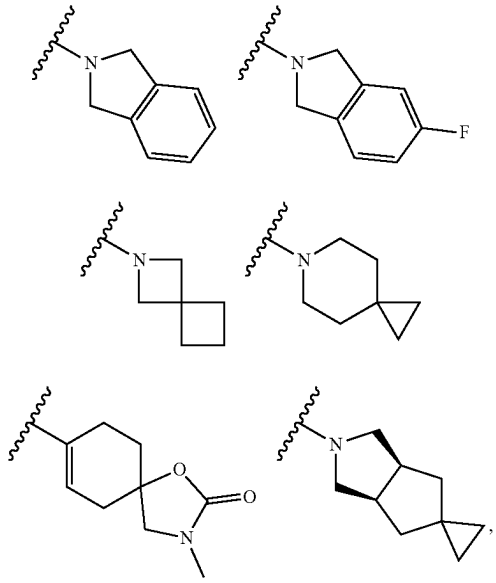
or b)



wherein M is —CH_2—, or —CH_2CH_2—;

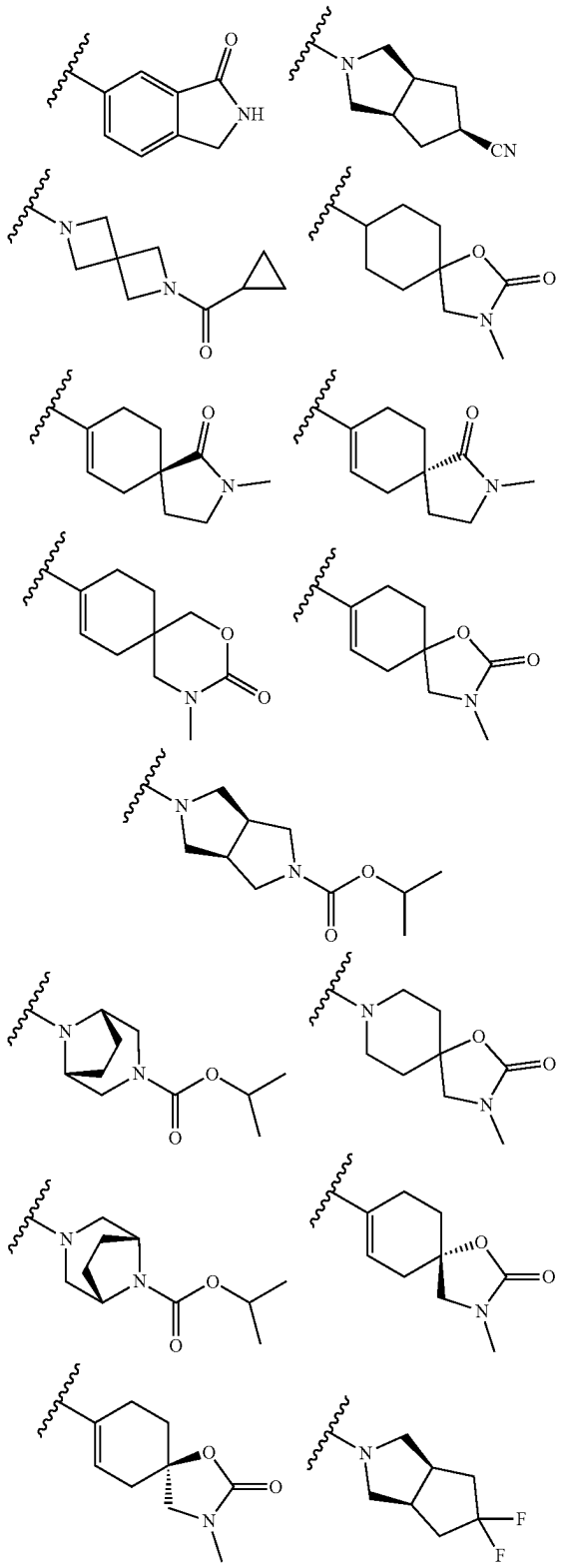
[0616] wherein each a) or b) is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—C(O)G^5, or C(O)G^5, wherein G^5 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0617] Embodiment B13. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from



or

[0618] R^1 is selected from



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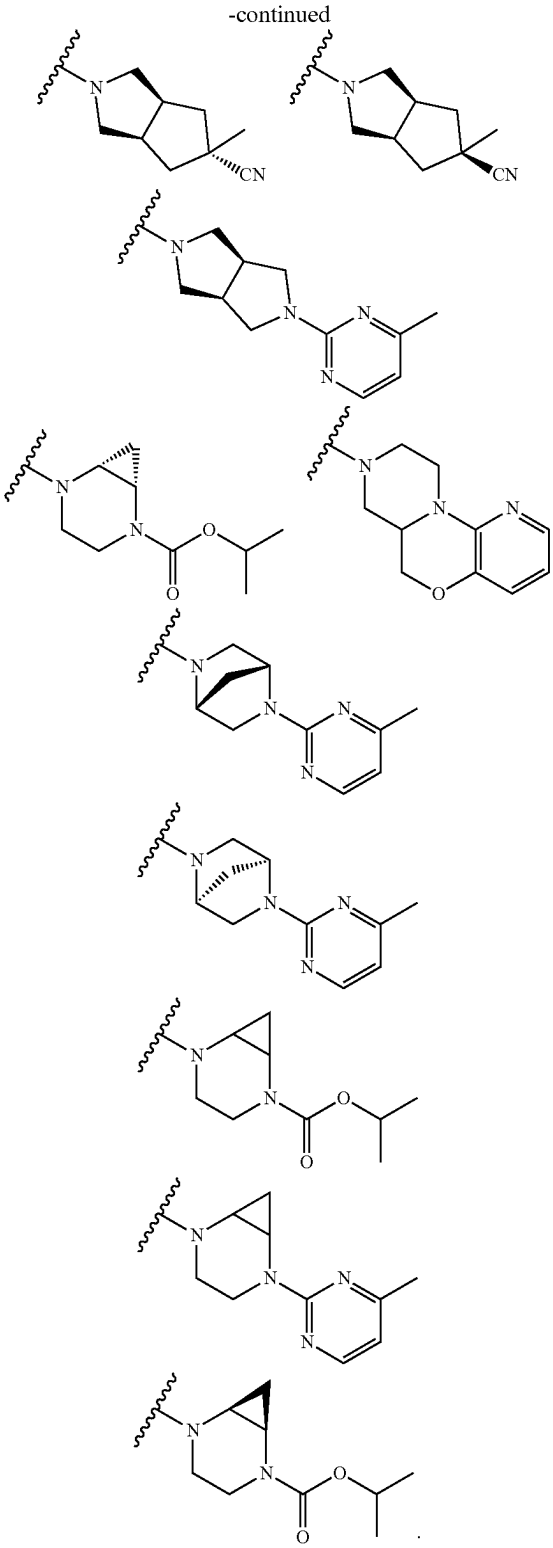
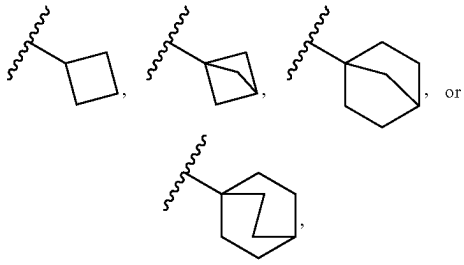
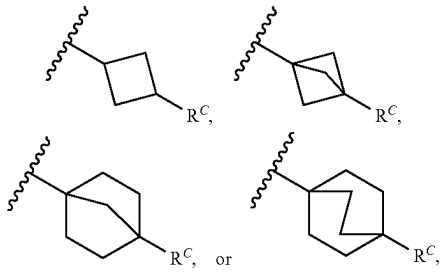


[0619] Embodiment B14. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-10 (e.g., 4, 5, 6, 7, 8, 9, or 10) membered carbocyclyl, such as

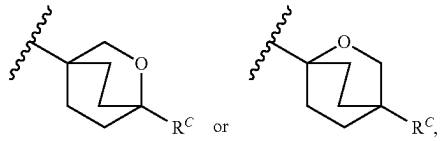


which is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$,

[0620] wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl or or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or



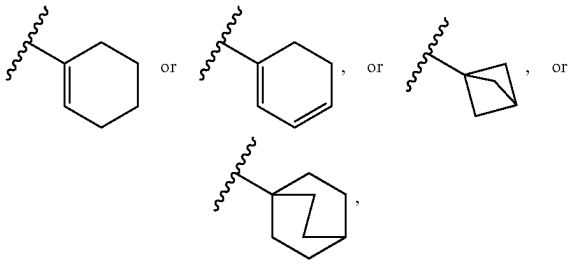
or R^1 is



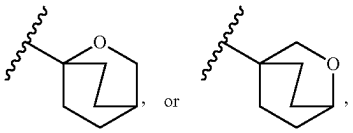
wherein R^C is CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl; (ii) a 3-12 membered ring, such as

3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

[0621] Embodiment B15. The compound of Embodiment B14, or a pharmaceutically acceptable salt thereof, wherein R^1 is

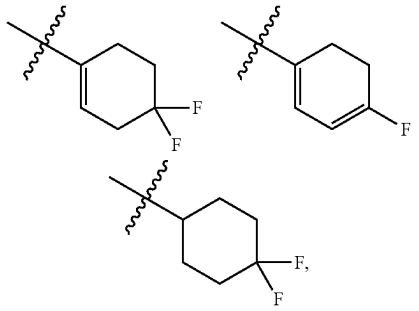


or R^1 is



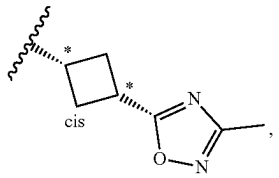
each of which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—C(O)G^5, or C(O)G^5, wherein G^5 at each occurrence is independently C_{1-4} alkyl or 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0622] Embodiment B16. The compound of Embodiment B14, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from



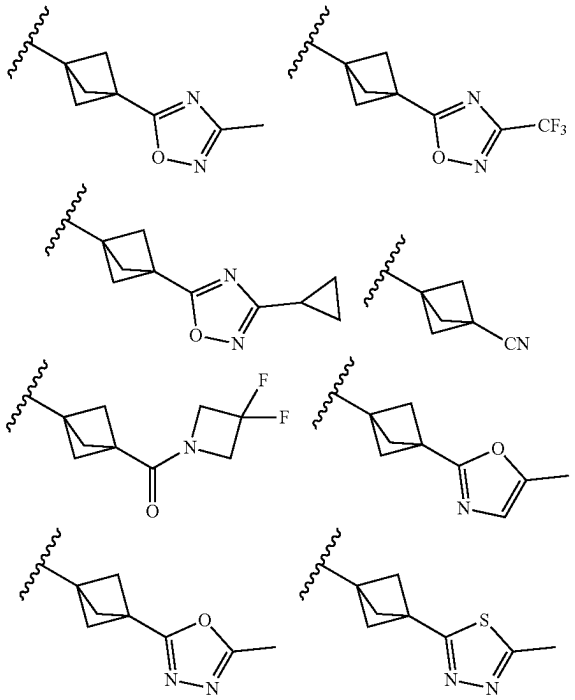
or

[0623] R^1 is



or,

[0624] R^1 is selected from



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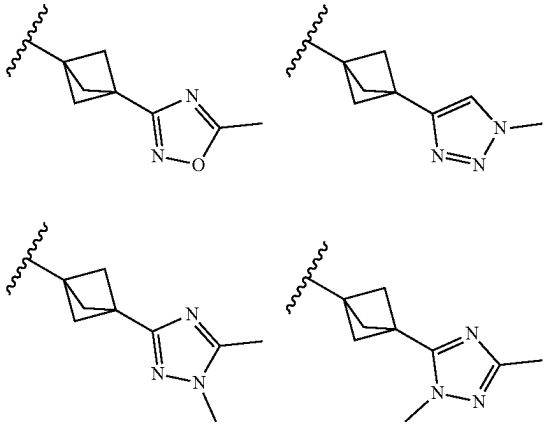

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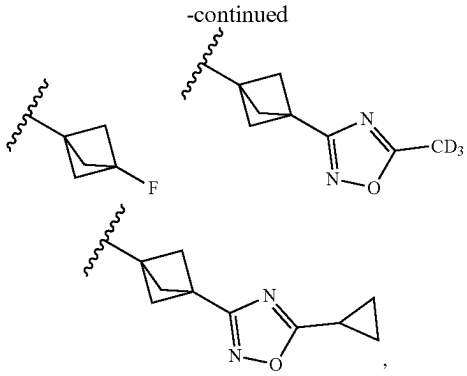
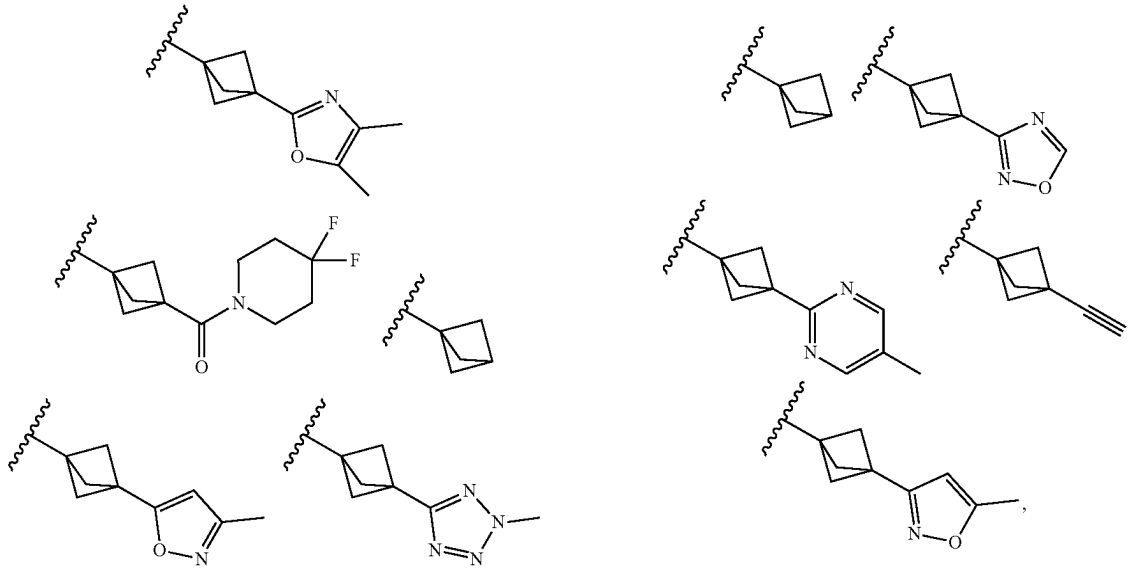


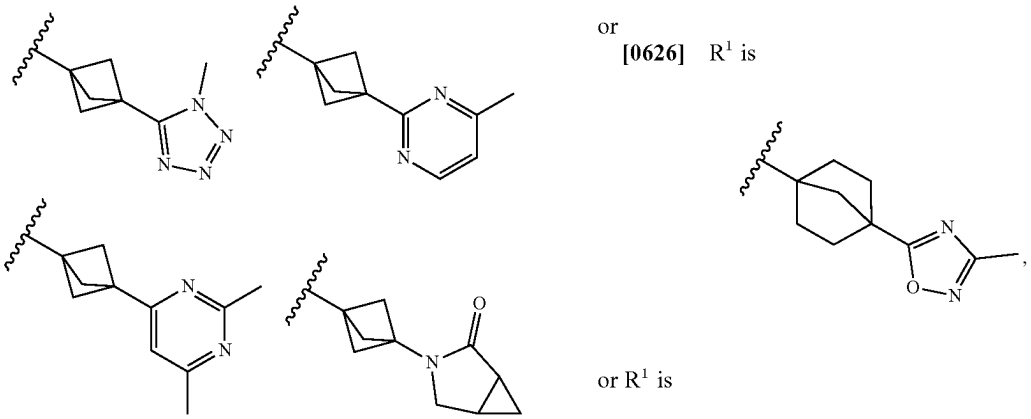
or

[0625] R^1 is selected from

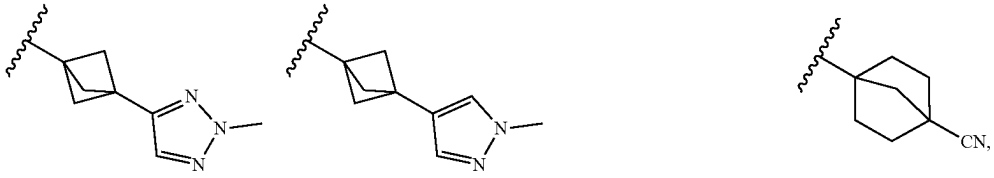


or

[0626] R^1 is

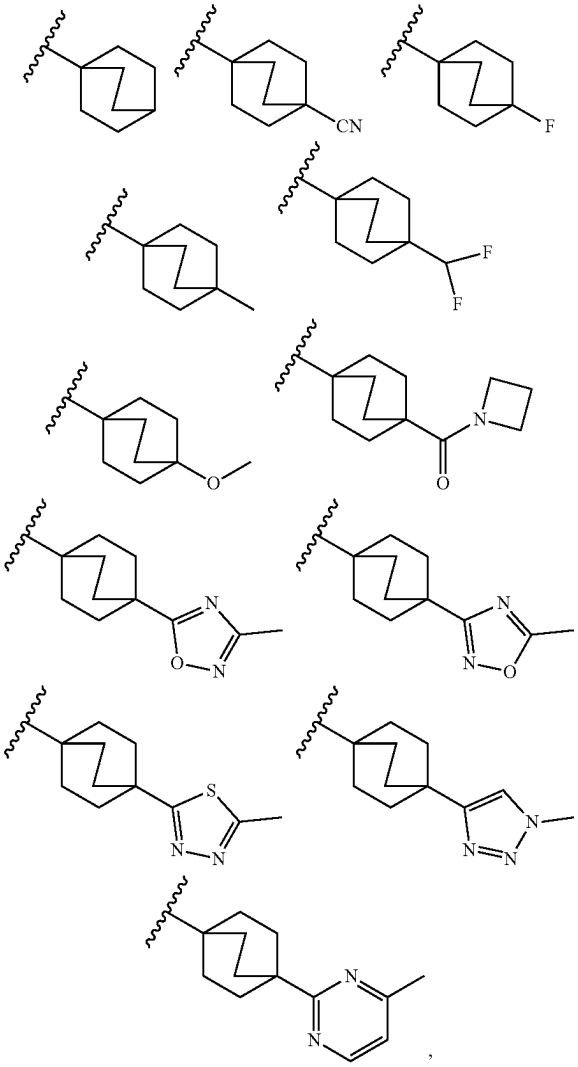


or R^1 is



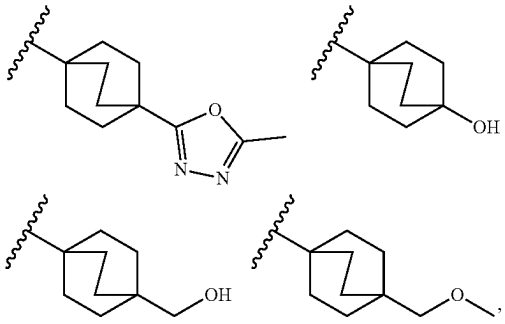
or

[0627] R^1 is selected from



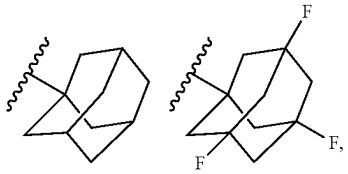
or

[0628] R^1 is selected from



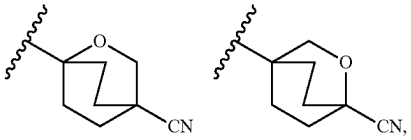
or

[0629] R^1 is selected from



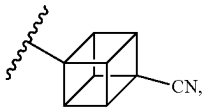
or

[0630] R^1 is selected from

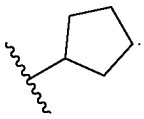


or

[0631] R^1 is selected from



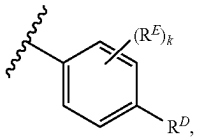
[0632] R^1 is



[0633] Embodiment B17. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is a phenyl, which is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium,

halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or

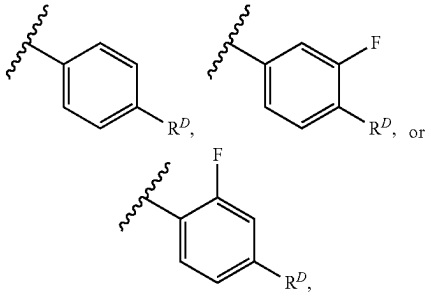
[0634] R^1 is



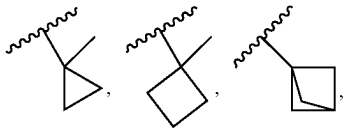
wherein R^D is halogen, CN, G^{4B}, OG^{4B}, NHG^{4B}, $NG^{4B}G^{4B}$, $C(O)G^{4B}$, $OC(O)G^{4B}$, $NHC(O)G^{4B}$, $NG^{4B}C(O)G^{4B}$, $C(O)OG^{4B}$, $C(O)NHG^{4B}$, $C(O)NG^{4B}G^{4B}$, SO_2G^{4B}, SO_2NHG^{4B}, or $SO_2NG^{4B}G^{4B}$, wherein G^{4B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl a 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; wherein R^E at each occurrence is independently F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, C_{1-4} heteroalkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and k is 0, 1, or 2.

[0635] Embodiment B18. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is a phenyl, which is optionally substituted with 1-3 substituents independently selected from deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, and C_{1-4} alkyl optionally substituted with 1-3F, or

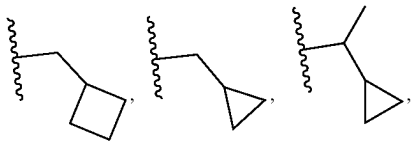
[0636] R^1 is



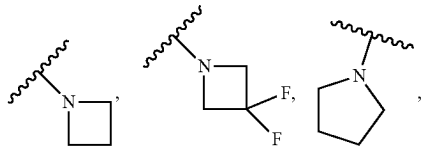
wherein R^D is G^{5B}, NHG^{5B}, $NG^{5B}G^{5B}$, $C(O)G^{5B}$, $C(O)OG^{5B}$, $C(O)NHG^{5B}$, $C(O)NG^{5B}G^{5B}$, SO_2G^{5B}, SO_2NHG^{5B}, or $SO_2NG^{5B}G^{5B}$, wherein G^{5B} at each occurrence is independently (i) C_{1-4} alkyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring, such as —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl a 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1}, or one or more (e.g., 1, 2, or 3) G^{B2}, wherein G^{B1} at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or cyclopropyl, wherein G^{B2} at each occurrence is independently deuterium, F, Cl, CN, OH, NH_2, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl; preferably, R^D is G^{5B}, $C(O)G^{5B}$, $C(O)OG^{5B}$, or SO_2G^{5B}, wherein G^{5B} is (i) C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.); (ii) C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



etc.; (iii) —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as,



etc.; (iv) 4-7 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



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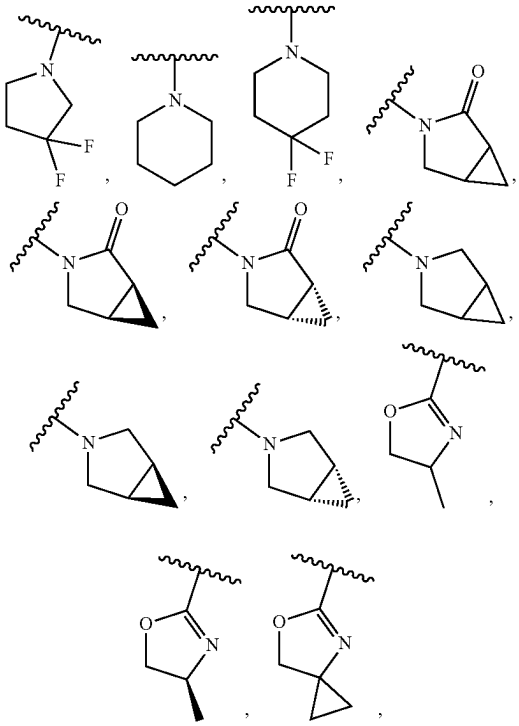
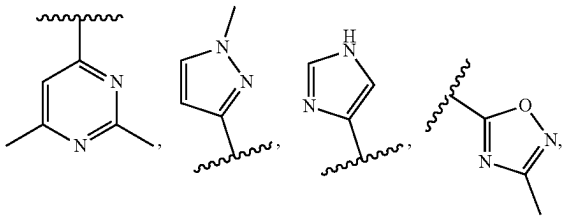


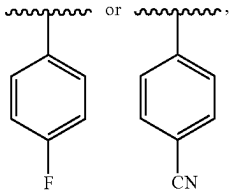
etc.; or (v 5- or 6-membered heteroaryl optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



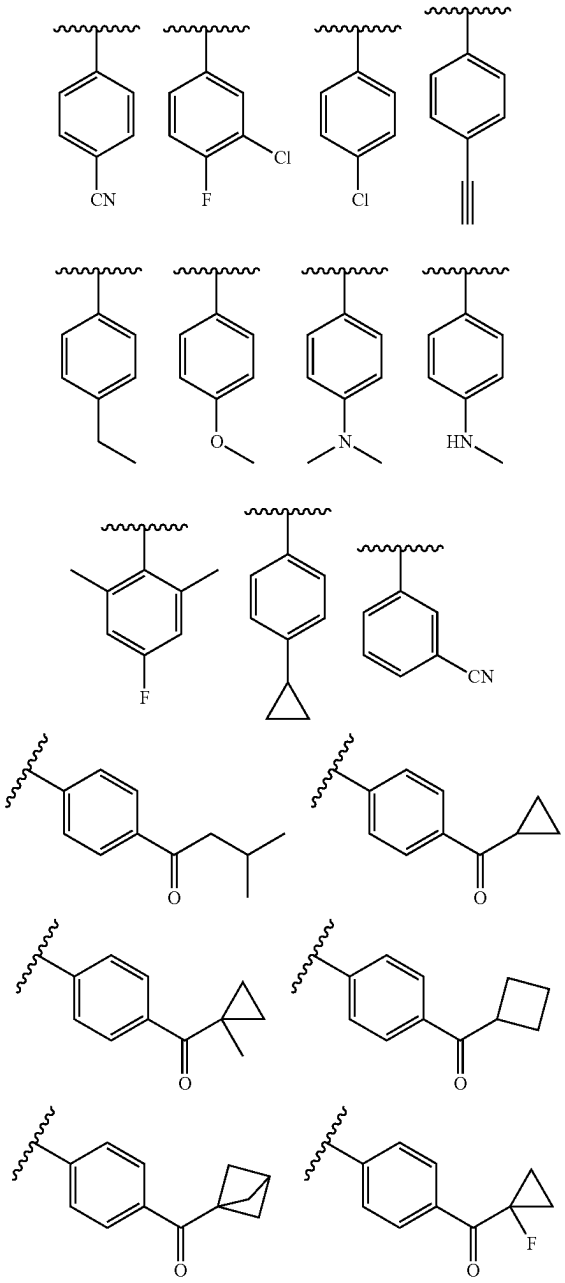
etc., or preferably, R^D is NHG^{5B}, $C(O)NHG^{5B}$ wherein G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.),

[0637] or R^D is $C(O)NG^{5B}G^{5B}$, wherein one instance of G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5B} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl.

[0638] Embodiment B19. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is



or R^1 is selected from



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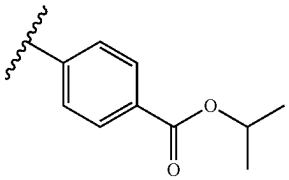

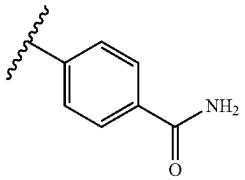

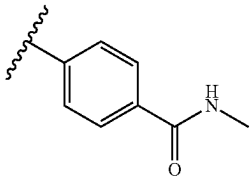

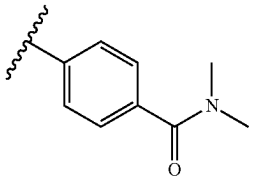

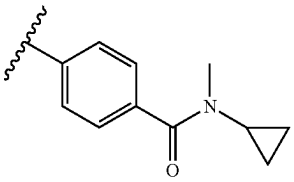

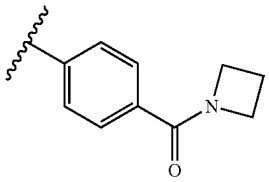

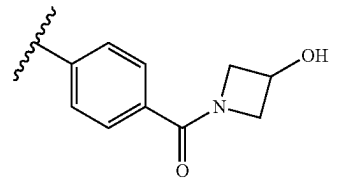

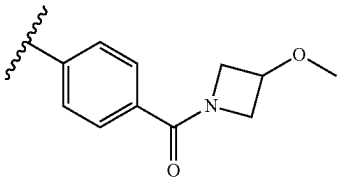

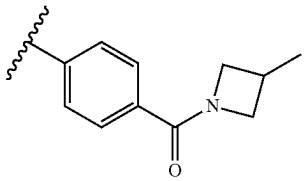

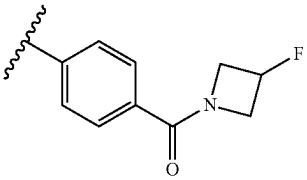

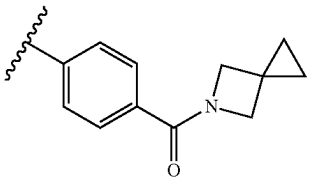

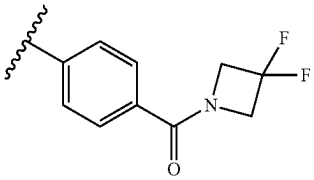

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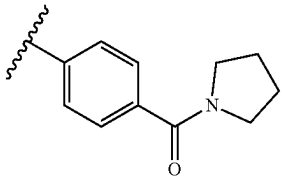

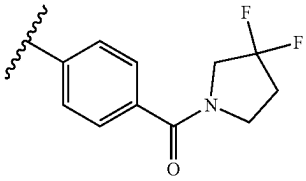

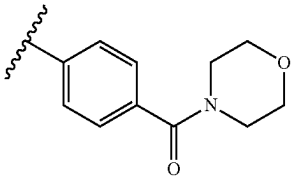

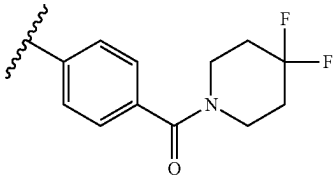

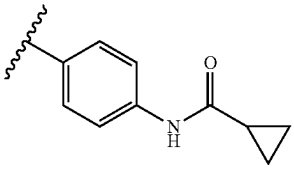

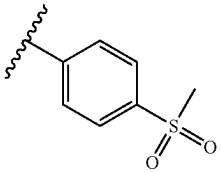

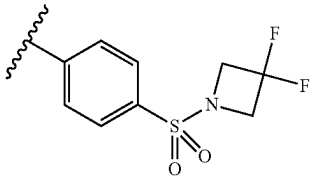

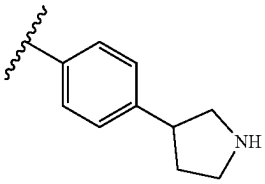

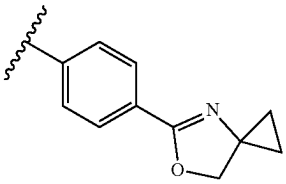

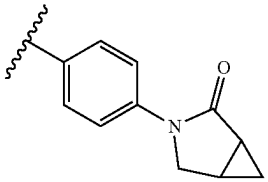

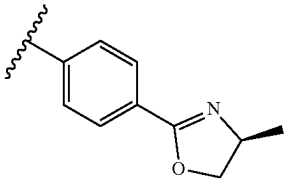

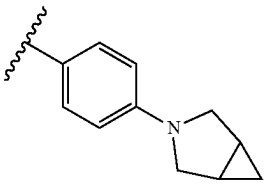

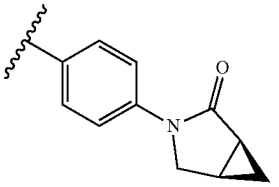

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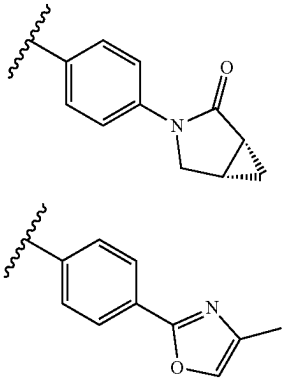

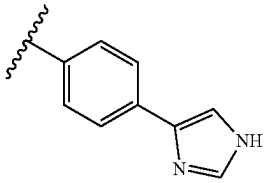

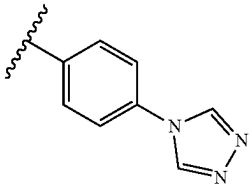

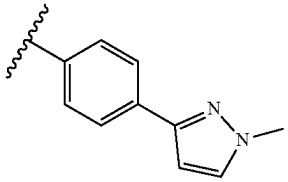

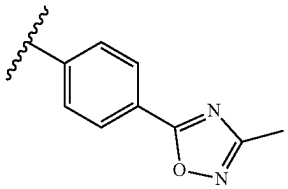

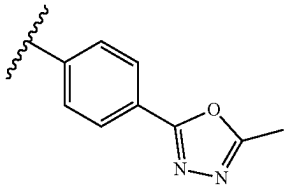

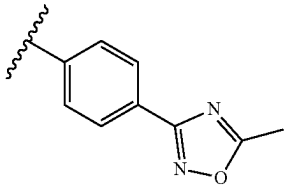

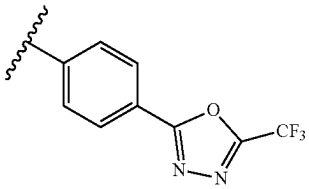

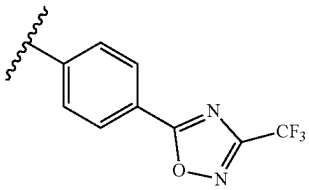

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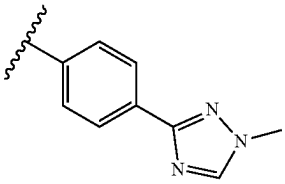

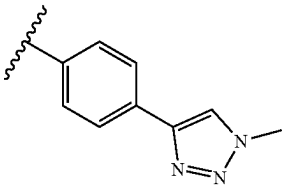

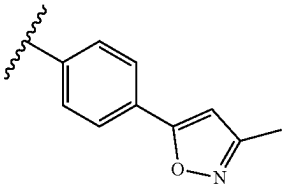

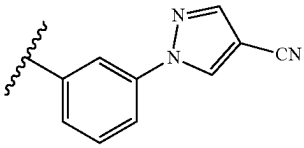

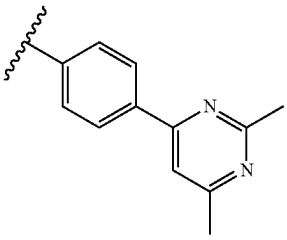

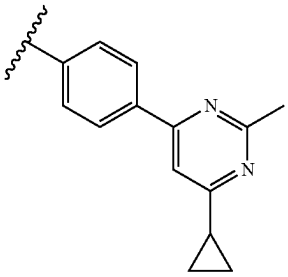

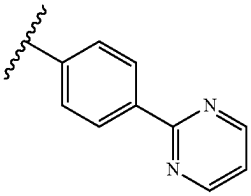

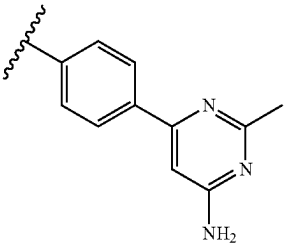

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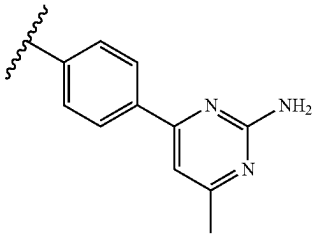

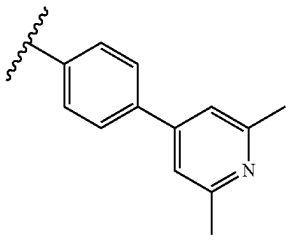

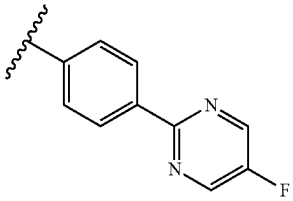

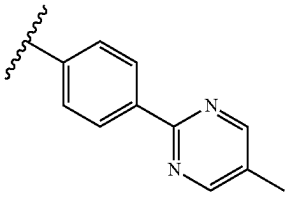

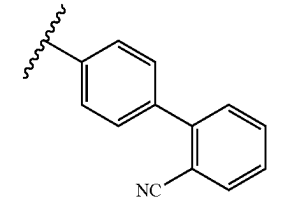

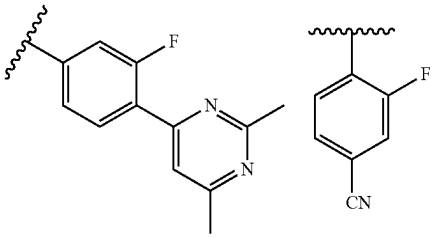

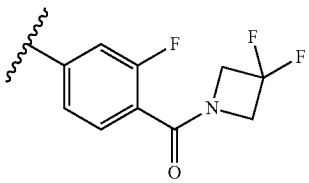

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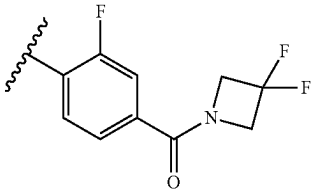
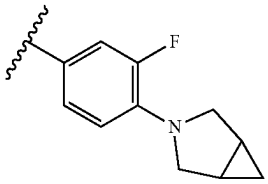
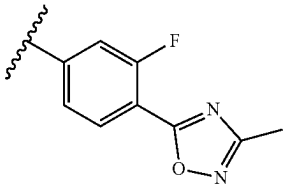
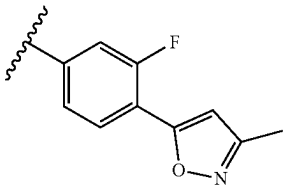
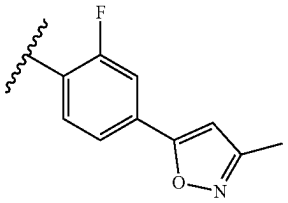


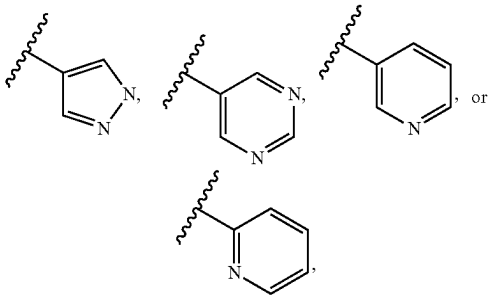






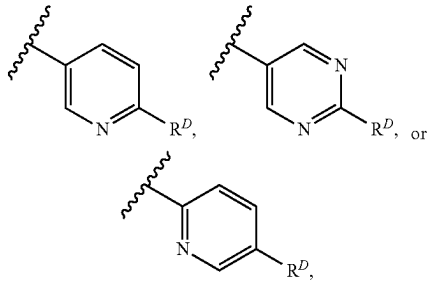


[0639] Embodiment B20. The compound ofany one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R is a 5- or 6-membered heteroaryl, such as pyrazolyl, pyridyl, or pyrimidinyl, e.g.,



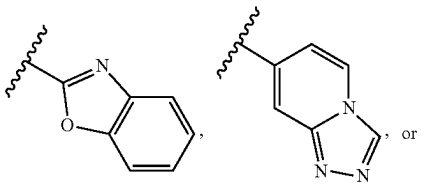
which is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring, e.g., cyclopro-

pyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or



wherein R^D is G^{4B}, OG^{4B}, NHG^{4B}, $NG^{4B}G^{4B}$, $C(O)G^{4B}$ $OC(O)G^{4B}$, $NHC(O)G^{4B}$, $NG^{4B}C(O)G^{4B}$, $C(O)OG^{4B}$, $C(O)NHG^{4B}$, $C(O)NG^{4B}G^{4B}$, SO_2G^{4B}, SO_2NHG^{4B}, or $SO_2NG^{4B}G^{4B}$, wherein G^{4B} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 (e.g., 3-8) membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring, such as —(C_{1-4} alkylene)-3-8 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-8 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or 3-12 (e.g., 3-8) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

[0640] Embodiment B21. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is a bicyclic heteroaryl, such as benzoxazolyl, benzimidazolyl, triazolopyridinyl, e.g.,



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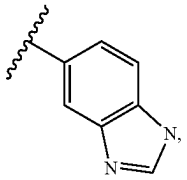
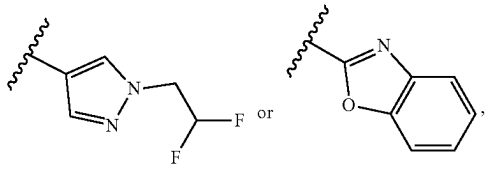
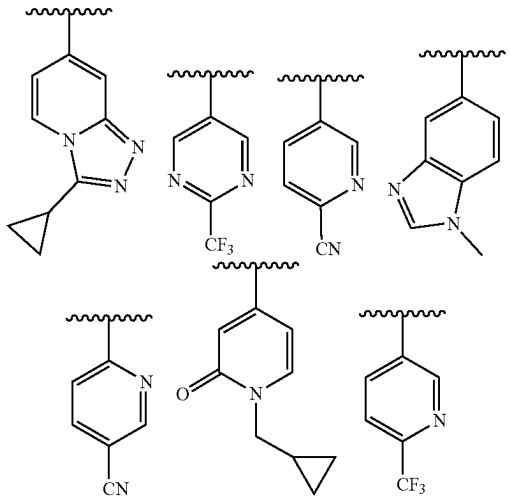


which is optionally substituted with one or more, such as 1 or 2, substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0641] Embodiment B22. The compound of any one of Embodiments B1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is



or R^1 is selected from



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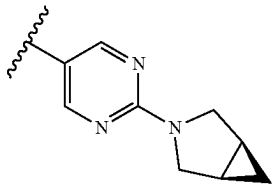

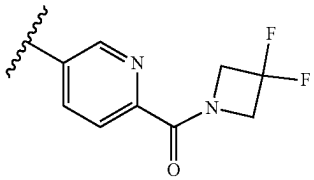

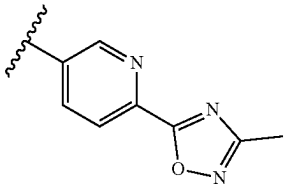

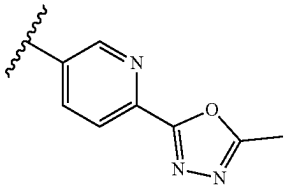

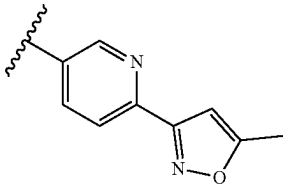

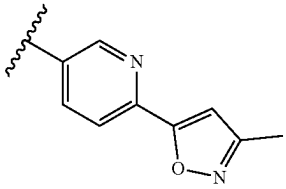

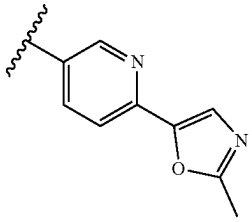

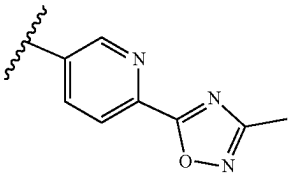

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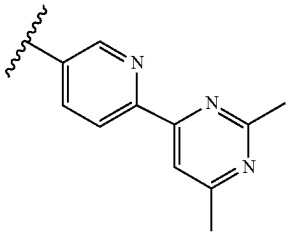

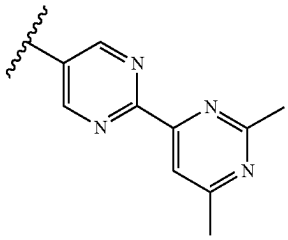

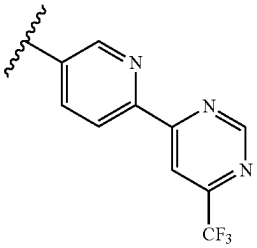

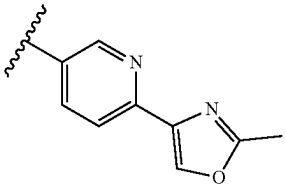

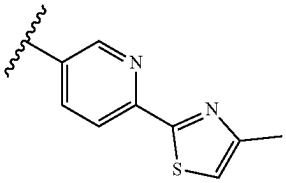

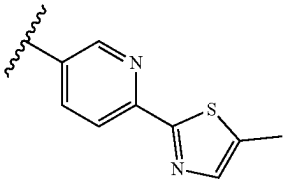

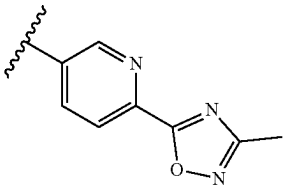

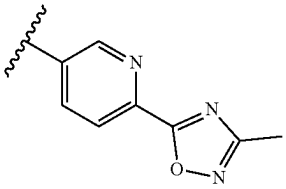

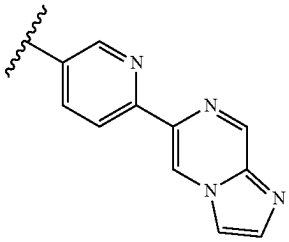

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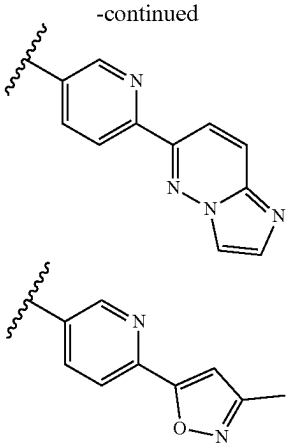
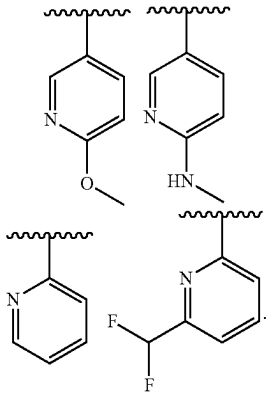


or or R^1 is selected from



[0642] Embodiment B23. The compound of any one of Embodiments B1-2 and 4-22, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

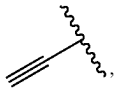
[0643] Embodiment B24. The compound of Embodiment B23, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl, or R^2 is CD_3 or CF_3.

[0644] Embodiment B25. The compound of any one of Embodiments B1-24, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0645] Embodiment B26. The compound of Embodiment B25, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

[0646] Embodiment B27. The compound of any one of Embodiments B1-26, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0647] Embodiment B28. The compound of any one of Embodiments B1-26, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl, or R^4 is F, Cl, Br, or



or R^4 is CD_3 or CF_3.

[0648] Embodiment B29. The compound of any one of Embodiments B1-28, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0649] Embodiment B30. The compound of Embodiment B27, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

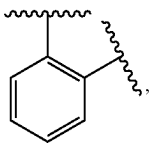
[0650] Embodiment B31. The compound of any one of Embodiments B1-30, or a pharmaceutically acceptable salt thereof, wherein both R^6 and R^7 are hydrogen.

[0651] Embodiment B32. The compound of any one of Embodiments B1-30, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, which is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, or C_{1-4} alkoxy optionally substituted with 1-3F.

[0652] Embodiment B33. The compound of any one of Embodiments B1-30, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl.

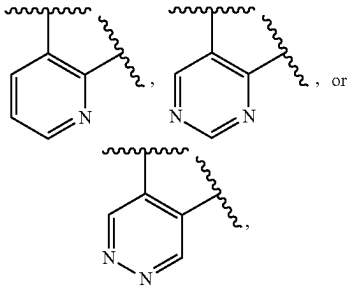
[0653] Embodiment B34. The compound of any one of Embodiments B1-33, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

[0654] Embodiment B35. The compound of any one of Embodiments B1-34, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted phenylene, such as



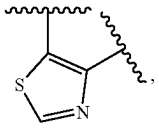
which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0655] Embodiment B36. The compound of any one of Embodiments B1-34, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 6-membered heteroarylene, such as



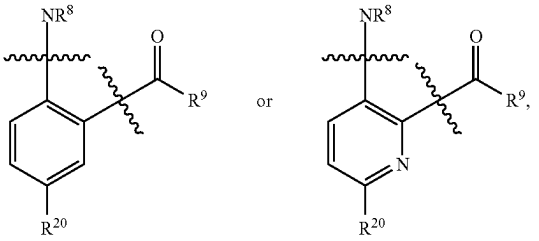
each of which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0656] Embodiment B37. The compound of any one of Embodiments B1-34, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 5-membered heteroarylene, such as

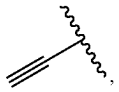


which is optionally substituted with halogen, CN, OH, COOH, G^6, or OG^1, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

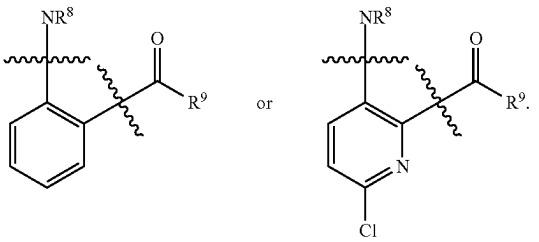
[0657] Embodiment B38. The compound of any one of Embodiments B1-34, or a pharmaceutically acceptable salt thereof, wherein L^2 is (NR^8 and $C(O)R^9$ are shown to show direction of attachment to the remainder of the molecule):



wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^1, or OG^6, or R^{20} is

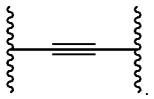


wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, preferably, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3, preferably, L^2 is



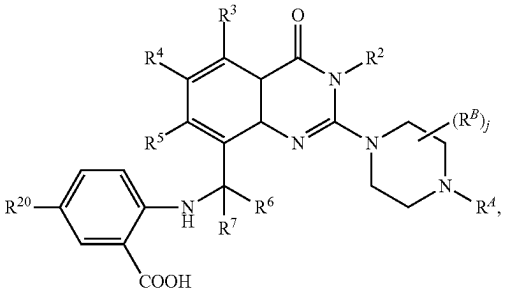
[0658] Embodiment B39. The compound of any one of Embodiments B1-38, or a pharmaceutically acceptable salt thereof, wherein R^9 is OH.

[0659] Embodiment B40. The compound of any one of Embodiments B1-39, or a pharmaceutically acceptable salt thereof, wherein as applicable, L^1 is absent, O, CH_2, or

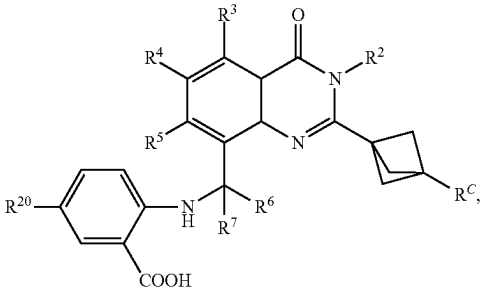


[0660] Embodiment B41. The compound of any one of Embodiments B1-2, or a pharmaceutically acceptable salt thereof, having a structure according to Formula I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, or I-1-a-2-d:

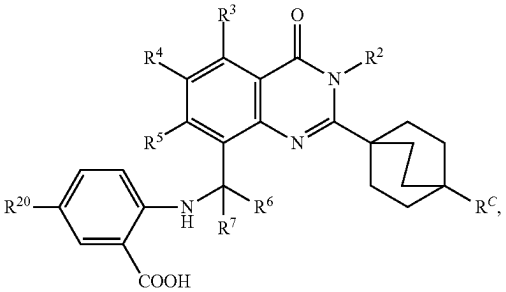
Formula III-1-a-2-a



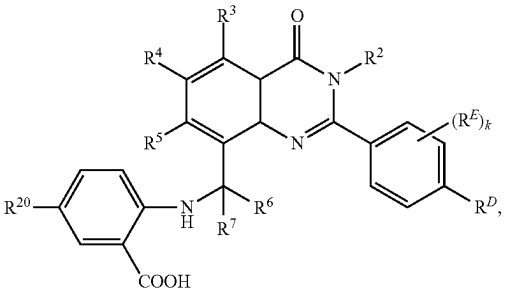
Formula III-1-a-2-b



Formula III-1-a-2-c



Formula III-1-a-2-d



[0661] wherein:

[0662] R^{20} is as defined in Embodiment B38,

[0663] R^A, R^B, and j each has its respective definition as defined in Embodiment B8 or 9,

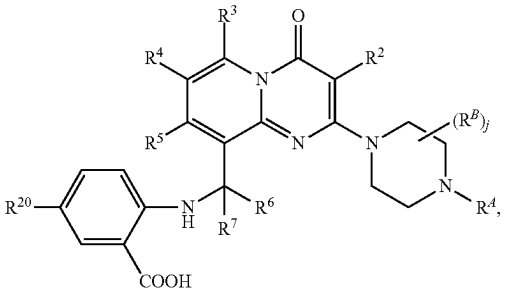
[0664] R^C is as defined in Embodiment B14,

[0665] R^D, R^E, and k each has its respective definition as defined Embodiment B17 or 18, and

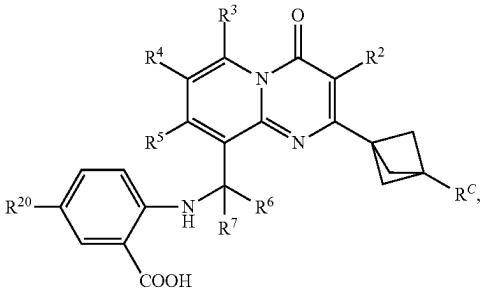
[0666] R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in any of Embodiments B1-40 as applicable.

[0667] Embodiment B42. The compound of any one of Embodiments B1 and 4, or a pharmaceutically acceptable salt thereof, having a structure according to Formula III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, or III-1-a-2-d:

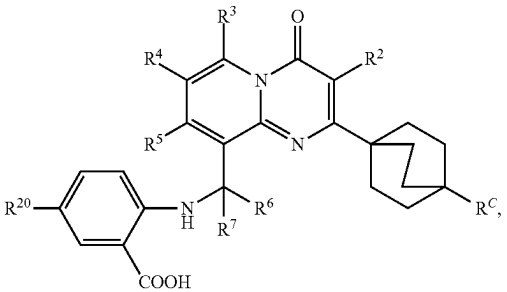
Formula III-1-a-2-a



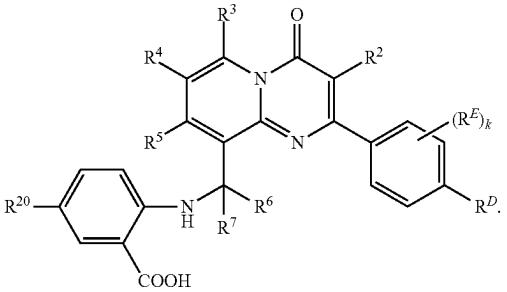
Formula III-1-a-2-b



Formula III-1-a-2-c



Formula III-1-a-2-d



[0668] wherein:

[0669] R^{20} is as defined in Embodiment B38,

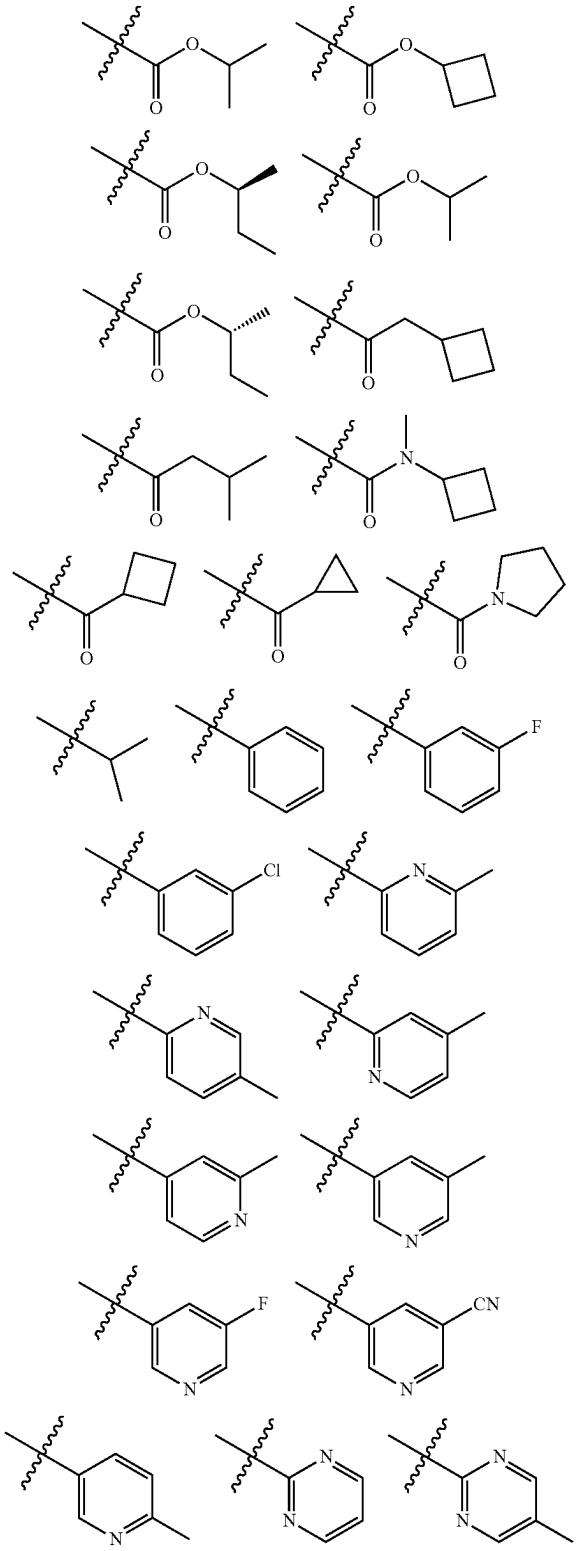
[0670] R^A, R^B, and j each has its respective definition as defined in Embodiment B8 or 9,

[0671] R^C is as defined in Embodiment B14,

[0672] R^D, R^E, and k each has its respective definition as defined Embodiment B17 or 18, and

[0673] R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in any of Embodiments B1-40 as applicable.

[0674] Embodiment B43. The compound of any one of Embodiments B41-42, or a pharmaceutically acceptable salt thereof, wherein R^A is selected from:



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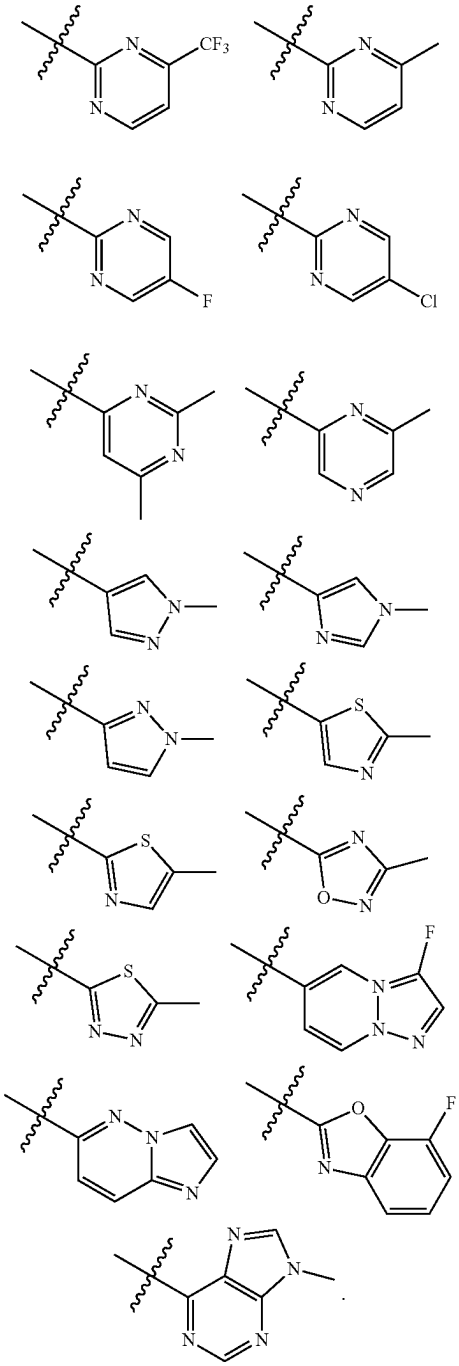
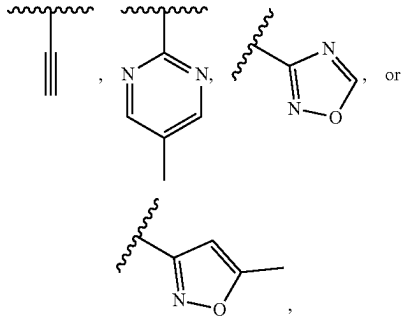
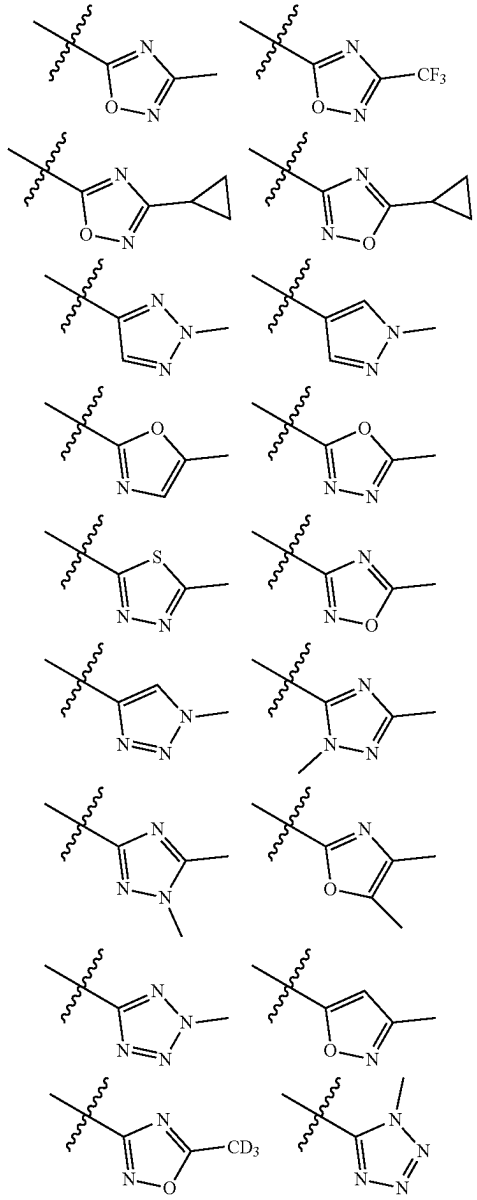


[0675] Embodiment B44. The compound of any one of Embodiments B41-43, or a pharmaceutically acceptable salt thereof, wherein j is 0, or R^B is methyl and j is 1.

[0676] Embodiment B45. The compound of any one of Embodiments B41-42, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3, or R^C is OH, NH_2, CH_2OH, or CH_2OCH_3, or R^C is



or R^C is selected from:



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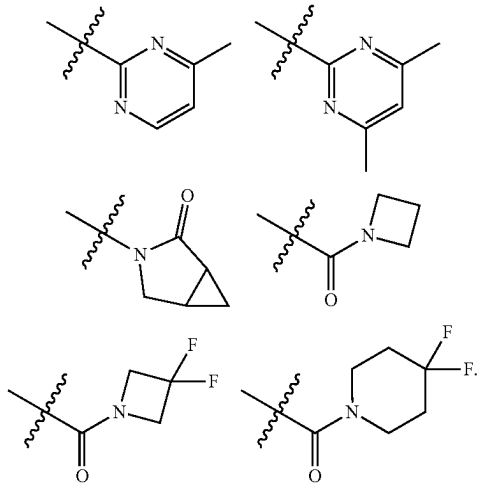
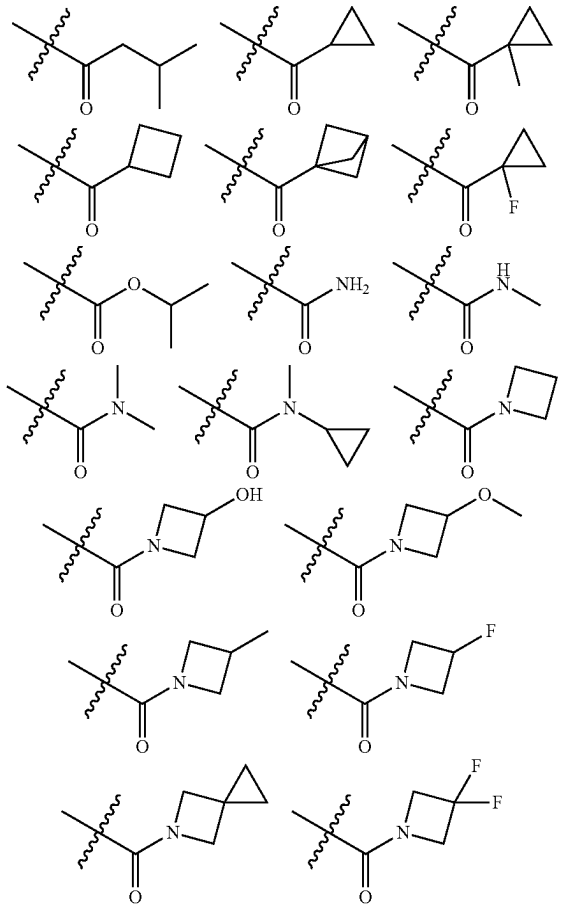


[0677] Embodiment B46. The compound of any one of Embodiments B41-42, or a pharmaceutically acceptable salt thereof, wherein R^D is H, F, CN, acetenyl, methyl, ethyl, OCH_3, $NHCH_3$, or cyclopropyl, or

[0678] R^D is selected from:



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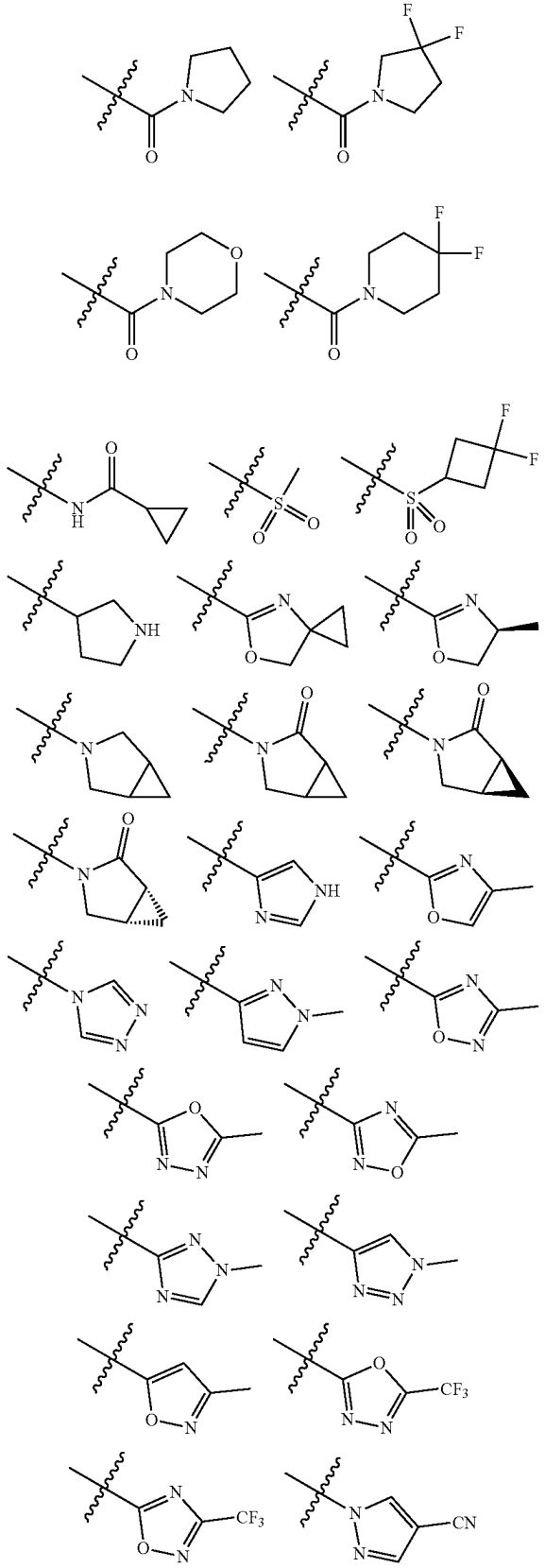

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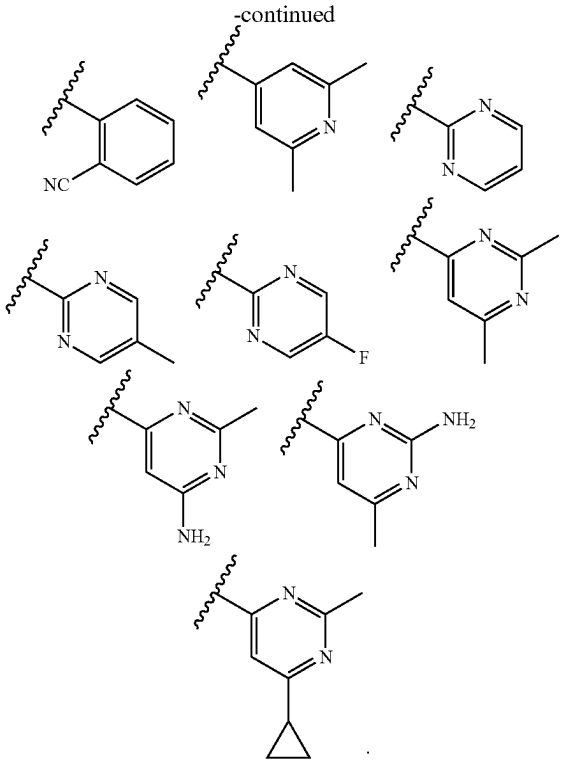
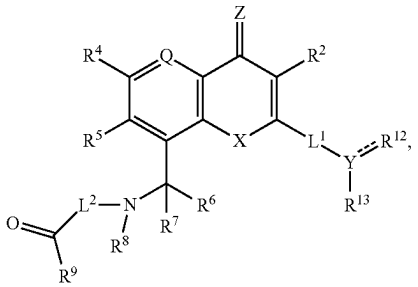


[0679] Embodiment B47. The compound of any one of Embodiments B41-42 and 46, or a pharmaceutically acceptable salt thereof, wherein k is 0, or k is 1, and R^E is F, Cl, CN, methyl, or k is 2 and each R^E is independently F or methyl.

[0680] Embodiment B48. The compound of any one of Embodiments B41-47, or a pharmaceutically acceptable salt thereof, wherein R^{20} is H.

[0681] Embodiment B49. A compound of Formula V, or a pharmaceutically acceptable salt thereof,

Formula V



[0682] wherein:

[0683] X is O, NR^{14}, or S, wherein R^{14} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine;

[0684] Q is N or CR^3, wherein R^3 is hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0685] L^1 is null, O, C(O), S, S(O), SO_2, NR^1, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered

ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0686] R^2, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0687] wherein G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0688] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_2-6 alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

[0689] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0690] L^2 is optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene);

[0691] R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$, wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure;

[0692] wherein:

[0693] (1) Z is NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; or

[0694] (2) Z is O, and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; provided that (a) Y is C when the bond between Y and R^{12} is a double bond; (b) Y is CR^1S, when the bond between Y and R^{12} is a single bond, wherein R^{18} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; or (c) Y is C or N, when Y is included in a a heteroaryl, such as a 5-membered heteroaryl;

[0695] (3) Z is O or NR^1, wherein R^1 is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; R^2 and R^{12}, together with the intervening atoms, are joined together to form a ring structure, wherein (a) Y is N; (b) Y is C when the bond between Y and R^{12} is a double bond; or (c) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and R^{13} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms; or

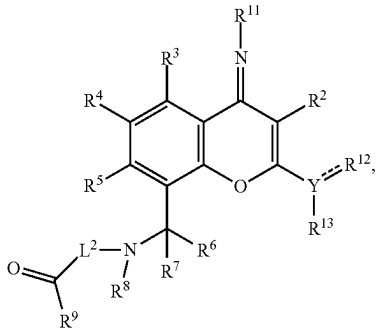
[0696] (4) Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; L^1 is defined above but not null; and

[0697] (i) R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; or

[0698] (ii) R^2 and R^{12}, together with the intervening atoms, are joined together to form a ring structure, wherein (a) Y is N; (b) Y is C when the bond between Y and R^{12} is a double bond; or (c) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and R^{13} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms.

[0699] Embodiment B50. The compound of Embodiment B49, or a pharmaceutically acceptable salt thereof, having a structure according to Formula V-1:

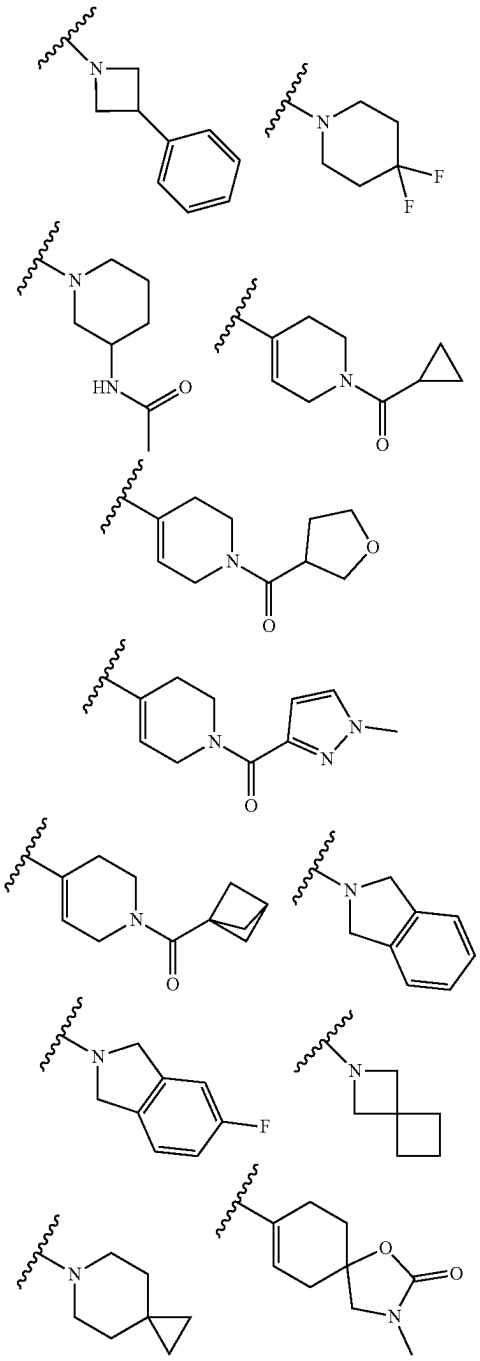
Formula V-1



[0700] wherein: R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring struc-

ture is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S.

[0701] Embodiment B51. The compound of Embodiment B49 or 50, or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and Y are joined together to form a moiety selected from:



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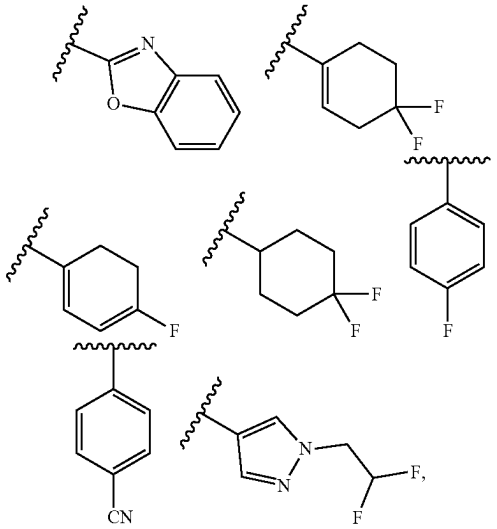
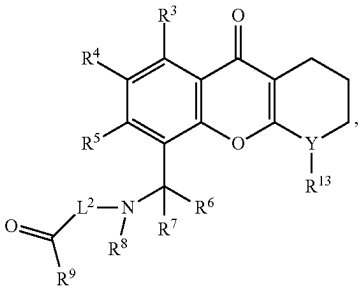


or R^{12}, R^{13}, and Y are joined together to form a moiety as defined for R^1 in any of Embodiments B7-22 above.

[0702] Embodiment B52. The compound of Embodiment B49, or a pharmaceutically acceptable salt thereof, having a structure according to Formula V-2:

Formula V-2

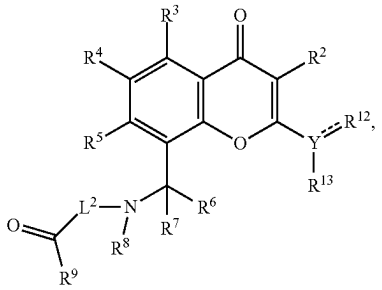


[0703] wherein: Y is N or CR^{15}, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and R^{13} is an optionally substituted C_{1-6} alkyl, such as unsubstituted C_{1-6} alkyl or C_{1-6} alkyl substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or a 3-12 membered ring, such as 3-7 membered ring (e.g., cyclopropyl), wherein the 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0704] Embodiment B53. The compound of Embodiment B52, or a pharmaceutically acceptable salt thereof, wherein Y is N and R^{13} is —CH_2-cyclopropyl.

[0705] Embodiment B54. The compound of Embodiment B49, or a pharmaceutically acceptable salt thereof, having a structure according to Formula V-3:

Formula V-3

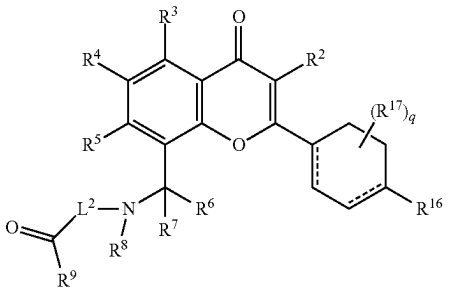


[0706] wherein:

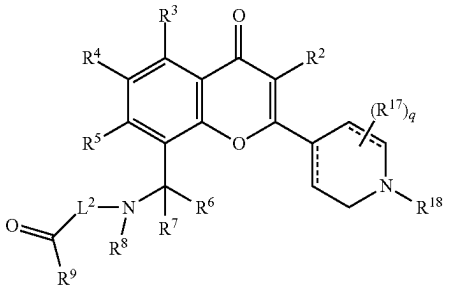
[0707] R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; provided that (a) Y is C when the bond between Y and R^1 is a double bond; (b) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{11} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; or (c) Y is C or N, when Y is included in a heteroaryl, such as a 5-membered heteroaryl.

[0708] Embodiment B55. The compound of Embodiment B49, or a pharmaceutically acceptable salt thereof, having a structure according to Formula V-4, V-5, V-6, or V-7:

Formula V-4



Formula V-5



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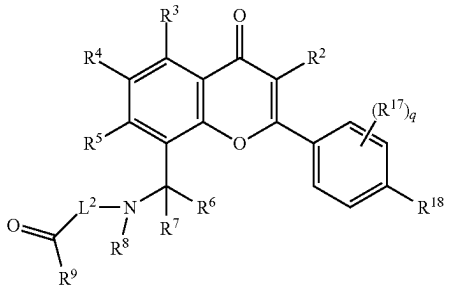
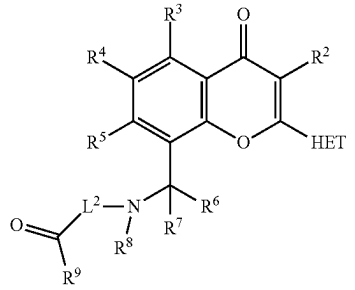
Formula V-6



Formula V-7



[0709] wherein:

[0710] R^{16} is hydrogen, deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$;

[0711] R^{18} is hydrogen, $CONH_2$, CN, G^4, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, or $C(O)NG^4G^4$; HET represents (i) a 5 or 6-membered heteroaryl optionally substituted with 1 or 2 instances of R^{11}; or (ii) a 8-10 membered bicyclic heteroaryl optionally substituted with 1-3 instances of R^{17};

[0712] q is 0, 1, or 2;

[0713] R^{17} at each occurrence is independently deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$; and

[0714] G^4 at each occurrence is independently C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^Aat each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F;

[0715] or as applicable, R^{16} and one instance of R^{17}, together with the intervening atom(s), are joined to form a 3-12 membered, such as 3-7 membered ring structure, which is optionally substituted;

[0716] or as applicable, R^{18} and one instance of R^{17}, together with the intervening atom(s), are joined to form a 3-12 membered, such as 3-7 membered ring structure, which is optionally substituted,

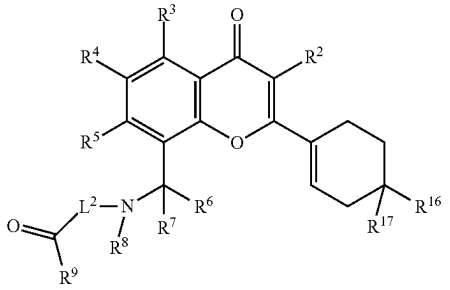
[0717] or R^{16} in Formula V-6 is a structure as defined for R^D in Embodiment B17 or 18, and R^{17} at each occurrence is independently F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, C_{1-4} heteroalkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and q is 0, 1, or 2;

[0718] or R^{18} in Formula V-5 is a structure as defined for R^A in Embodiment B8, or 9, and R^{17} at each occurrence is independently F, CN, OH, C_{1-4} alkyl optionally substituted with 1-3F, or a 3-4 membered ring optionally substituted with 1-2 substituents each independently F or methyl, and q is 0, 1, or 2;

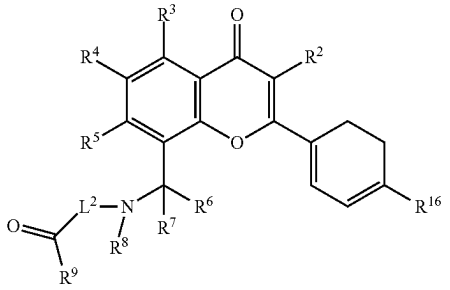
[0719] or HET in Formula V-7 is a structure as defined for R^1 in Embodiment B20, 21, or 22.

[0720] Embodiment B56. The compound of Embodiment B55, or a pharmaceutically acceptable salt thereof, having a structure according to Formula V-4-a, V-4-b, V-4-c, or V-5-a,

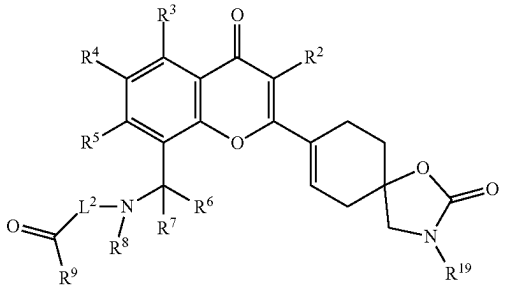
Formula V-4-a



Formula V-4-b



Formula V-4-c



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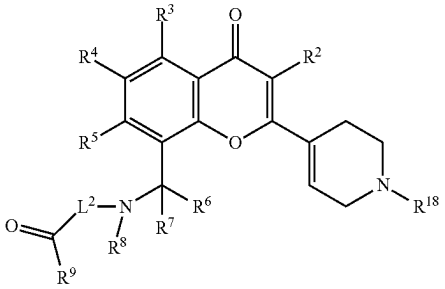
Formula V-5-a



[0721] wherein:

[0722] R^{19} is hydrogen, G^4, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, or $C(O)NG^4G^4$, wherein G^4 is defined in Embodiment B55.

[0723] Embodiment B57. The compound of Embodiment B56, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^{19} is C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0724] Embodiment B58. The compound of any of Embodiments B55-57, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^{16} is hydrogen, deuterium, F, or methyl.

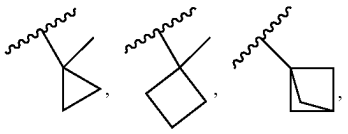
[0725] Embodiment B59. The compound of any of Embodiments B55-58, or a pharmaceutically acceptable salt thereof, wherein as applicable, q is 1, and R^{17} is hydrogen, deuterium, F, or methyl.

[0726] Embodiment B60. The compound of any of Embodiments B55-59, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^{18} is hydrogen, G^5, or $C(O)G^5$, wherein G^5 is C_{1-4} alkyl or a 3-12 membered ring, such as 3-7 membered ring, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or

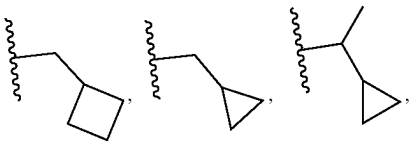
[0727] R^{18} is G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, $C(O)NHG^{5A}$, $C(O)NG^{5A}G^{5A}$, SO_2G^{5A}, SO_2NHG^{5A}, or

$SO_2NG^{5A}G^{5A}$, wherein G^{5A} at each occurrence is independently (i) C_{1-4} alkyl; (ii) 3-12 membered ring such as 3-7 membered ring, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl or 3-12 (e.g., 3-7) membered ring is optionally substituted with one or more (e.g., 1, 2, or 3) G^{B1}, wherein G^{B1} at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, C_{1-4} alkyl optionally substituted with 1-3F, or cyclopropyl;

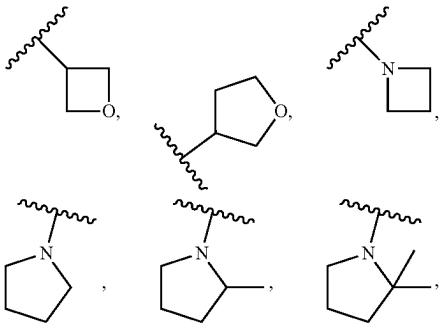
[0728] preferably, R^{18} is G^{5A}, $C(O)G^{5A}$, $C(O)OG^{5A}$, or SO_2G^{5A}, wherein G^{5A} is (i) C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.); (ii) C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F, or methyl, such as cyclopropyl, cyclobutyl, cyclopentyl,



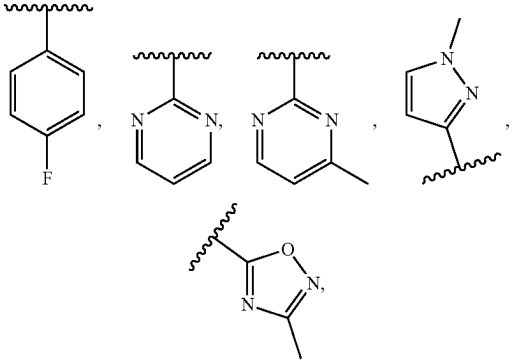
etc.; (iii) —(C_{1-3} alkylene)-(C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl), such as,



etc.; (iv) 4-6 membered heterocyclic optionally substituted with 1 or 2 substituents each independently F or methyl, such as



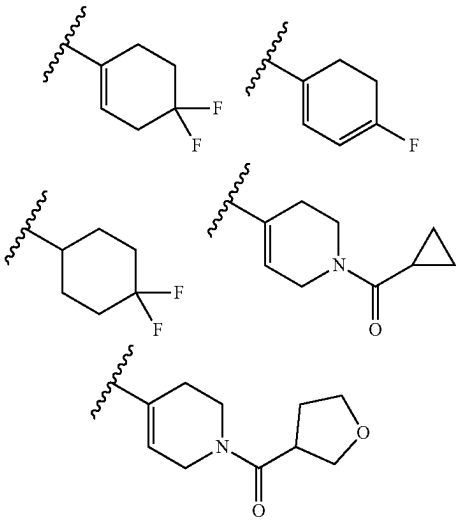
etc.; (v) phenyl or 5- or 6-membered heteroaryl optionally substituted with 1 or 2 substituents each independently F, Cl, CN, methyl optionally substituted with F, or cyclopropyl, such as



etc.,

[0729] or preferably, R^{18} is $C(O)NHG^{5A}$ wherein G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or R^{18} is $C(O)NG^{5A}G^{5A}$, wherein one instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.), and the other instance of G^{5A} is C_{1-4} alkyl optionally substituted with 1-3 F (e.g., methyl, ethyl, trifluoroethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, etc.) or C_{3-6} cycloalkyl optionally substituted with 1 or 2 substituents each independently F or methyl, such as cyclopropyl.

[0730] Embodiment B61. The compound of any of Embodiments B49, 50, and 54-60, or a pharmaceutically acceptable salt thereof, wherein as applicable, R^{12}, R^{13}, and Y are joined together to form a moiety selected from:



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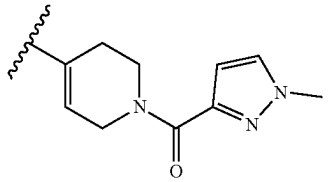
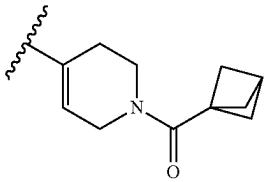
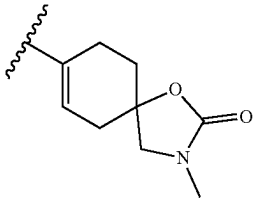
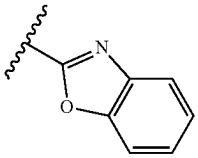
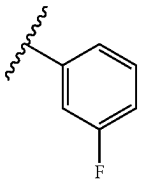
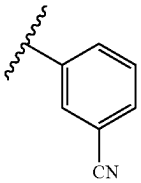


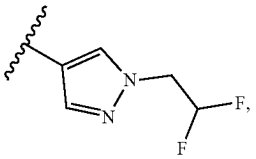




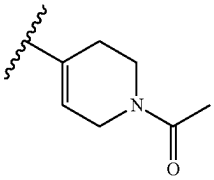


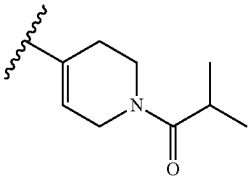


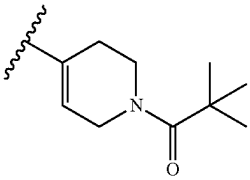


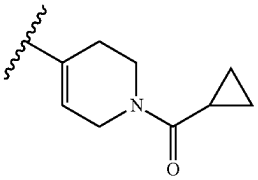


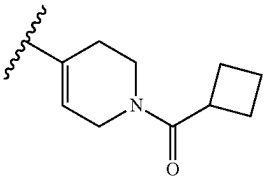
[0731] or R^{12}, R^{13}, and Y are joined together to form a moiety according to the applicable R^1 definition in any of Embodiments B7-22 above where Y is C or CR^{15} or Y is C or N when the ring including Y is a 5-membered heteroaryl, for example, R^{12}, R^{13}, and Y are joined together to form a moiety selected from:

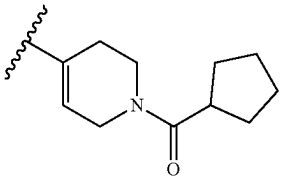












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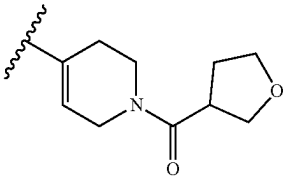

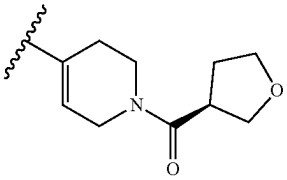

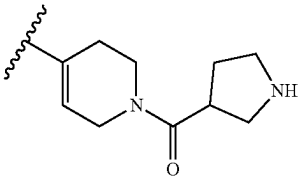

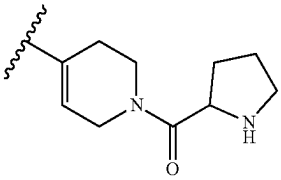

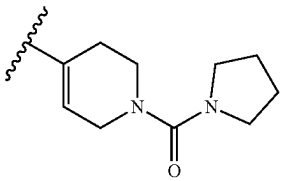

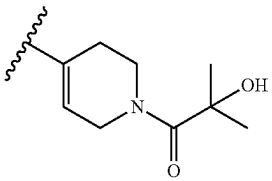

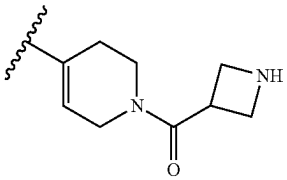

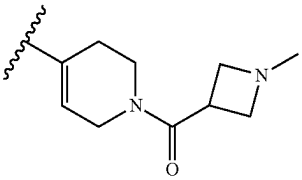

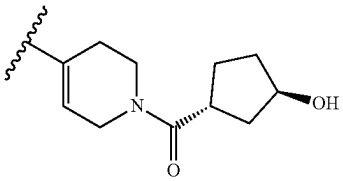

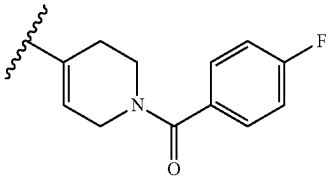

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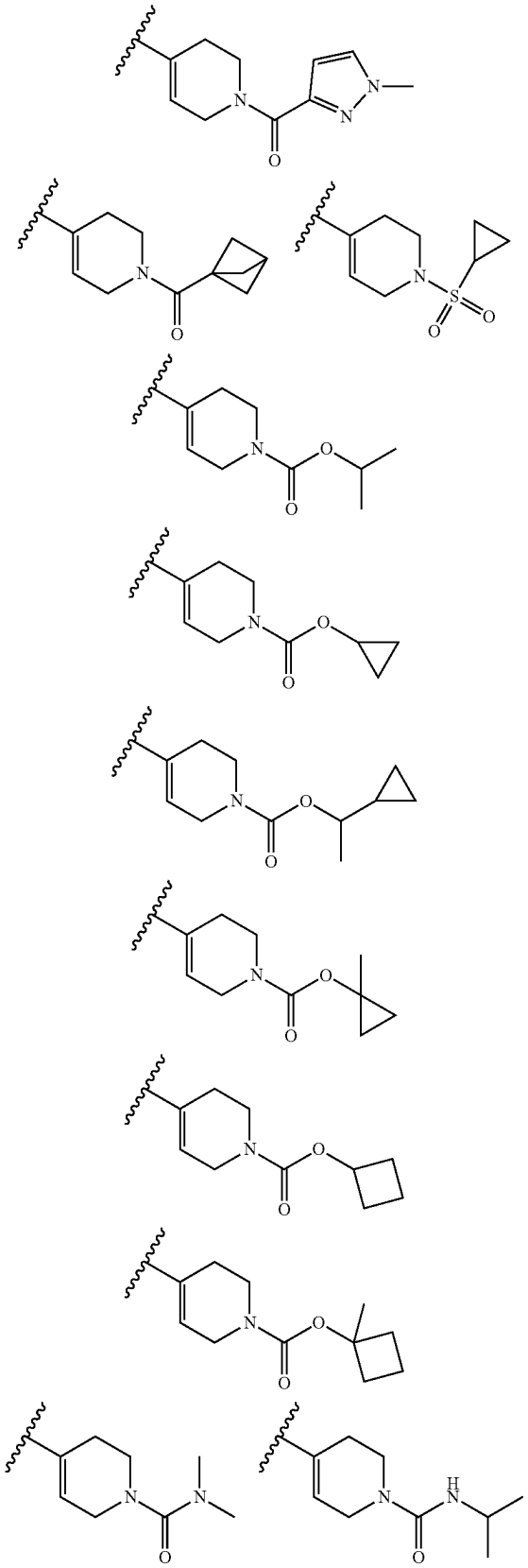

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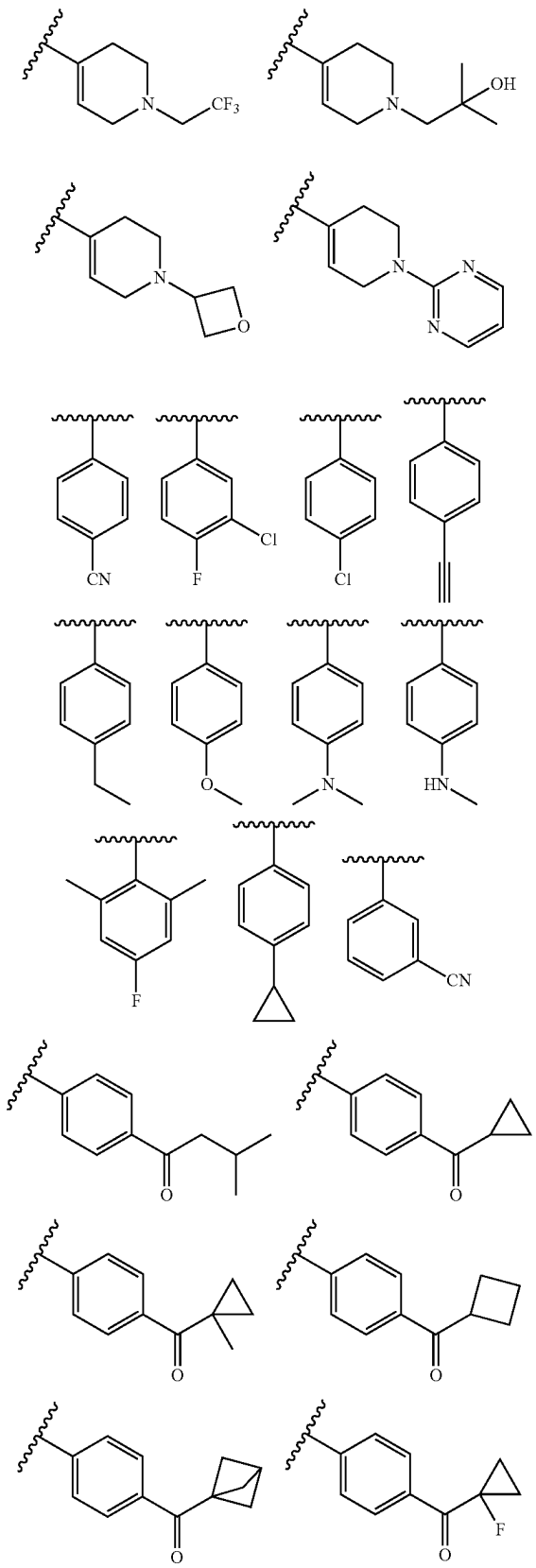

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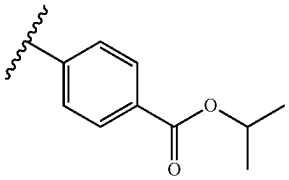

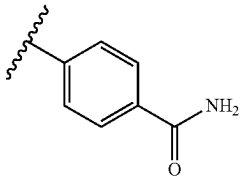

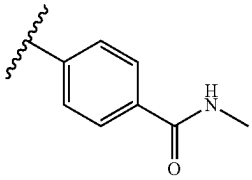

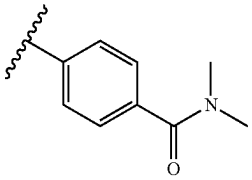

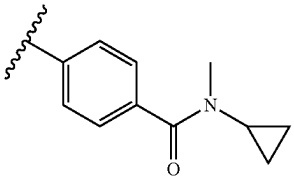

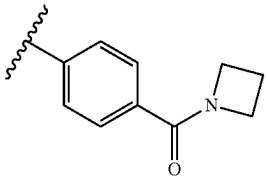

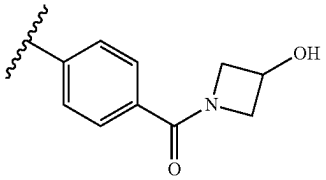

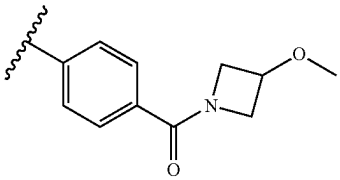

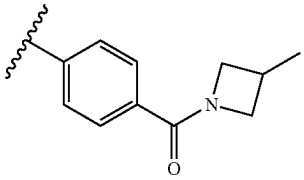

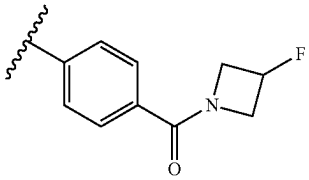

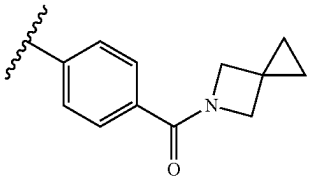

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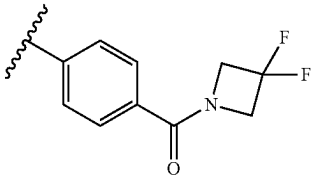

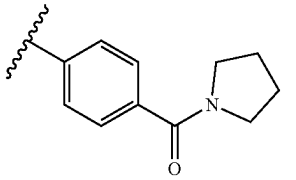

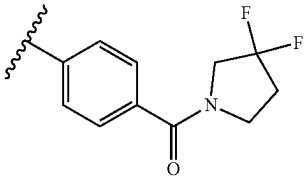

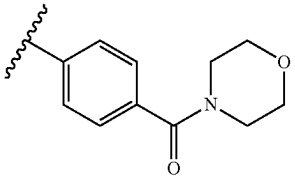

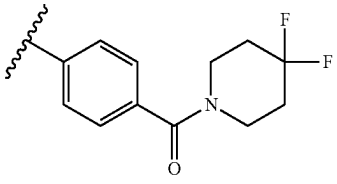

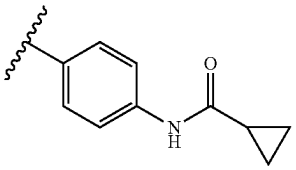

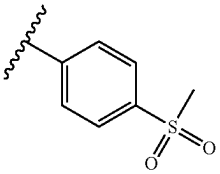

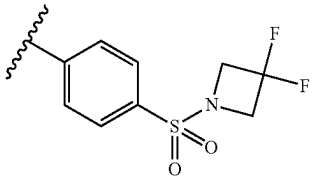

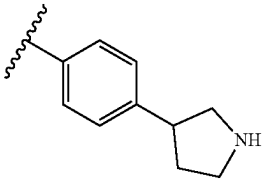

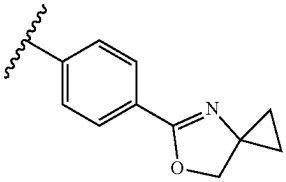

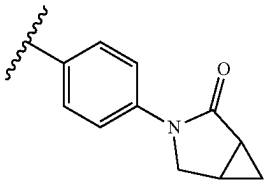

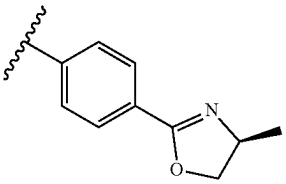

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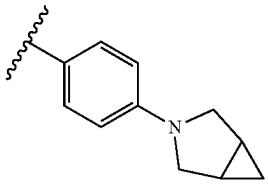

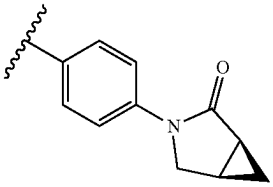

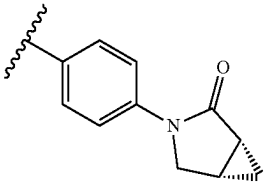

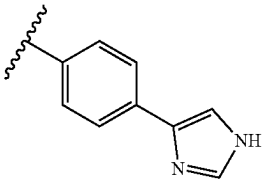

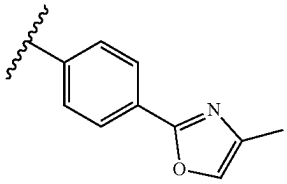

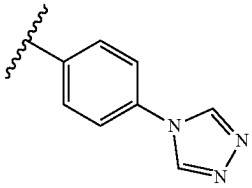

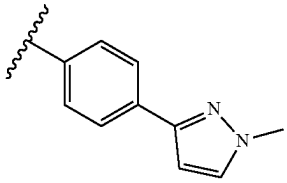

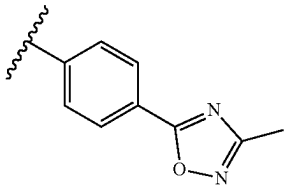

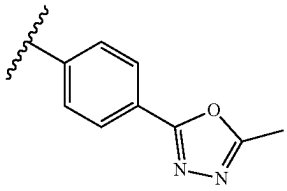

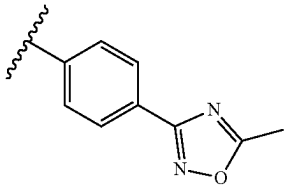

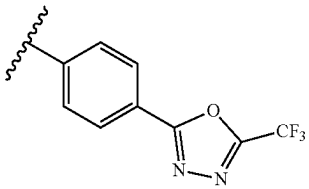

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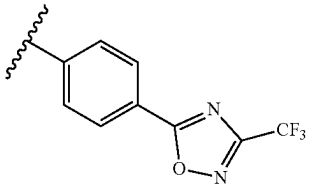

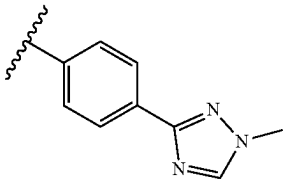

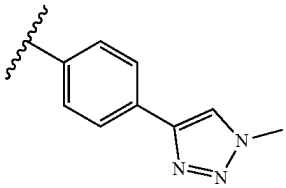

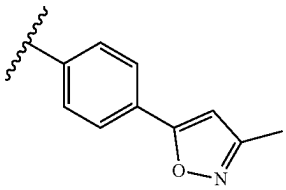

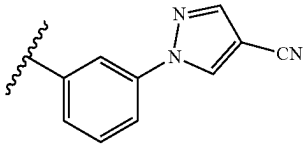

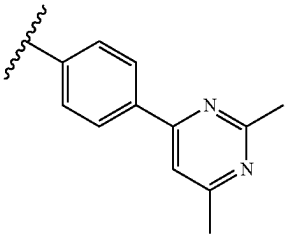

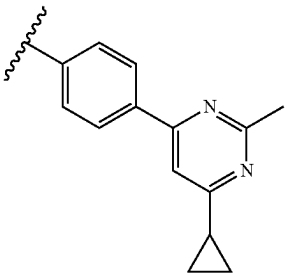

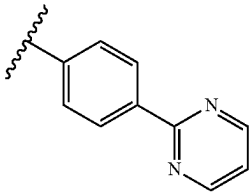

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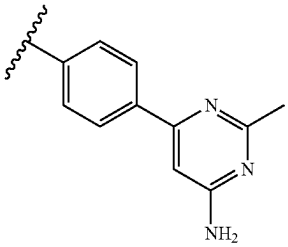

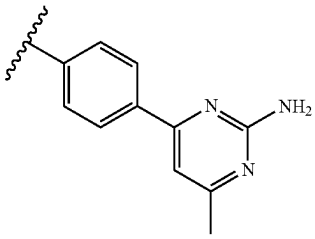

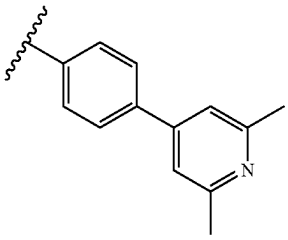

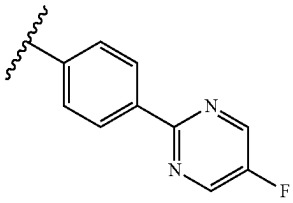

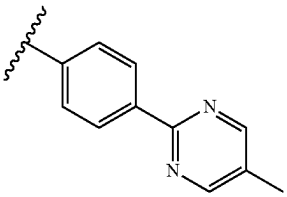

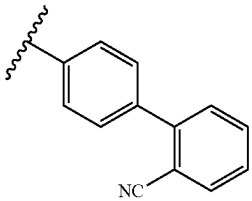

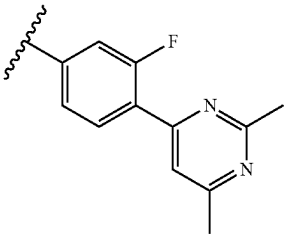

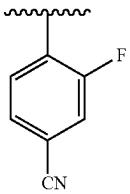

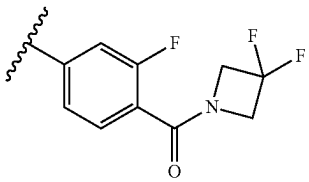

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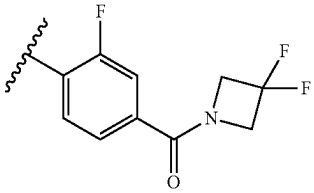

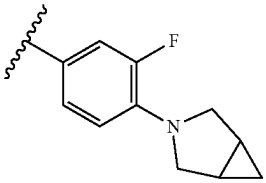

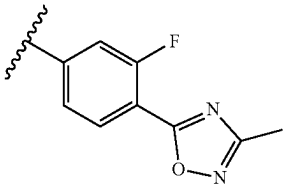

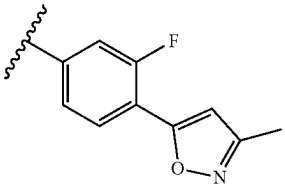

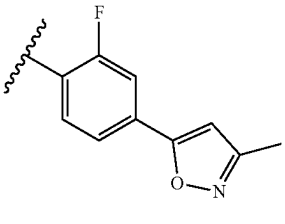

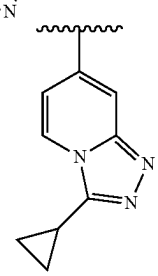

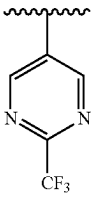

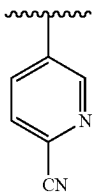

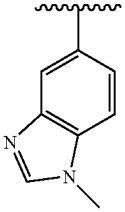

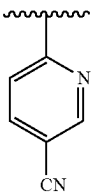

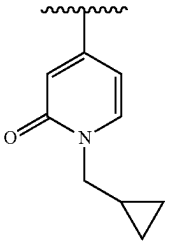

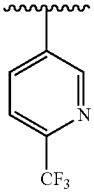

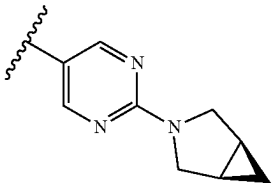

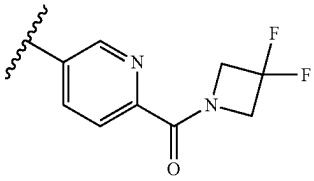

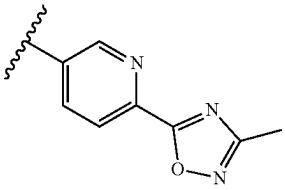

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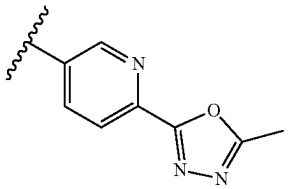

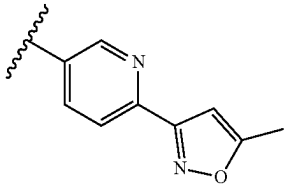

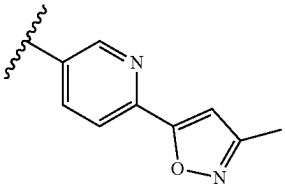

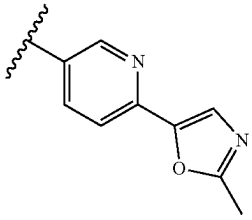

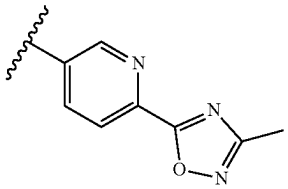

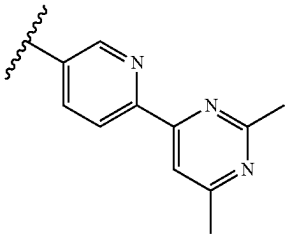

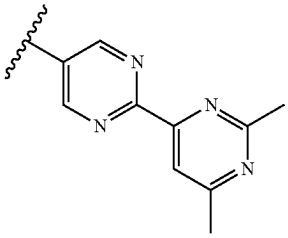

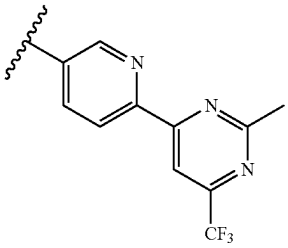

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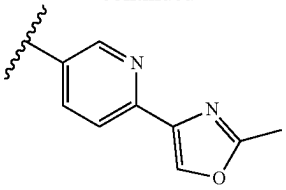
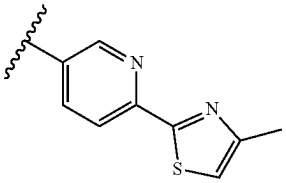
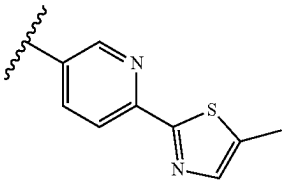
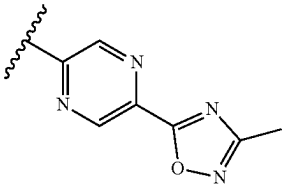
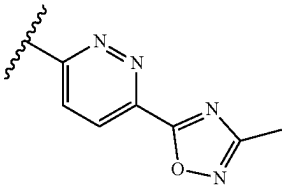
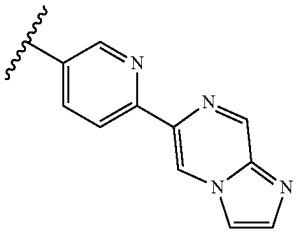


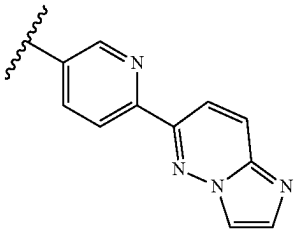


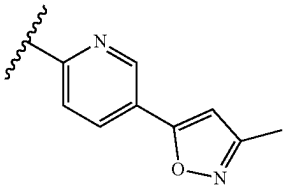












[0732] Embodiment B62. The compound of any one of Embodiments B49-51 and 54-61, or a pharmaceutically

acceptable salt thereof, wherein R^2 is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

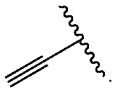
[0733] Embodiment B63. The compound of Embodiment B62, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

[0734] Embodiment B64. The compound of any one of Embodiments B49-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0735] Embodiment B65. The compound of Embodiment B64, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

[0736] Embodiment B66. The compound of any one of Embodiments B49-65, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0737] Embodiment B67. The compound of any one of Embodiments B49-65, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl or R^4 is F, Cl, Br, or



[0738] Embodiment B68. The compound of any one of Embodiments B49-67, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0739] Embodiment B69. The compound of Embodiment B68, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

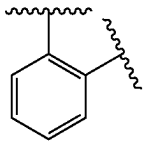
[0740] Embodiment B70. The compound of any one of Embodiments B49-69, or a pharmaceutically acceptable salt thereof, wherein both R^6 and R^7 are hydrogen.

[0741] Embodiment B71. The compound of any one of Embodiments B49-69, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is C_{1-4} alkyl, which is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, or C_{1-4} alkoxy optionally substituted with 1-3F.

[0742] Embodiment B72. The compound of any one of Embodiments B49-69, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen, and the other of R^6 and R^7 is methyl.

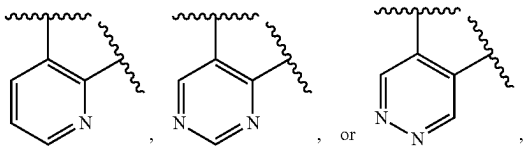
[0743] Embodiment B73. The compound of any one of Embodiments B49-72, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

[0744] Embodiment B74. The compound of any one of Embodiments B49-73, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted phenylene, such as



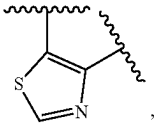
which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0745] Embodiment B75. The compound of any one of Embodiments B49-73, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 6-membered heteroarylene, such as



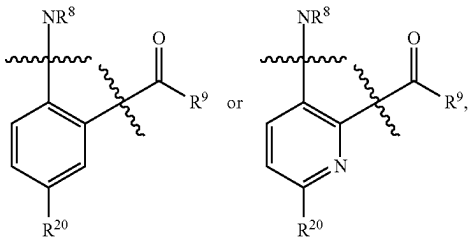
each of which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0746] Embodiment B76. The compound of any one of Embodiments B49-73, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 5-membered heteroarylene, such as

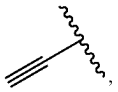


which is optionally substituted with halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

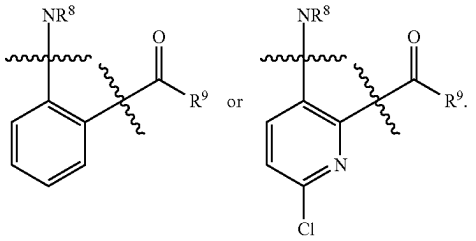
[0747] Embodiment B77. The compound of any one of Embodiments B49-73, or a pharmaceutically acceptable salt thereof, wherein L^2 is (NR^8 and $C(O)R^9$ are shown to show direction of attachment to the remainder of the molecule):



[0748] wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^1, or OG^6, or R^{20} is

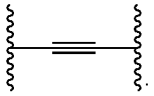


wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, preferably, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3, preferably, L^2 is



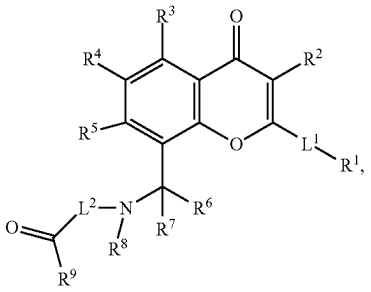
[0749] Embodiment B78. The compound of any one of Embodiments B49-77, or a pharmaceutically acceptable salt thereof, wherein R^9 is OH.

[0750] Embodiment B79. The compound of any one of Embodiments B49-78, or a pharmaceutically acceptable salt thereof, wherein as applicable, L^1 is absent, 0, CH_2, or



[0751] Embodiment B80. A compound of Formula VII, or a pharmaceutically acceptable salt thereof,

Formula VII



[0752] wherein:

[0753] L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0754] R^1 is a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

[0755] R^2, R^3, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

[0756] R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2;

[0757] R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

[0758] R^9 is OH, NH_2, OG^3. NHG^3, NG^3G^3, or $NHSO_2G^3$;

[0759] L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

[0760] wherein:

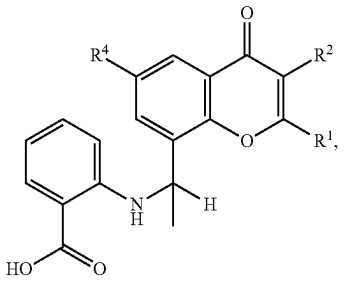
[0761] G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

[0762] G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

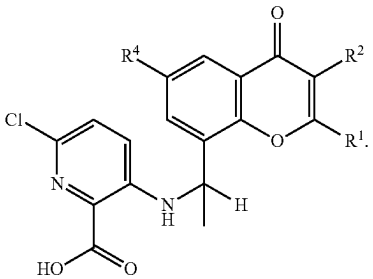
[0763] G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

[0764] Embodiment B81. The compound of Embodiment B80, or a pharmaceutically acceptable salt thereof, having a structure according to Formula VII-1 or VII-2:

Formula VII-1

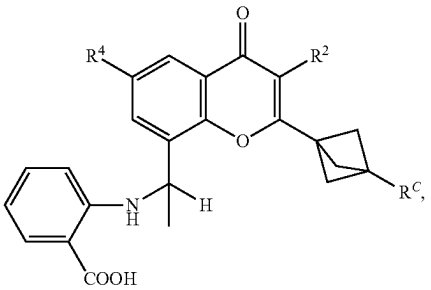


Formula VII-2



[0765] Embodiment B82. The compound of Embodiment B80 or 81, or a pharmaceutically acceptable salt thereof, having a structure according to Formula VII-1-a or VII-1-b:

Formula VII-1-a



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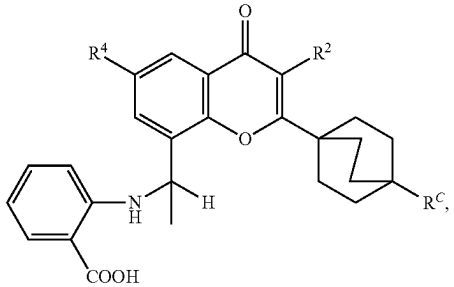
Formula VII-1-b

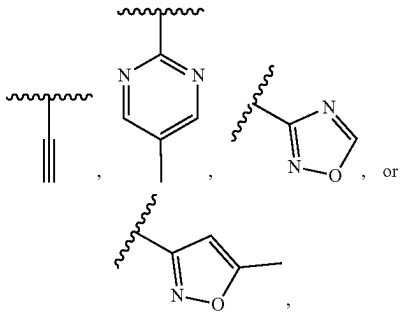


[0766] wherein R^C is as defined in Embodiment B14.

[0767] Embodiment B83. The compound of Embodiment B82, or a pharmaceutically acceptable salt thereof, where R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3, or

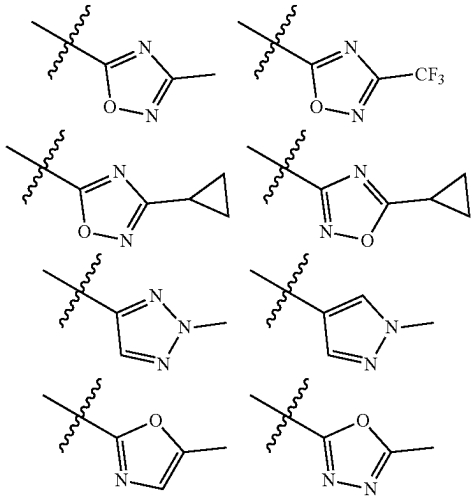
[0768] R^C is OH, NH_2, CH_2OH, or CH_2OCH_3, or

[0769] R^C is



or

[0770] R^C is selected from:



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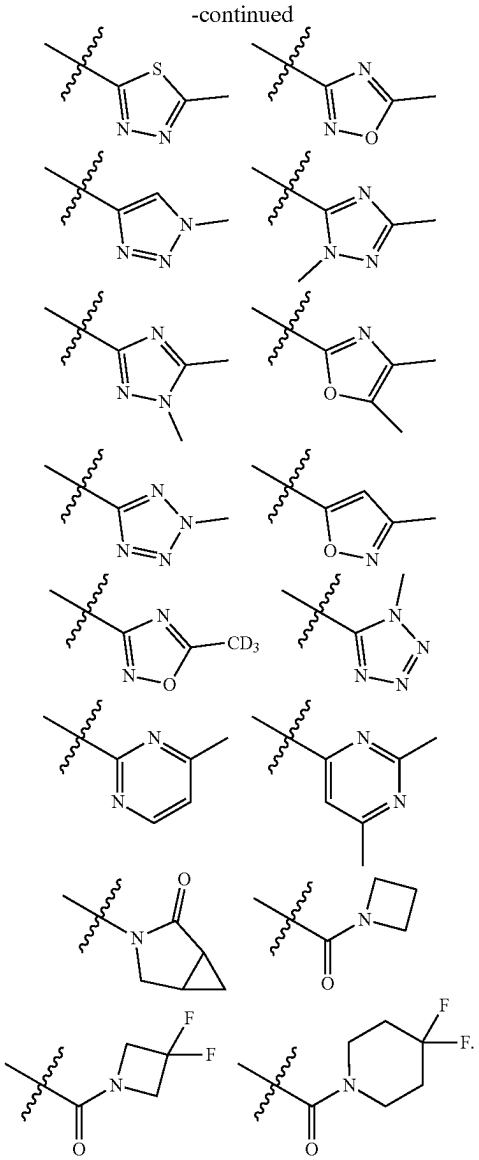
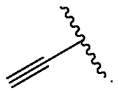


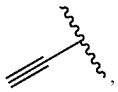
[0771] Embodiment B84. The compound of any one of Embodiments B80-83, or a pharmaceutically acceptable salt thereof, where R^2 is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0772] Embodiment B85. The compound of any one of Embodiments B80-84, or a pharmaceutically acceptable salt thereof, where R^2 is H, F, Cl, CH_3, CF_3, or CD_3, or



[0773] Embodiment B86. The compound of any one of Embodiments B80-85, or a pharmaceutically acceptable salt thereof, where R^4 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

[0774] Embodiment B87. The compound of any one of Embodiments B80-86, or a pharmaceutically acceptable salt thereof, where R^4 is F, Cl, Br, methyl, CF_3, or



or R^4 is CD_3.

[0775] In some embodiments, the present disclosure also provides a compound selected from the compounds shown in Examples section, or Compound Nos. 1-627, or a pharmaceutically acceptable salt thereof.

[0776] In some embodiments, the present disclosure also provides a compound selected from the compounds shown in Table A below, or a pharmaceutically acceptable salt thereof:

TABLE A

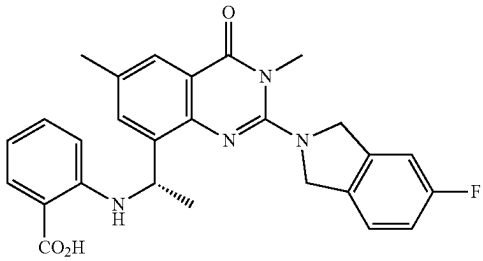
List of Compounds


TABLE A-continued

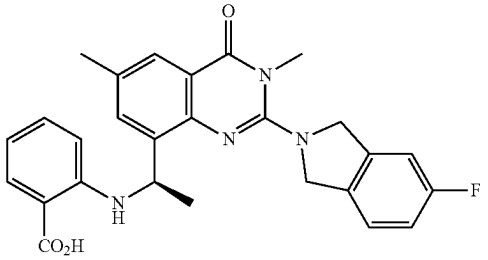
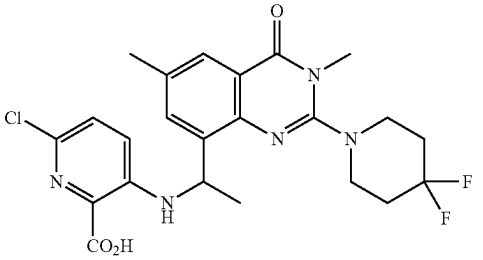
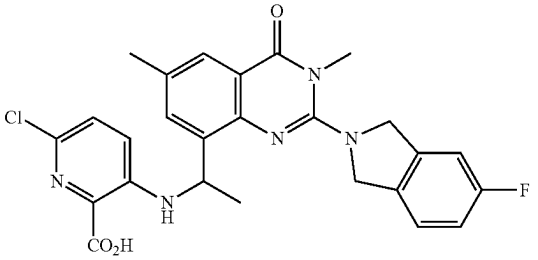
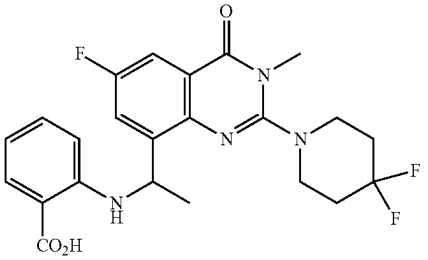
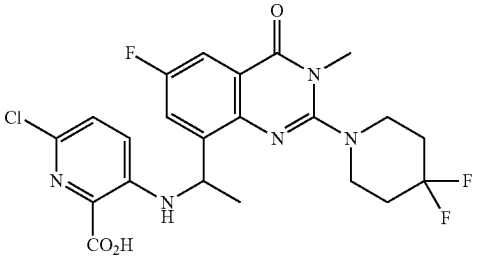
List of Compounds






TABLE A-continued

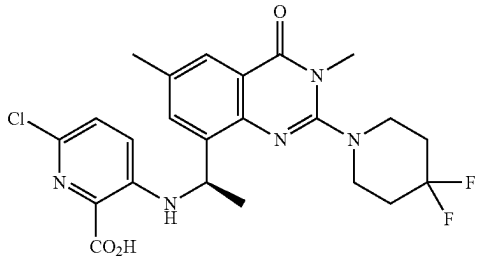
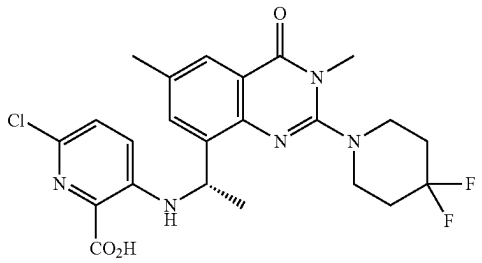
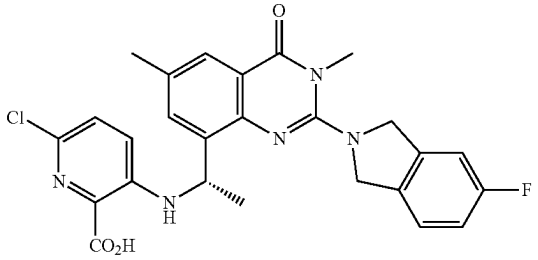
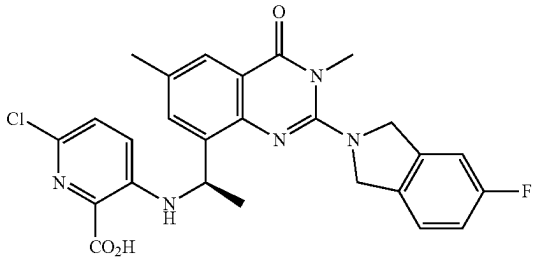
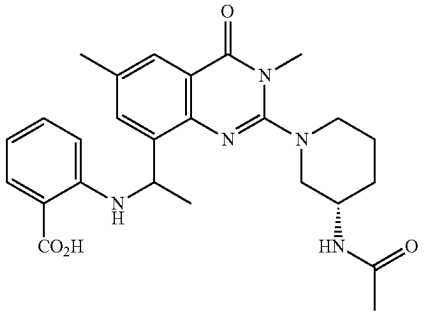
List of Compounds






TABLE A-continued

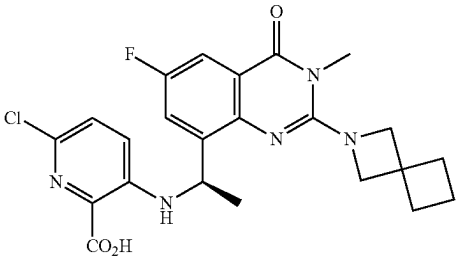
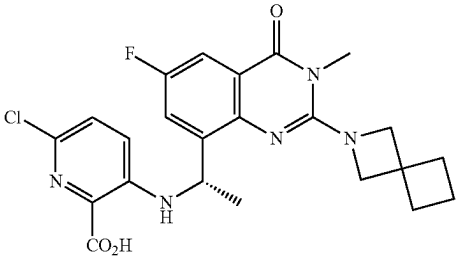
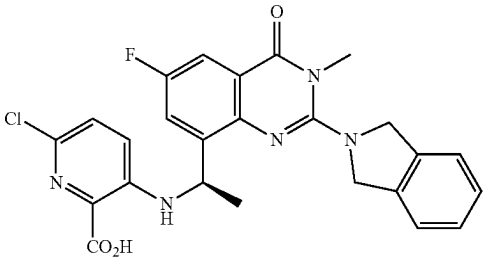
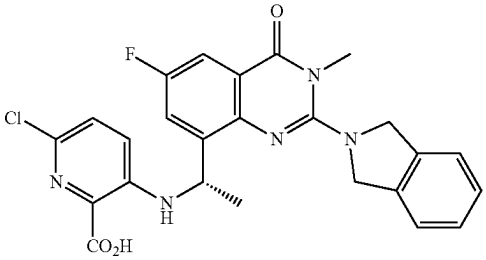
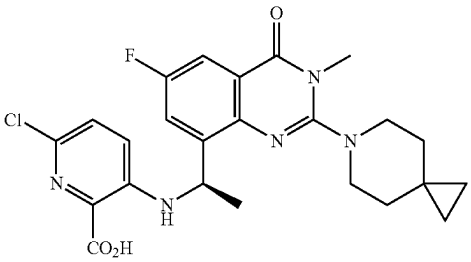
List of Compounds






TABLE A-continued

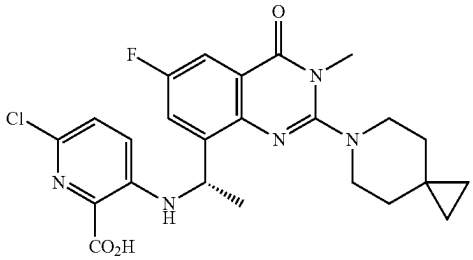
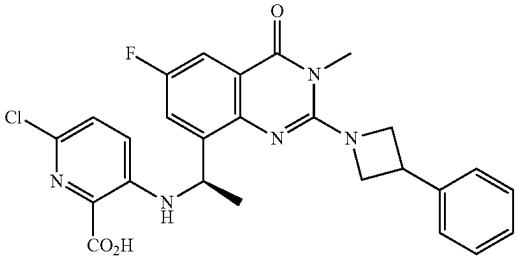
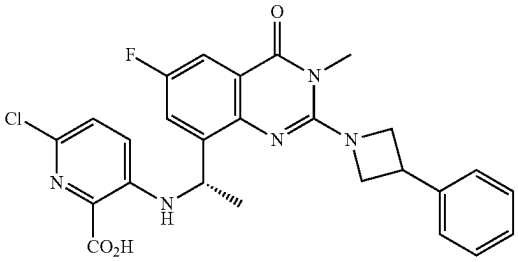
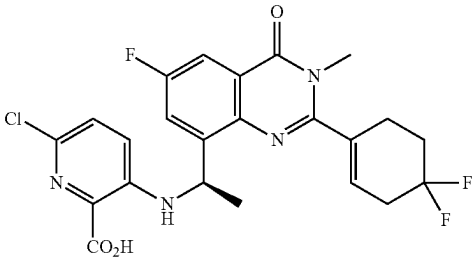
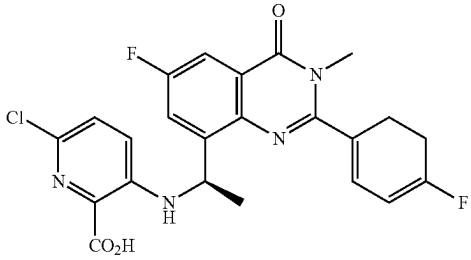
List of Compounds






TABLE A-continued

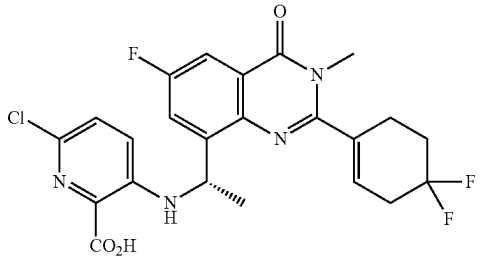
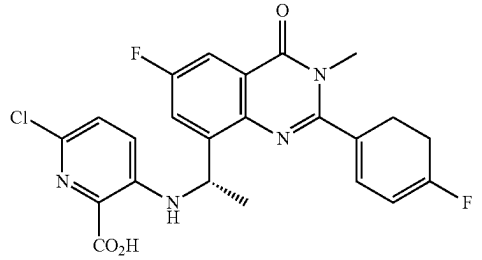
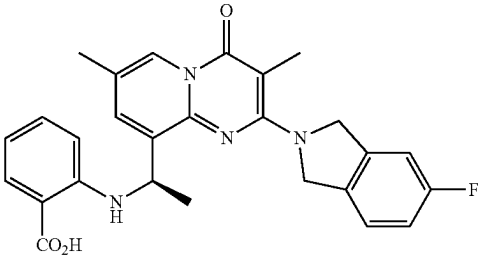
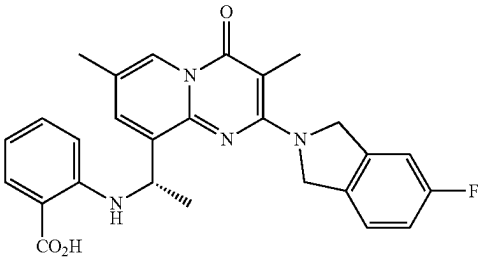
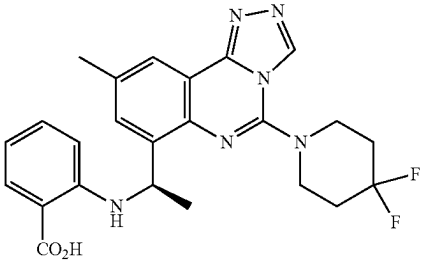
List of Compounds






TABLE A-continued

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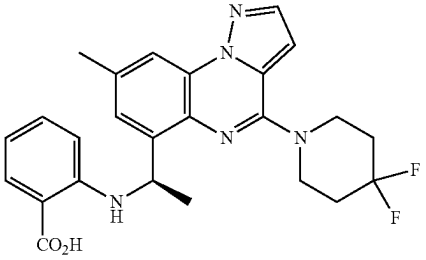
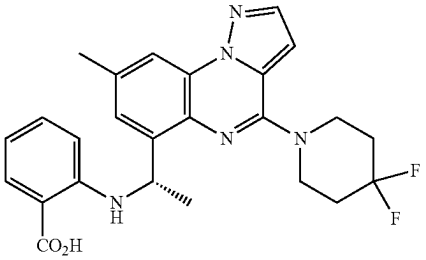
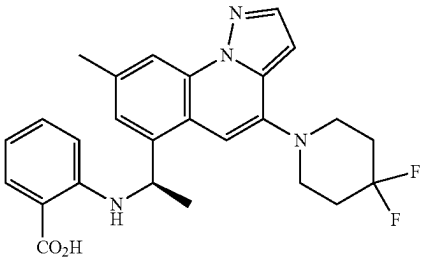
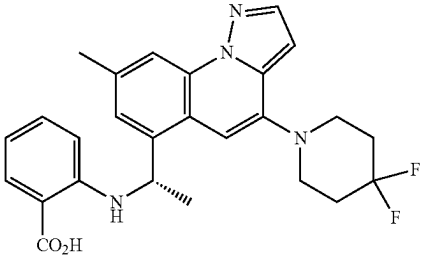
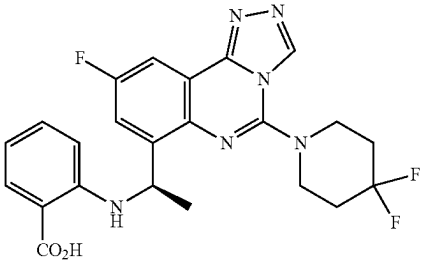

TABLE A-continued

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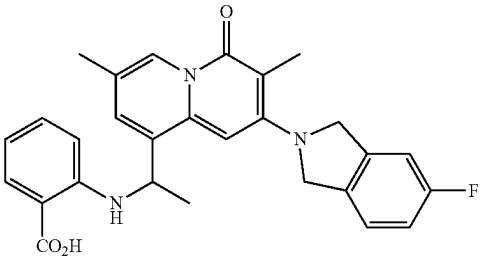
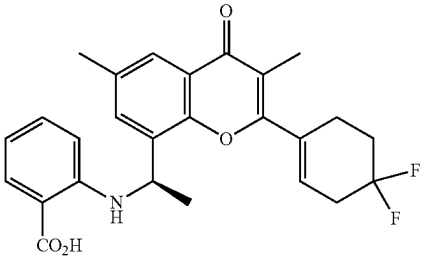
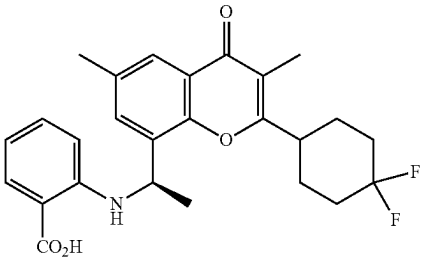
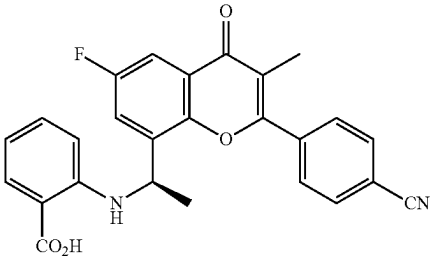
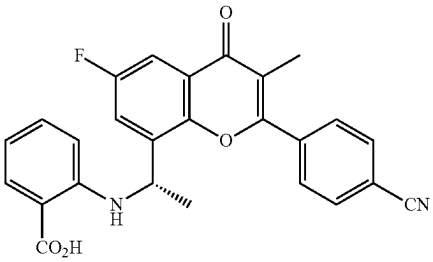

TABLE A-continued

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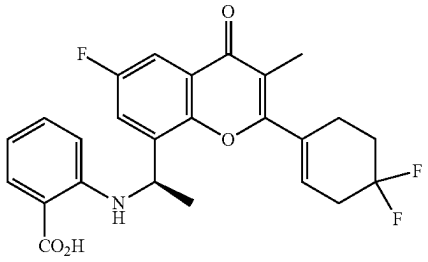
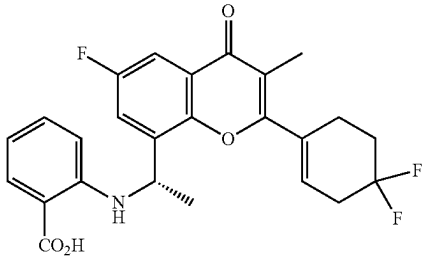
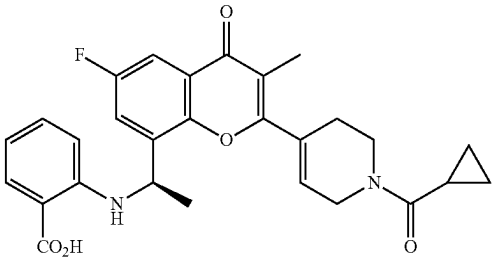
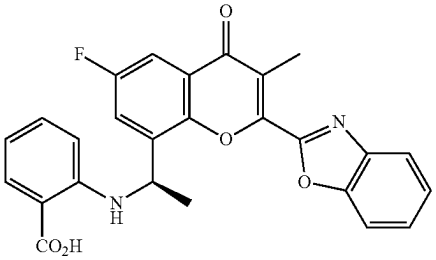
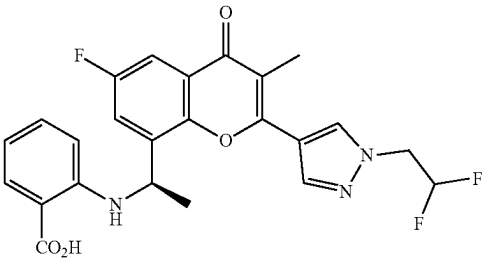

TABLE A-continued

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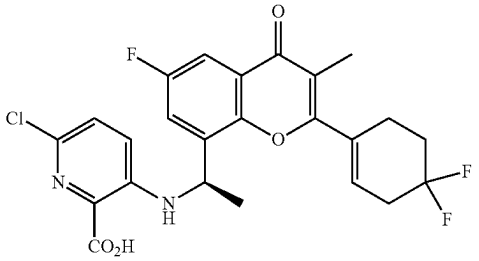
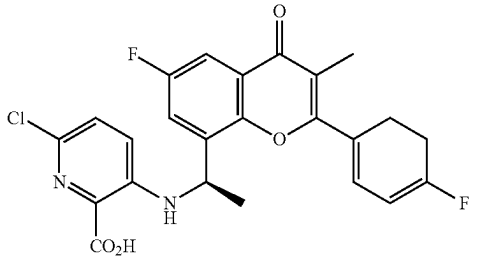
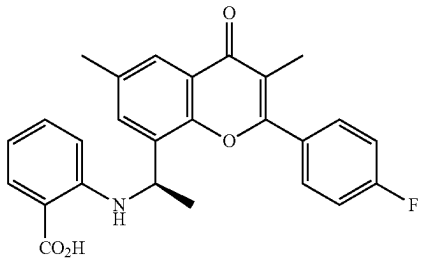
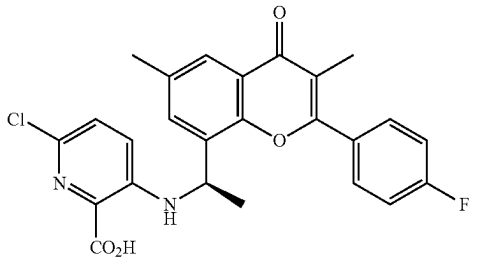
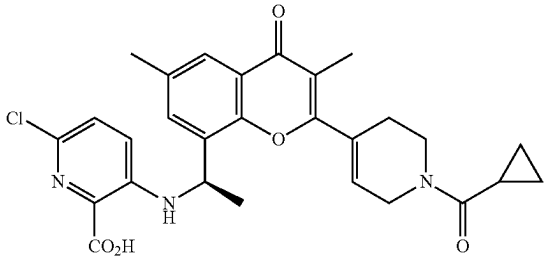

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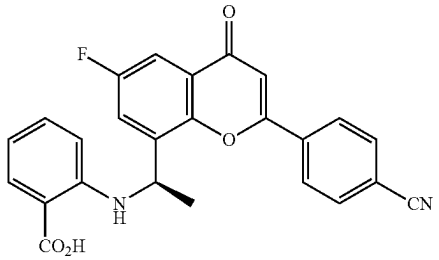
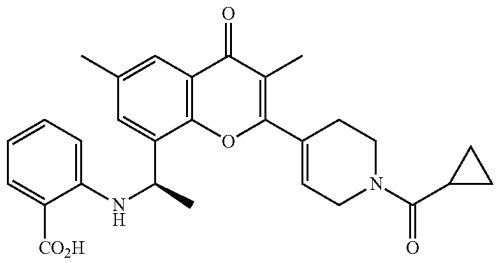
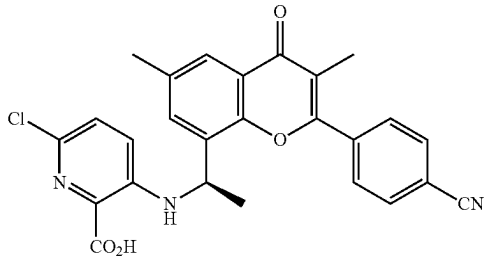
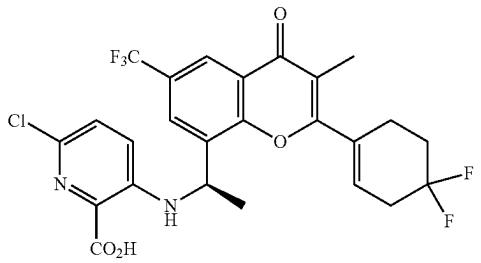
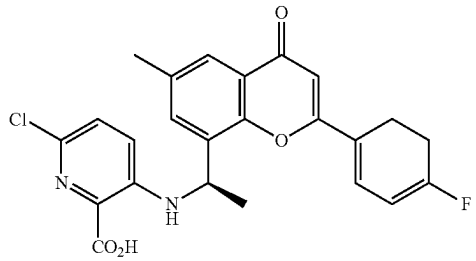

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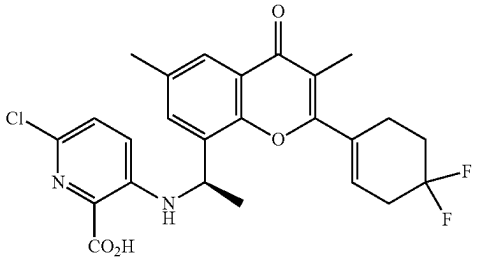
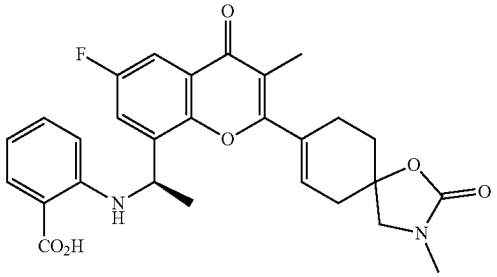
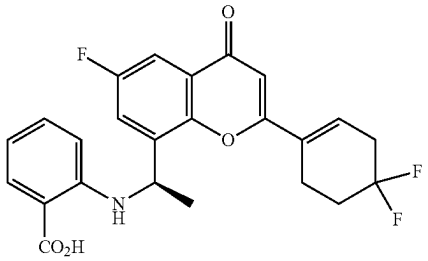
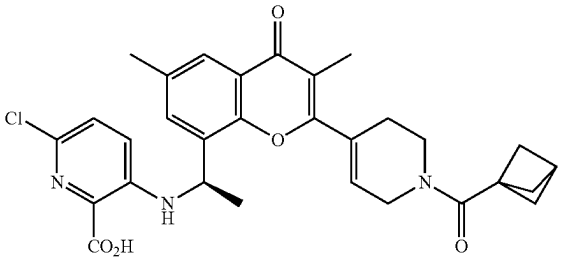
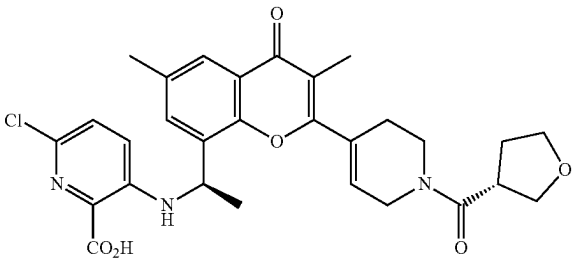

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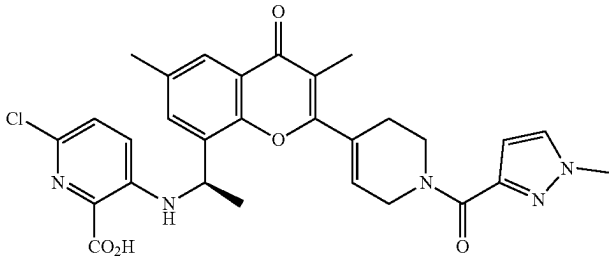
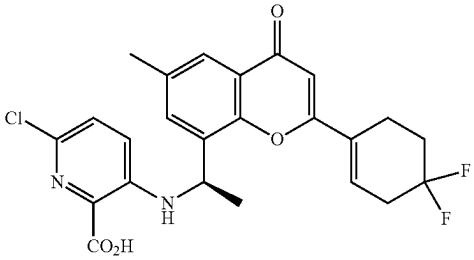
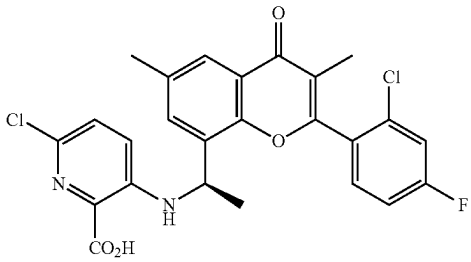
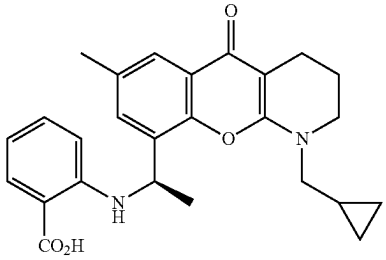
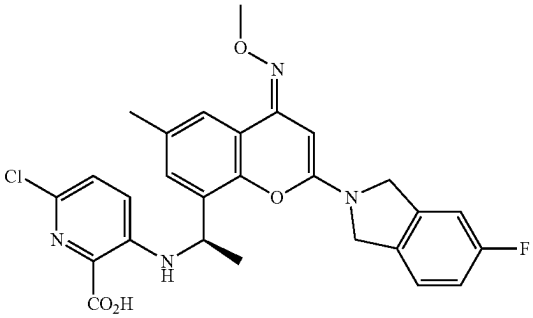

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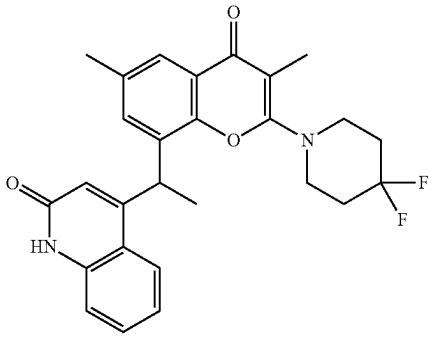
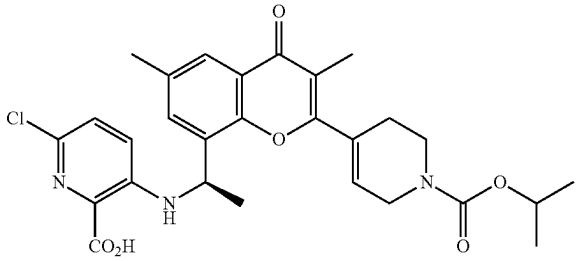
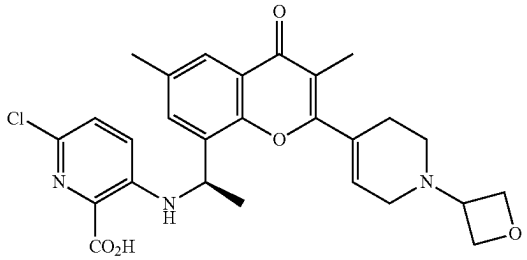
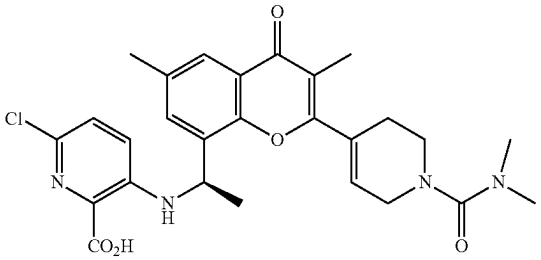
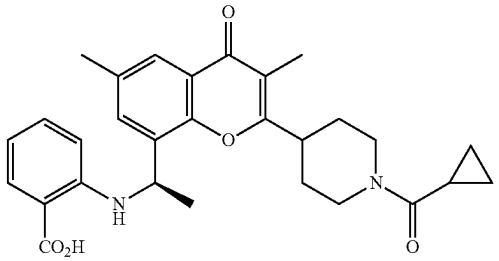

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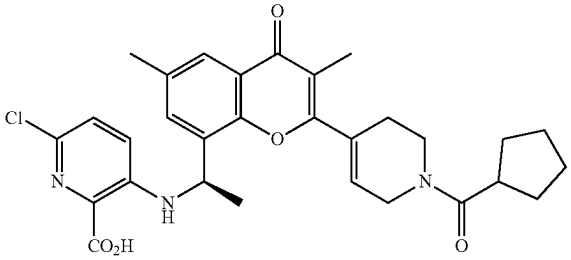
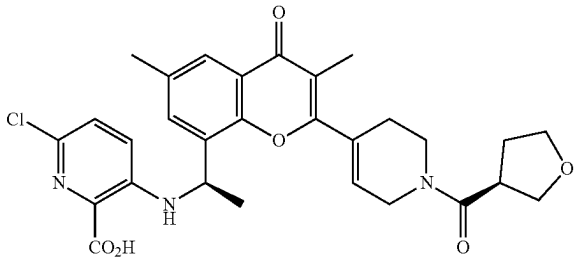
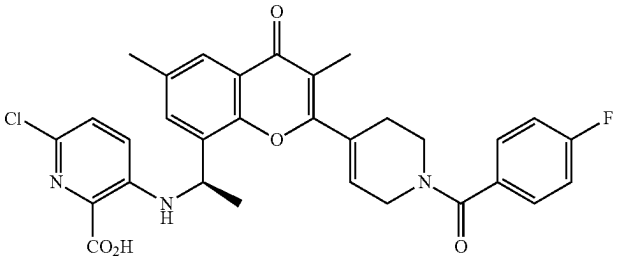
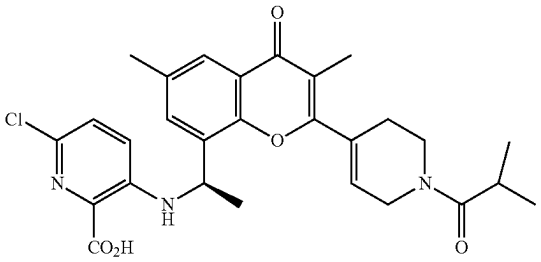
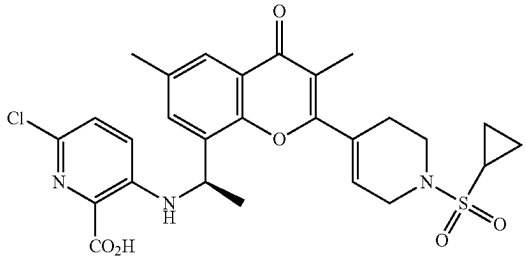

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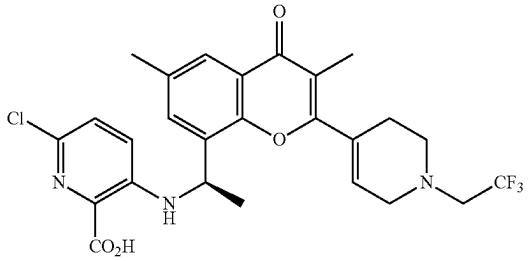
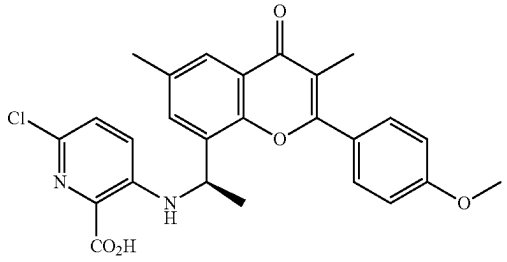
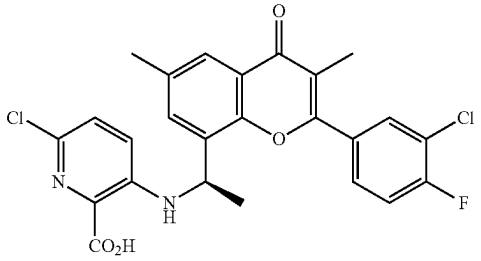
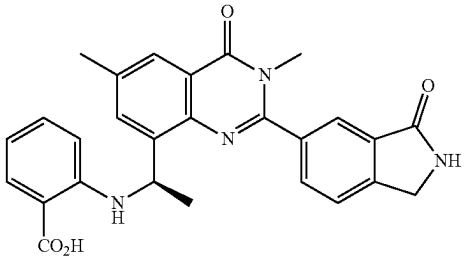
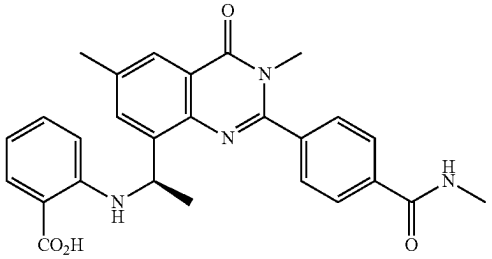

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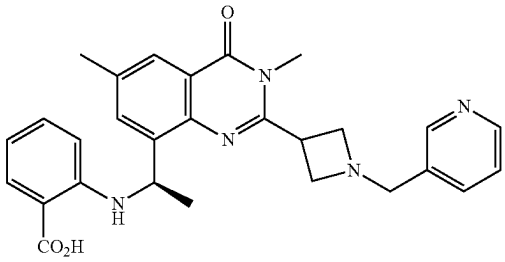
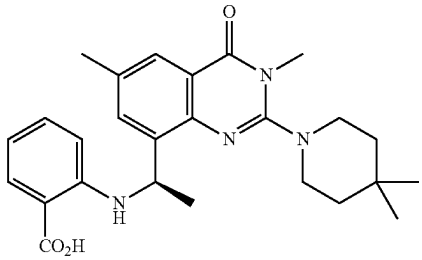
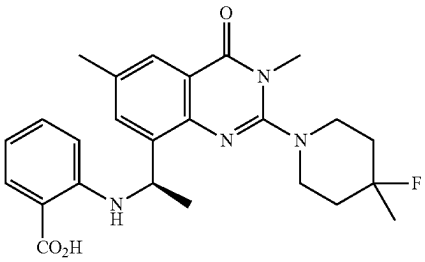
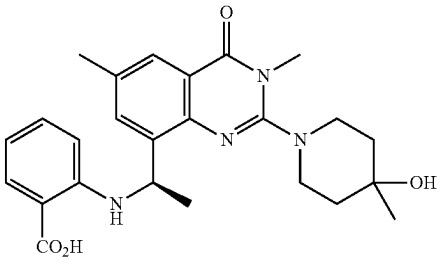
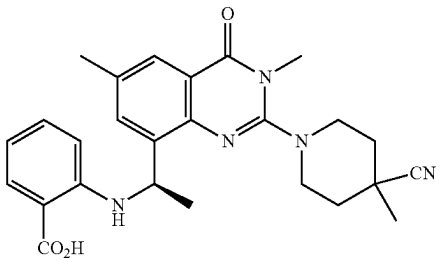

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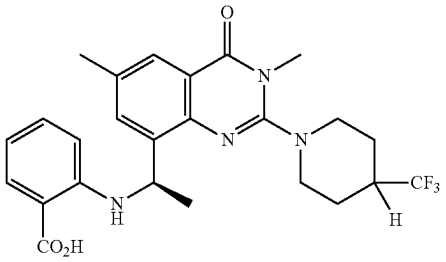
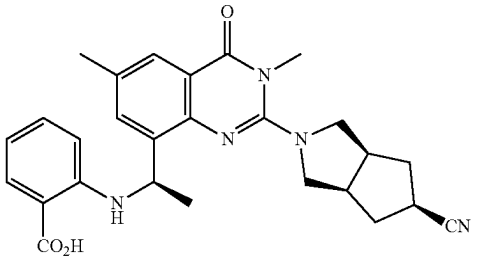
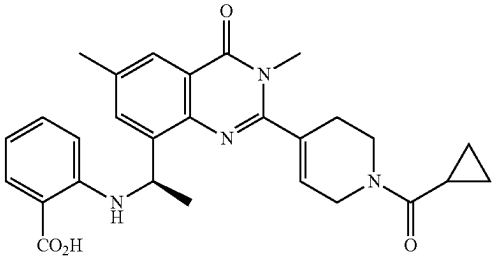
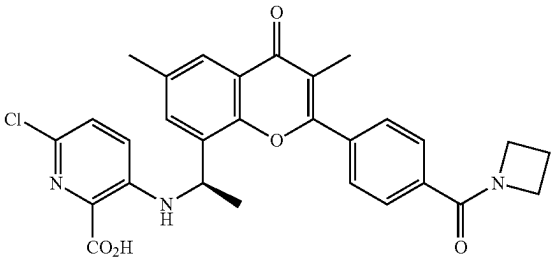
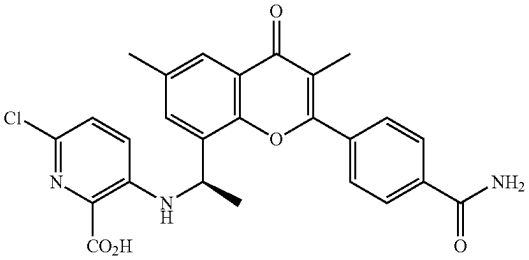

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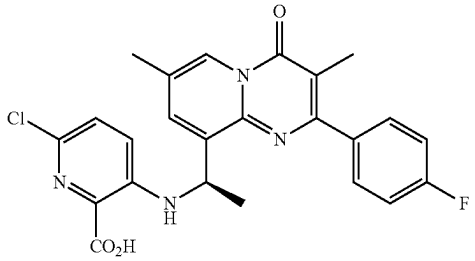
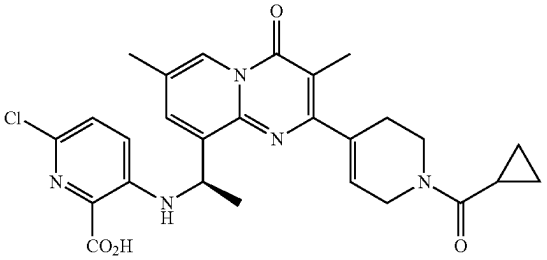
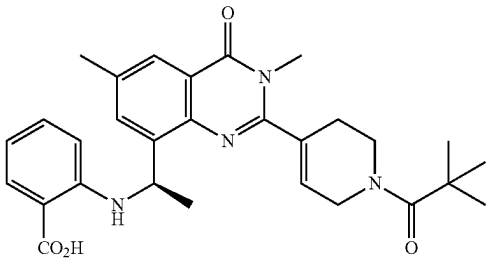
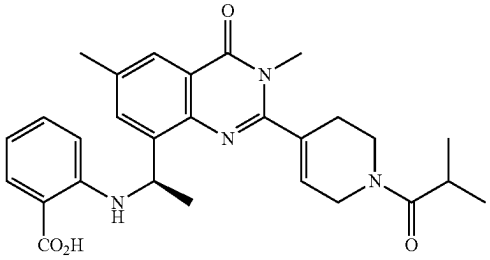
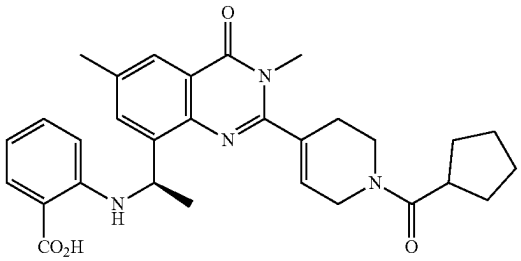

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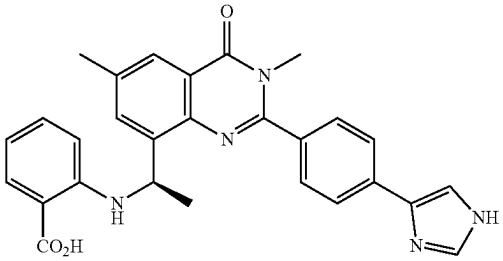
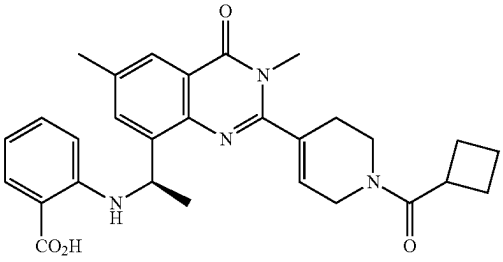
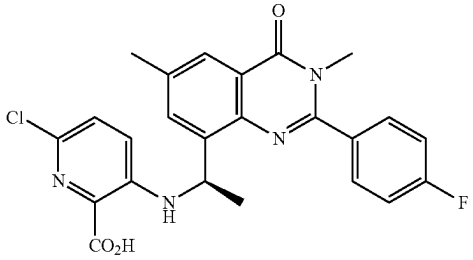
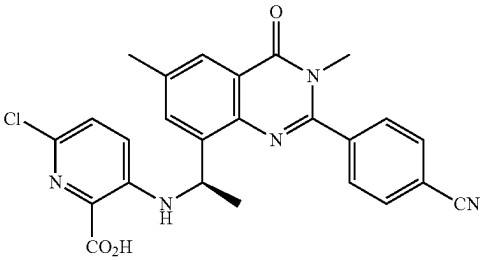
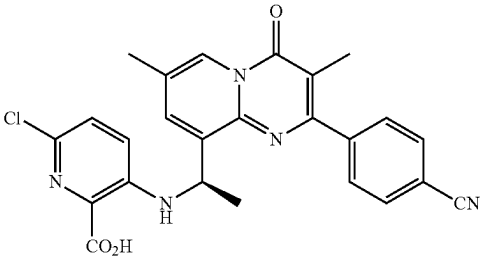

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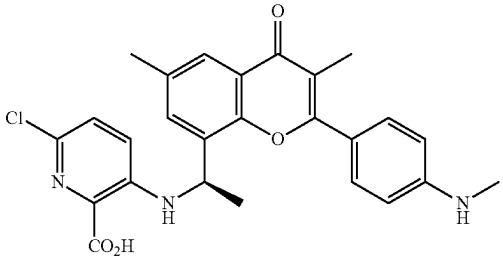
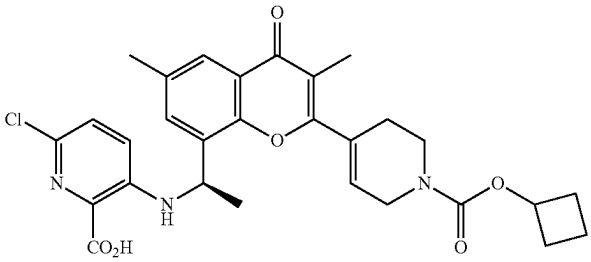
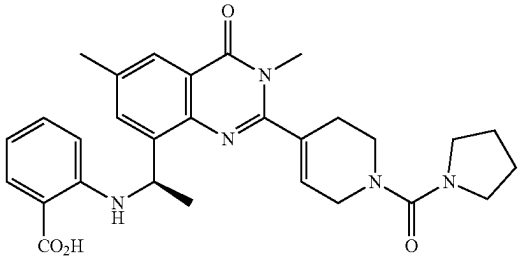
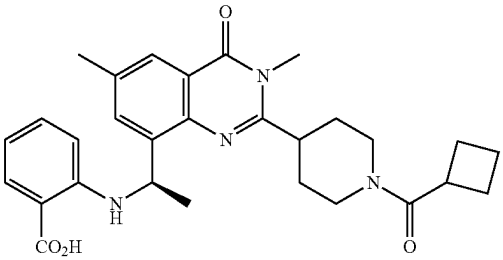
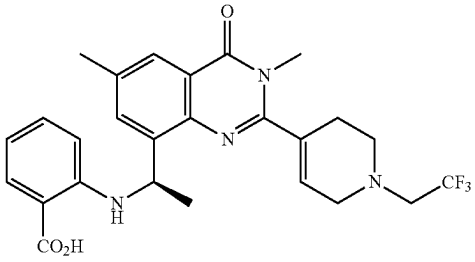

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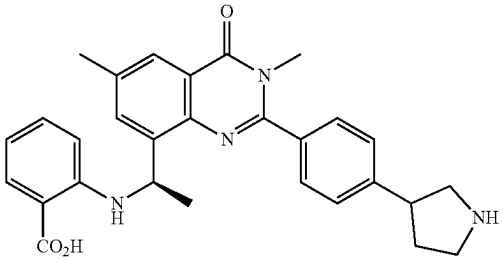
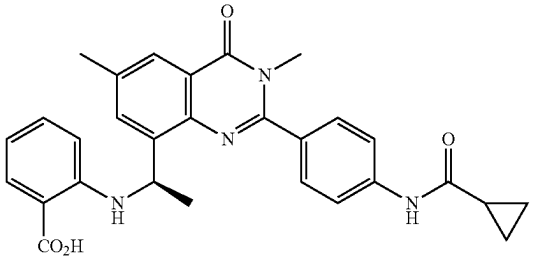
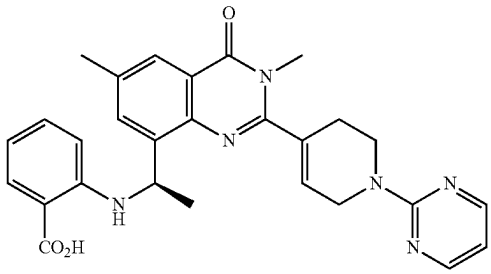
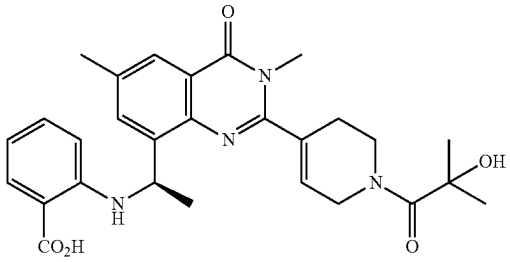
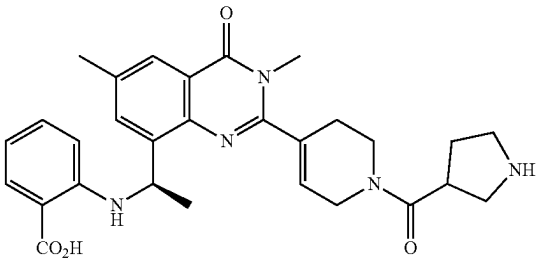

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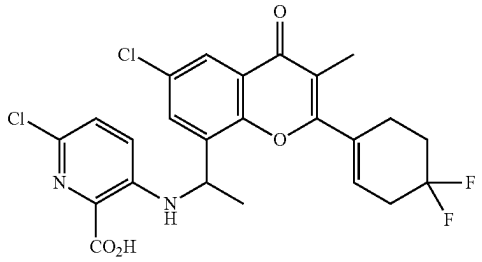
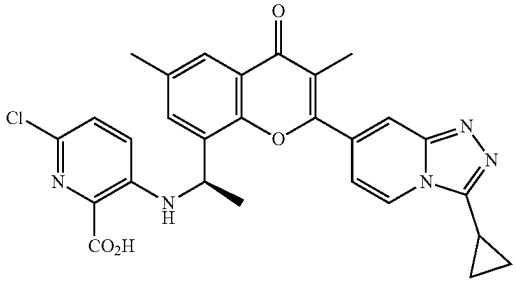
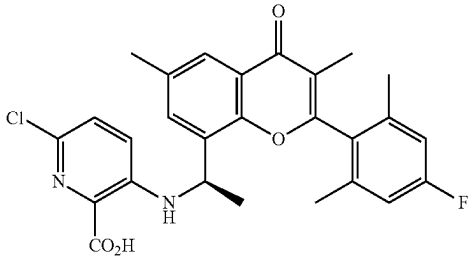
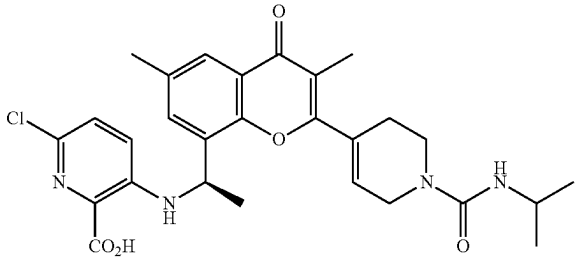
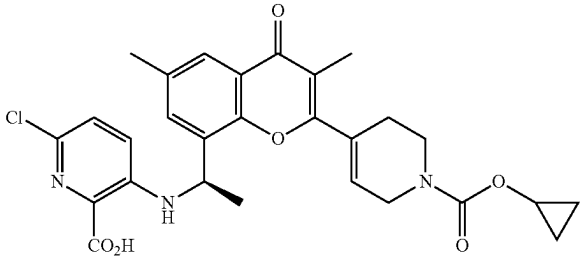

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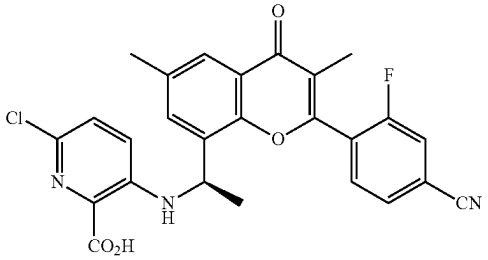
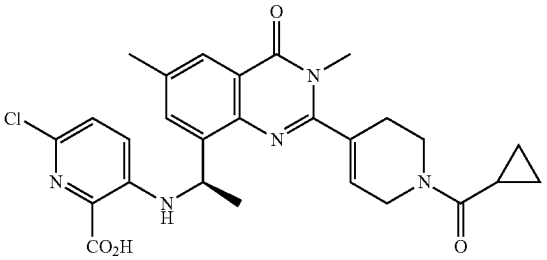
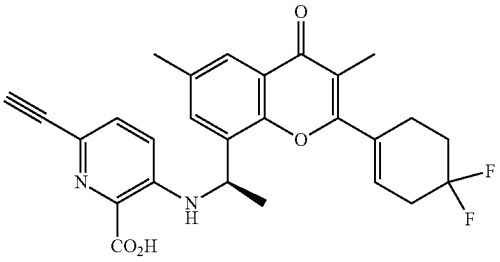
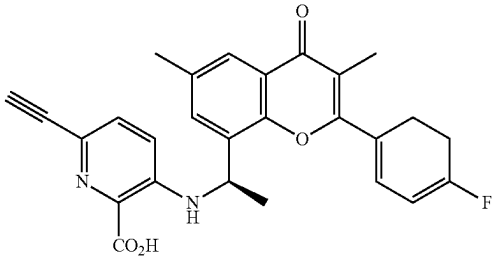
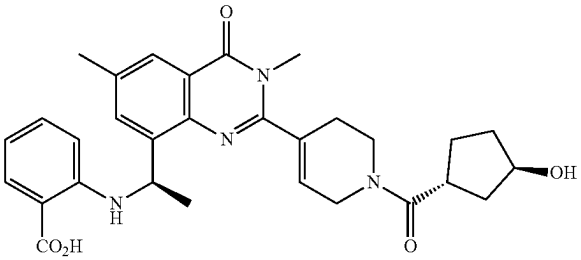

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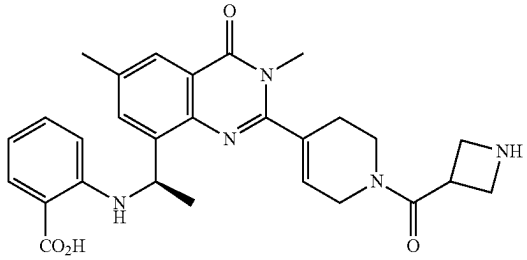
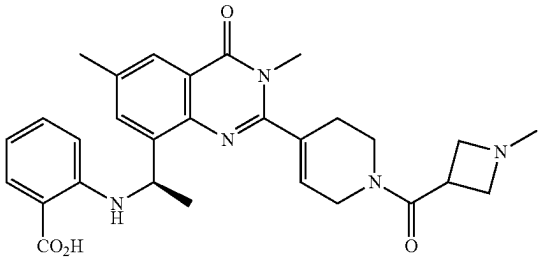
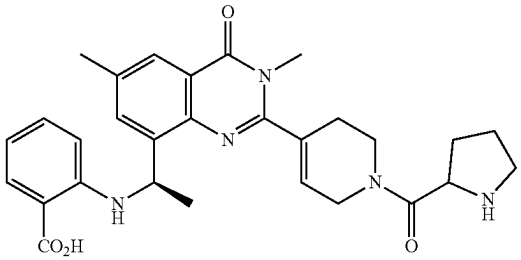
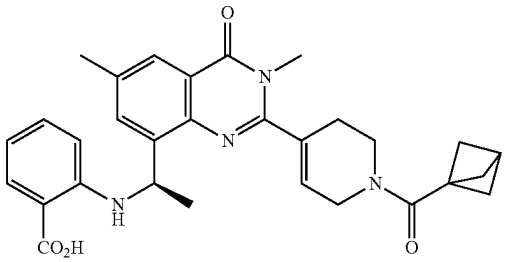
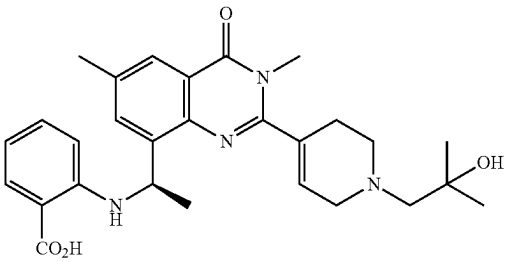

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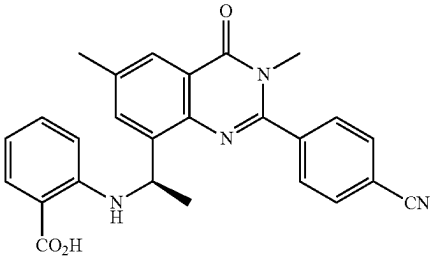
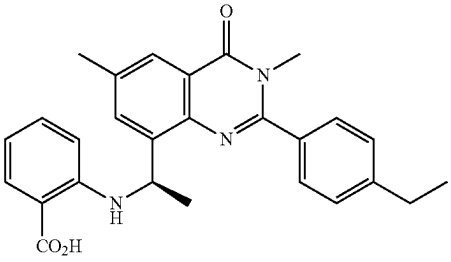
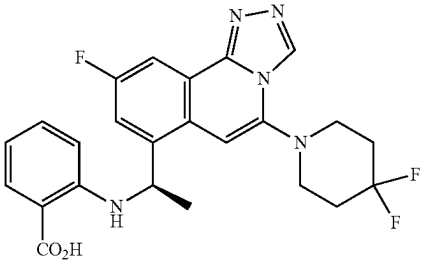
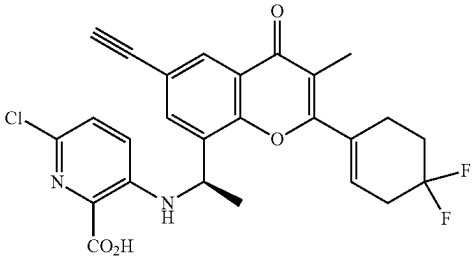
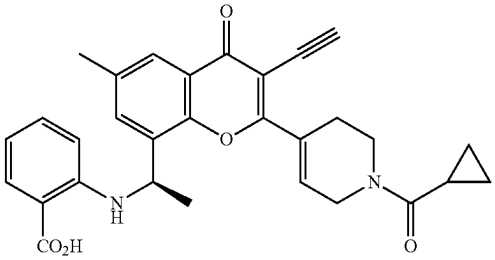

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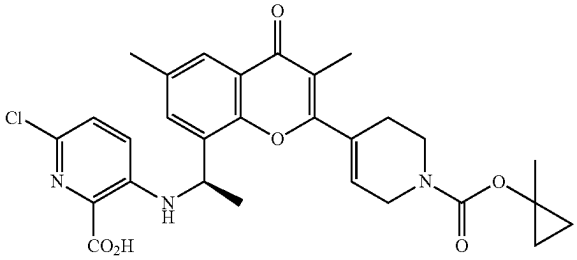
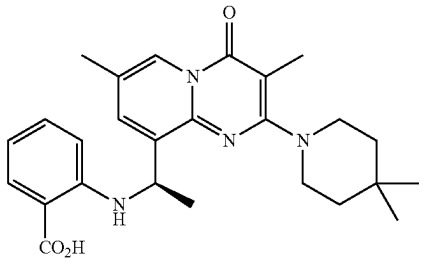
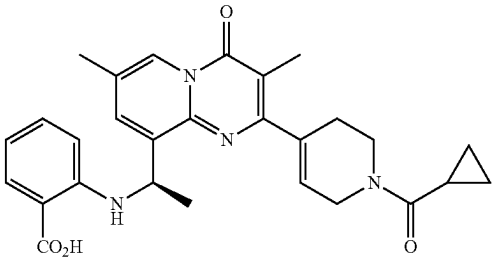
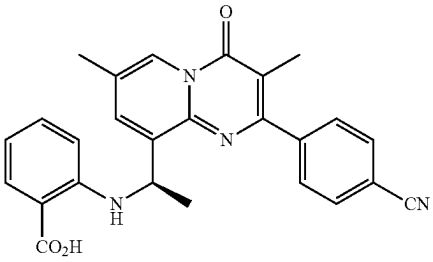
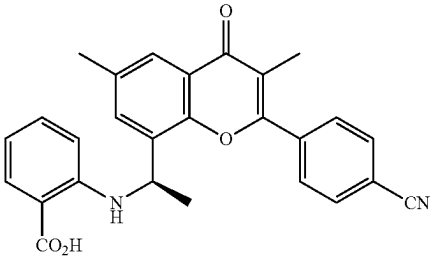

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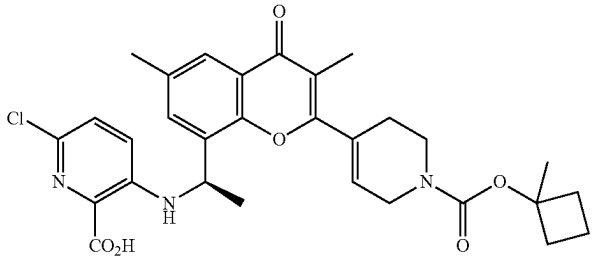
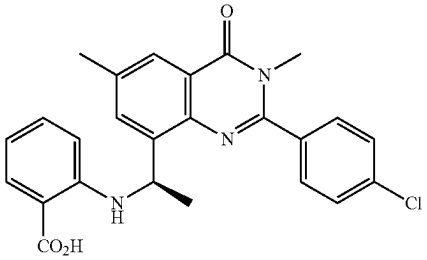
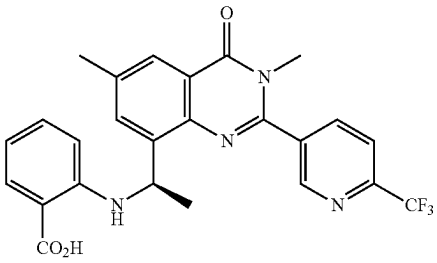
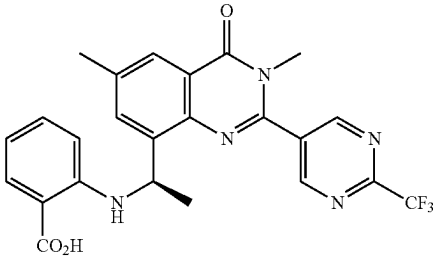
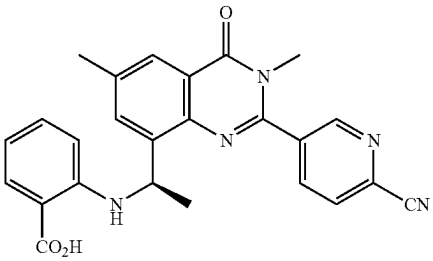

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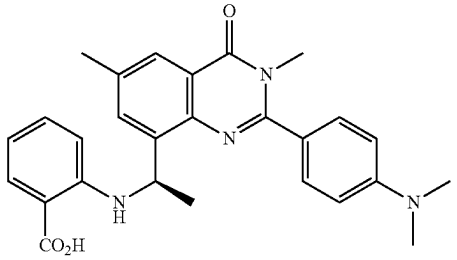
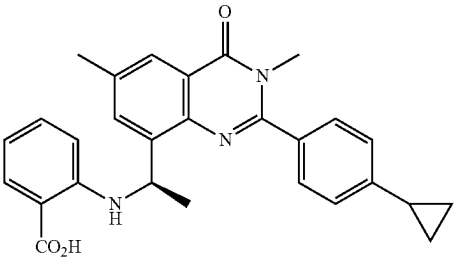
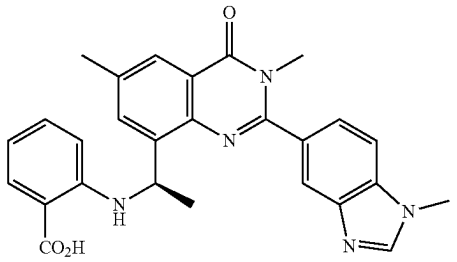
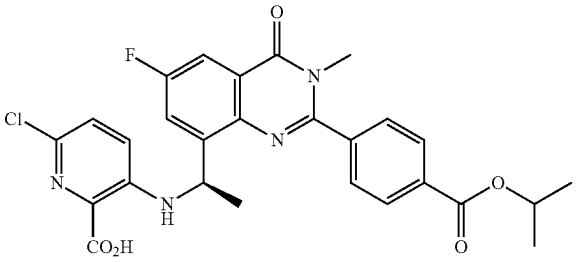
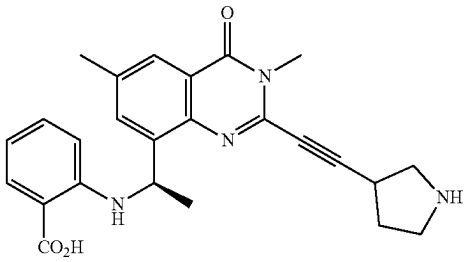

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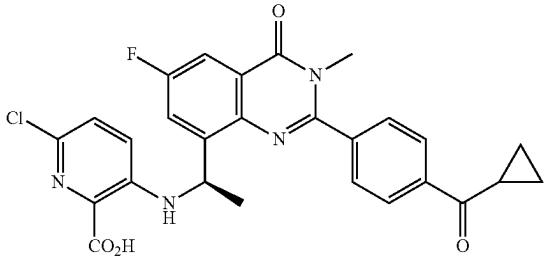
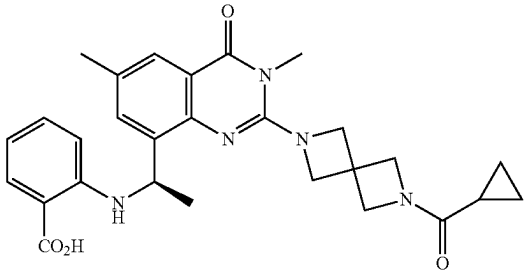
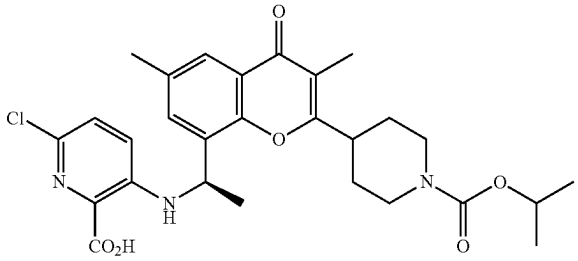
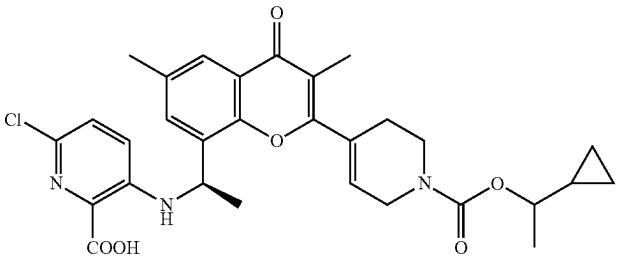
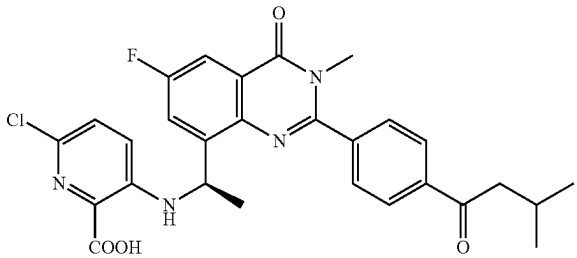

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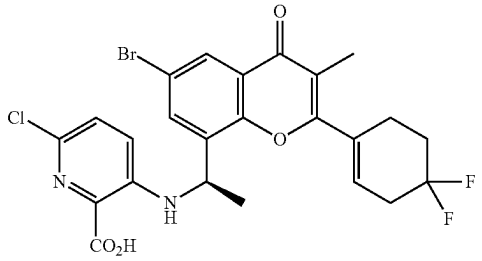
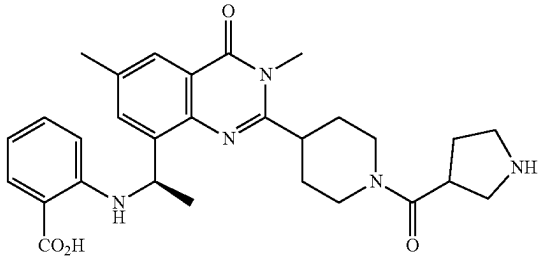
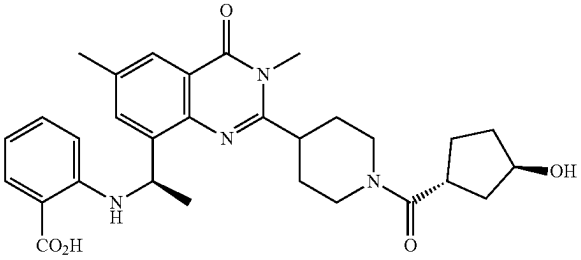
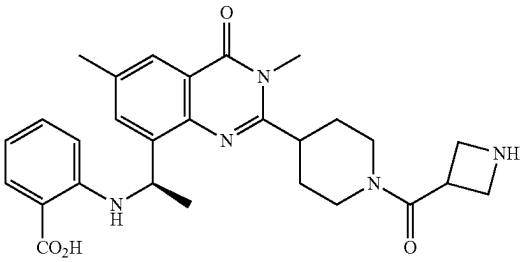
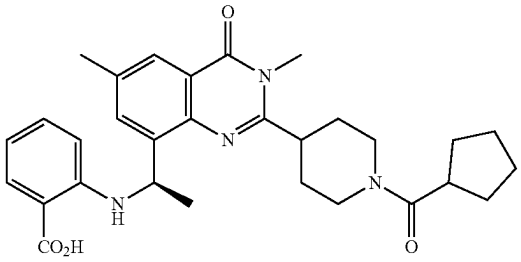

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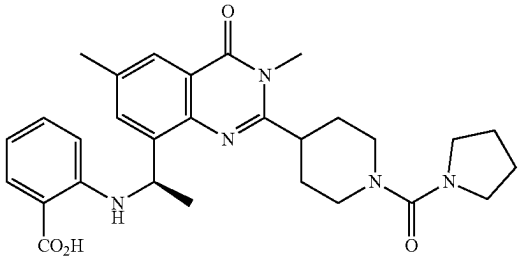
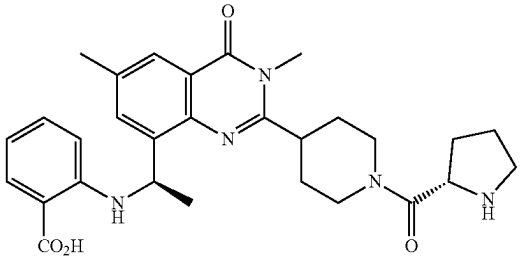
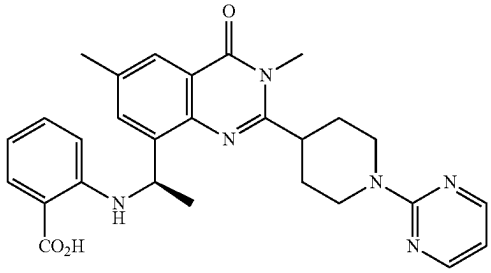
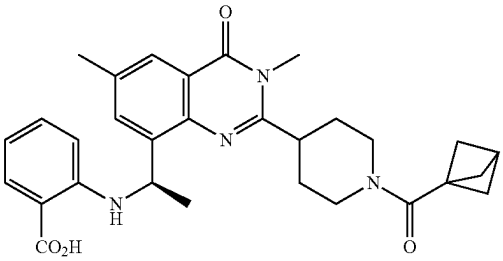
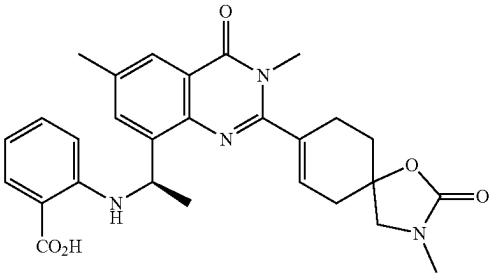

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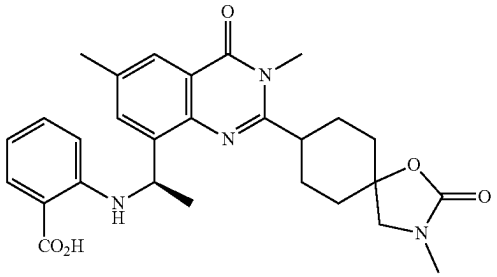
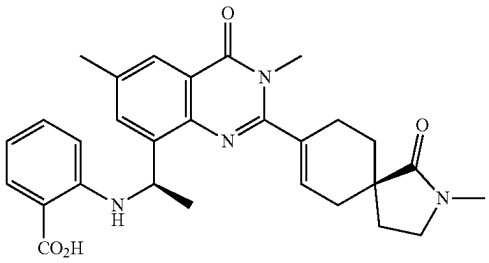
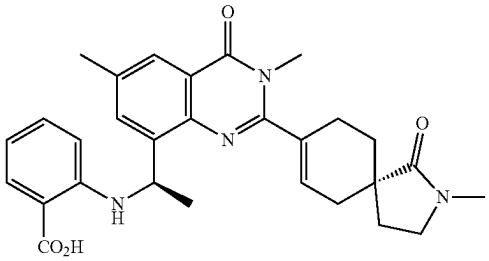
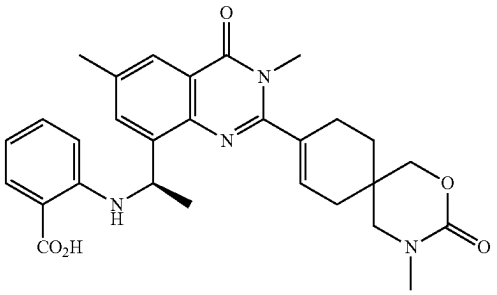
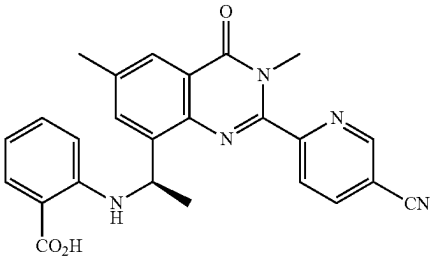

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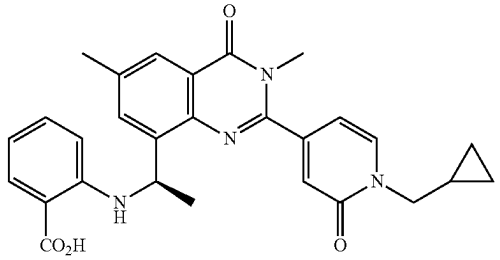
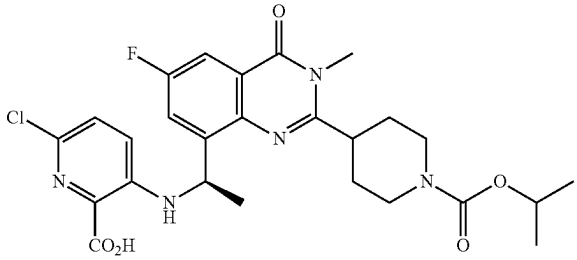
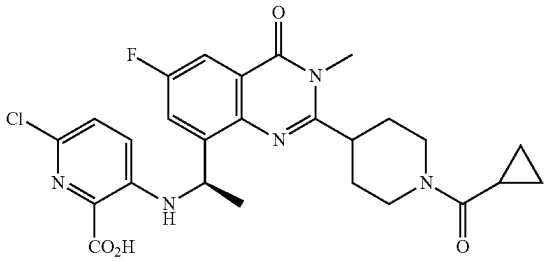
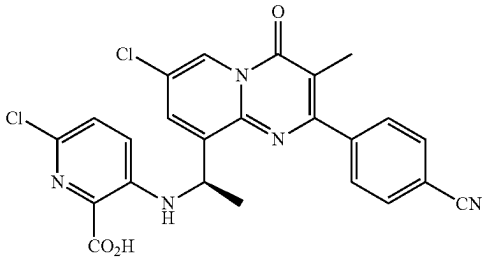
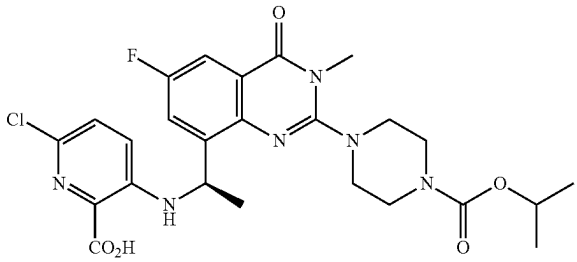

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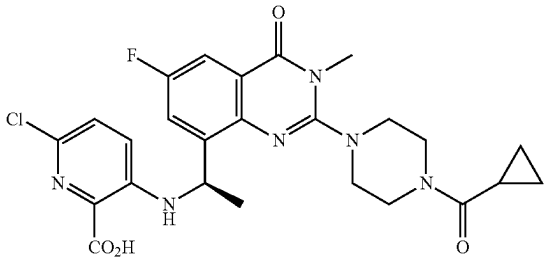
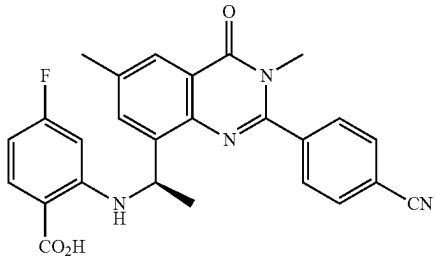
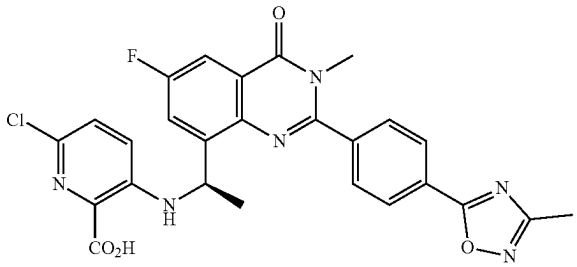
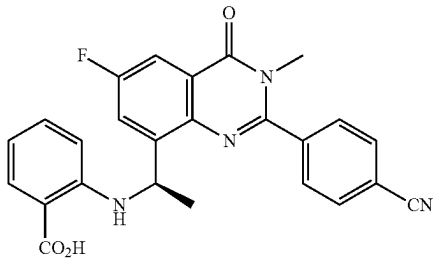
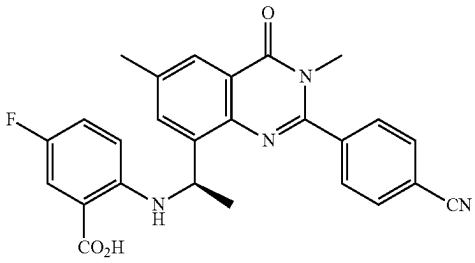

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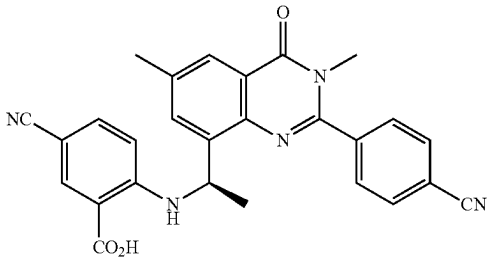
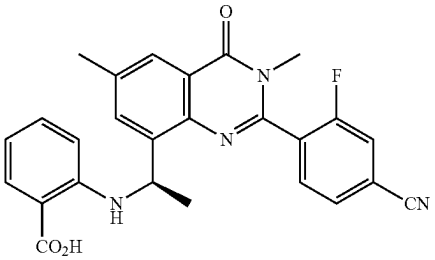
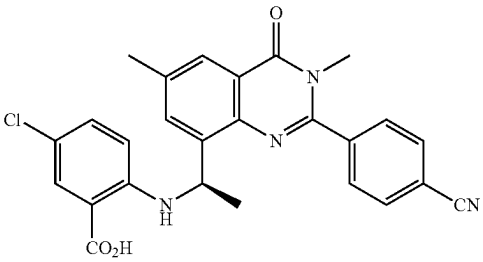
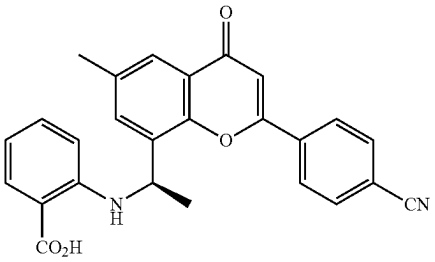
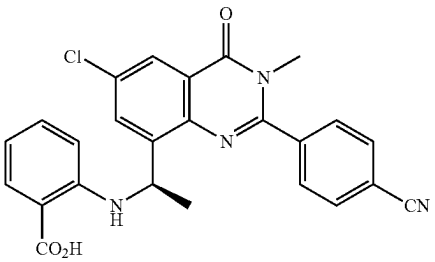

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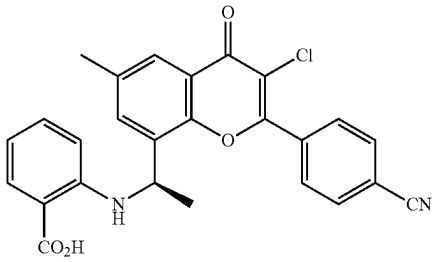
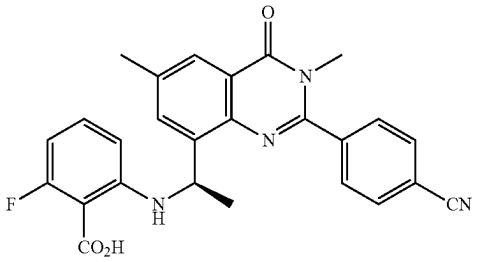
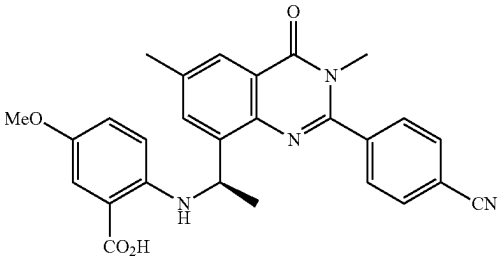
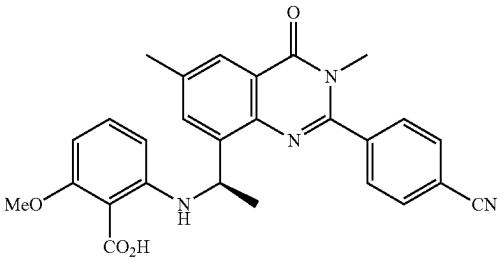
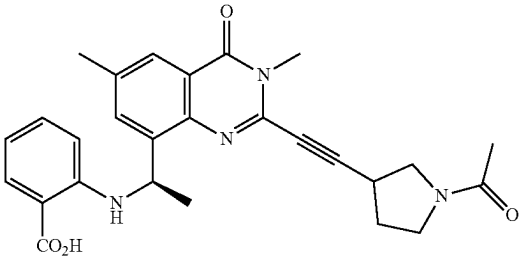

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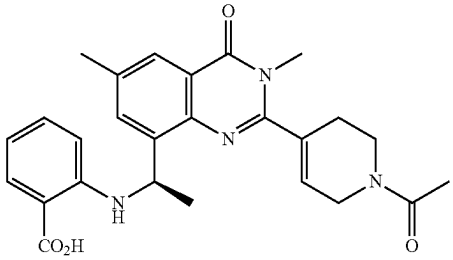
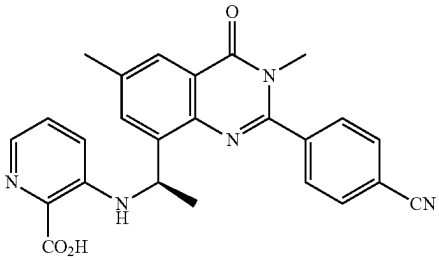
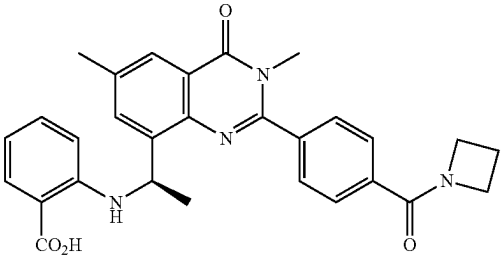
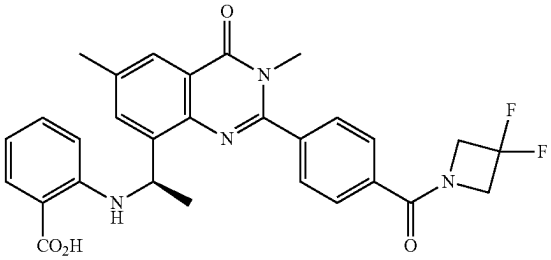
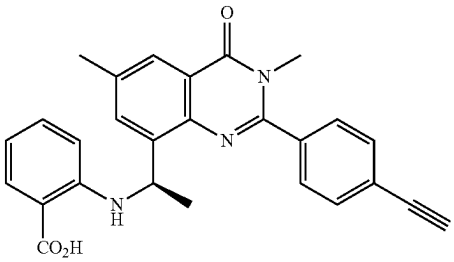

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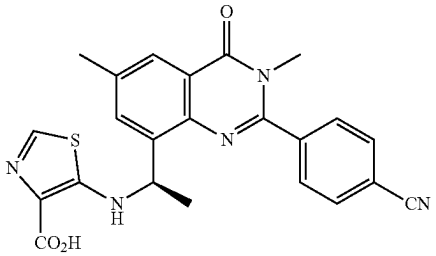
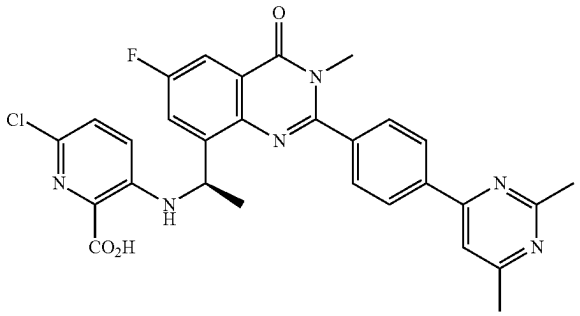
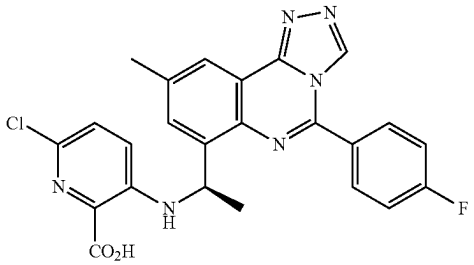
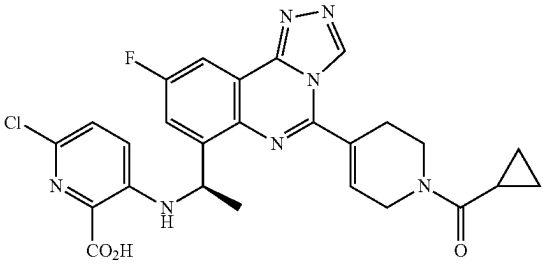
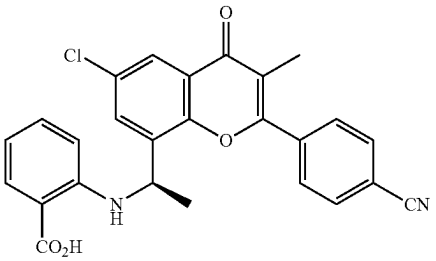

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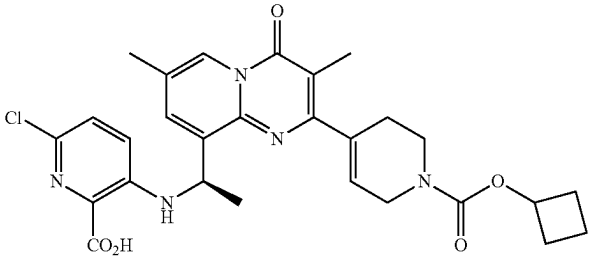
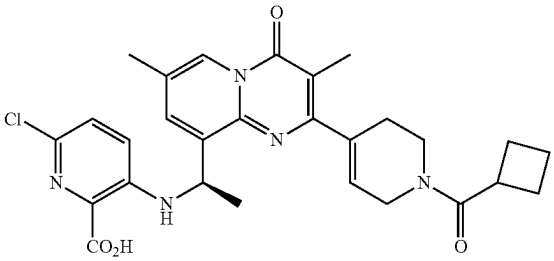
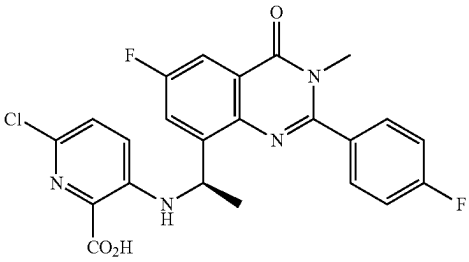
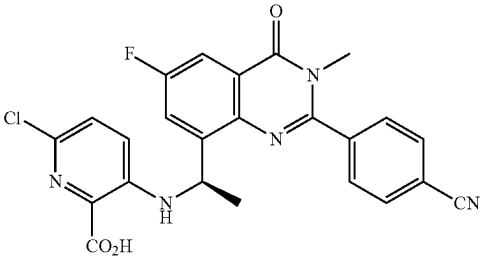
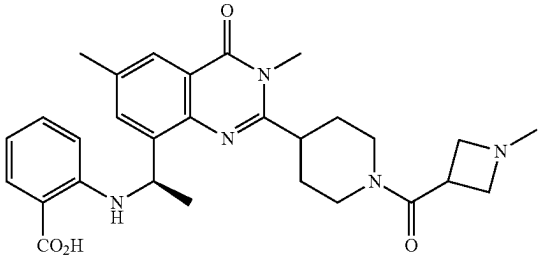

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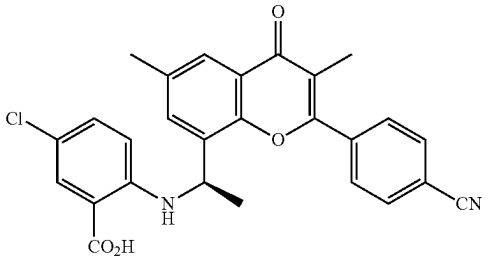
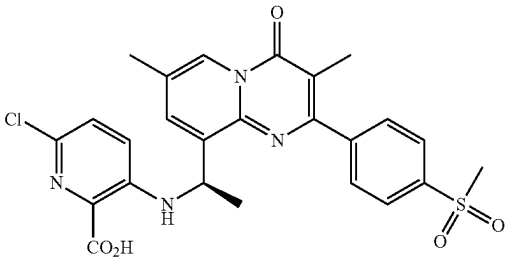
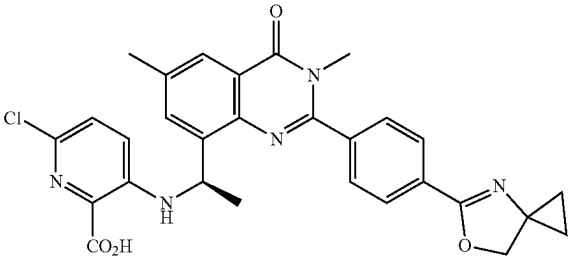
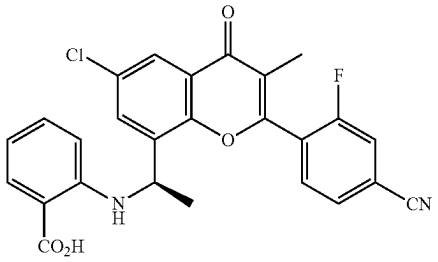
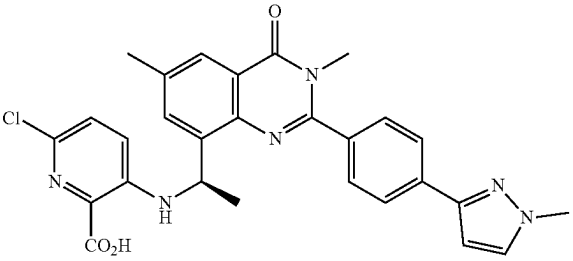

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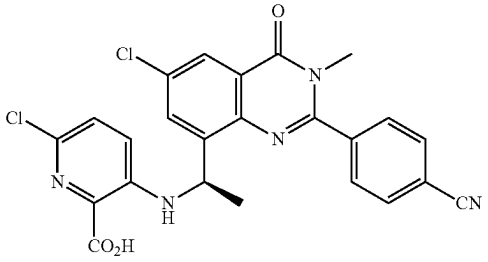
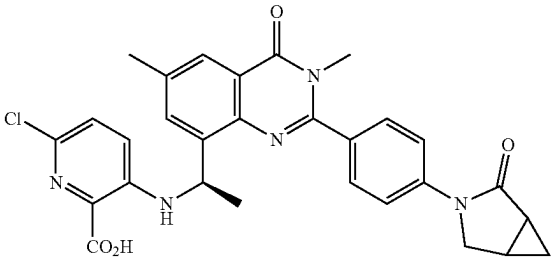
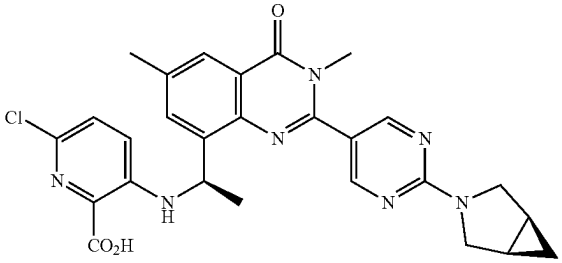
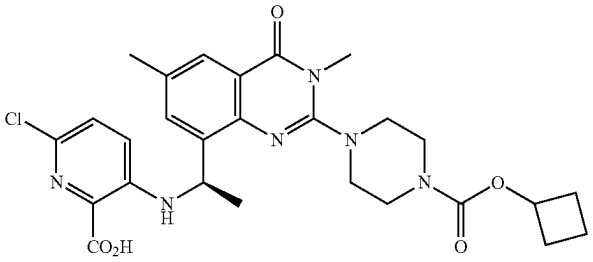
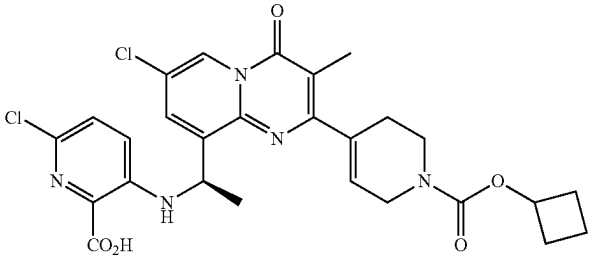

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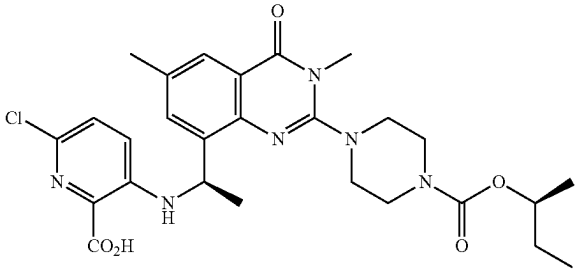
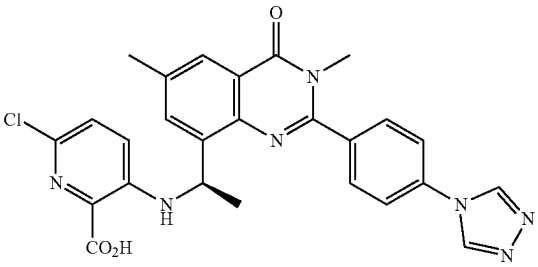
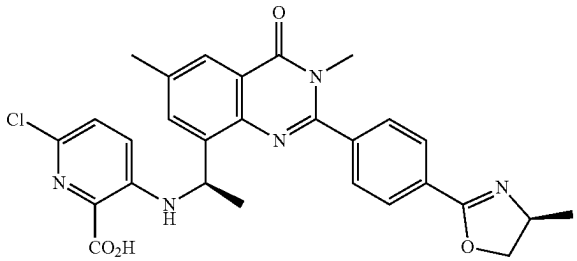
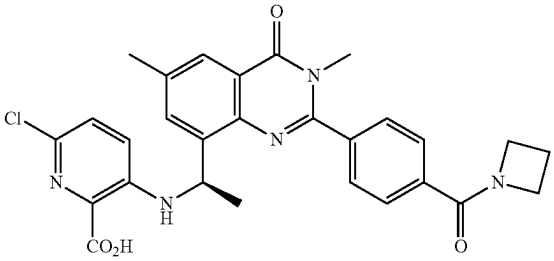
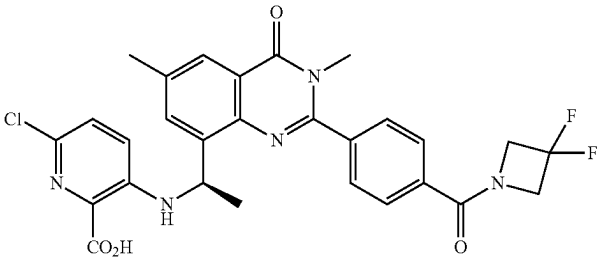

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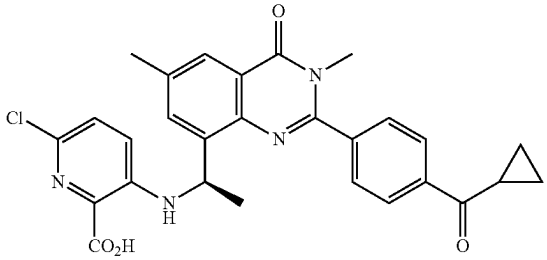
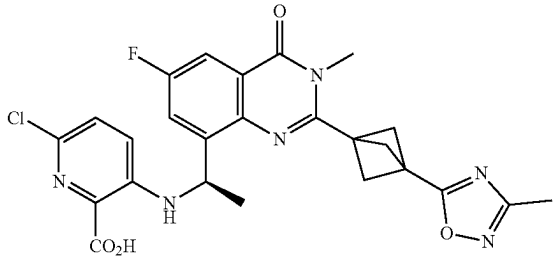
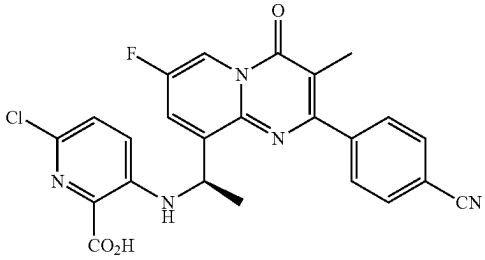
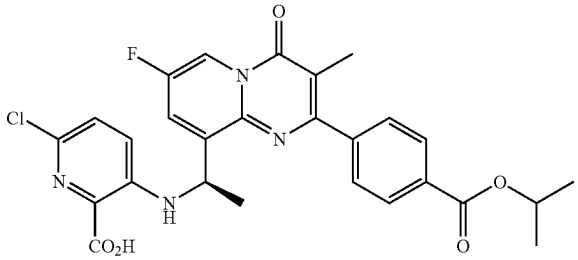
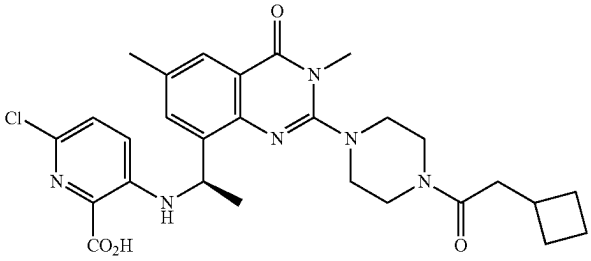

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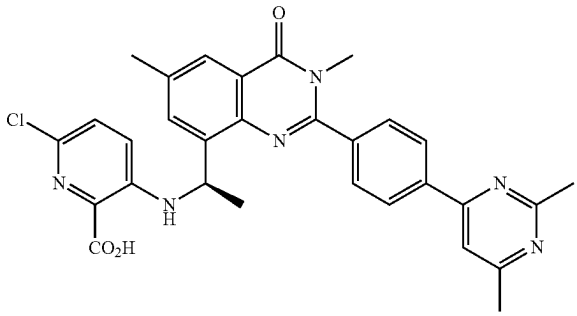
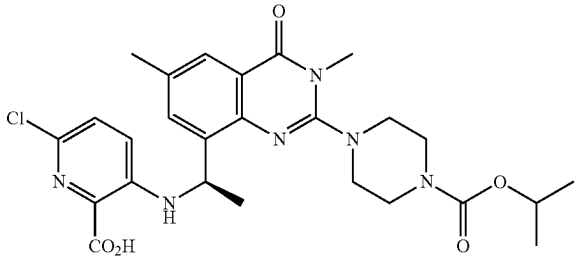
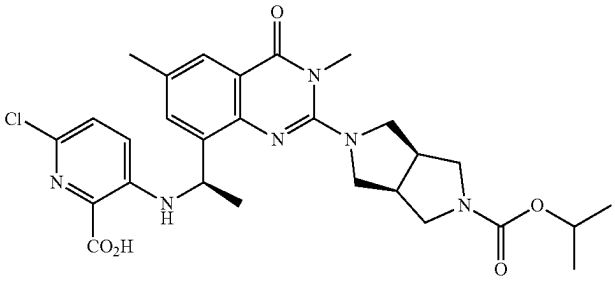
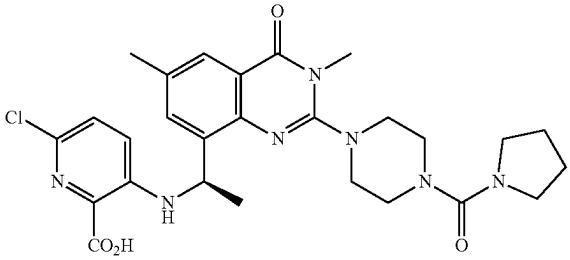
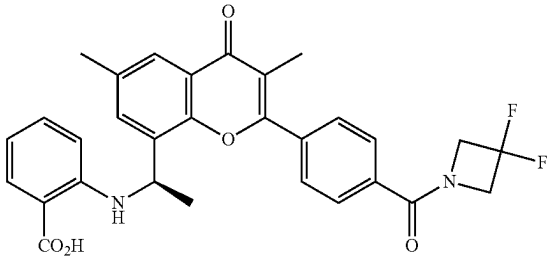

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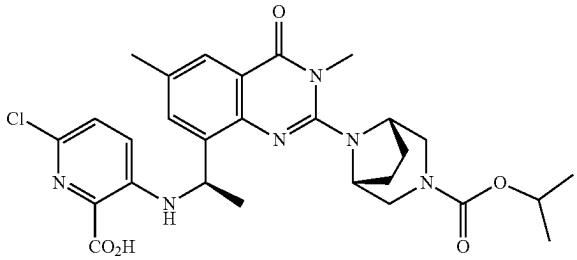
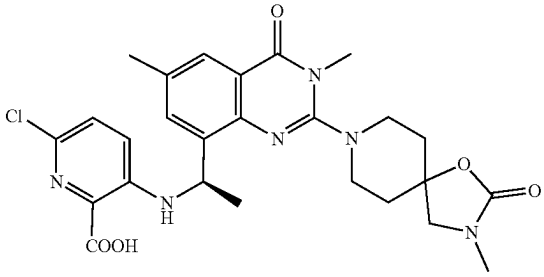
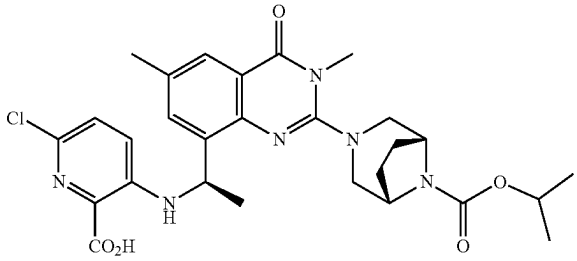
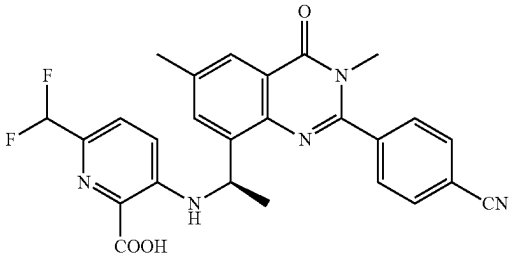
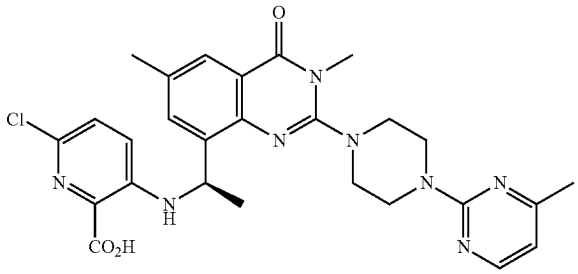

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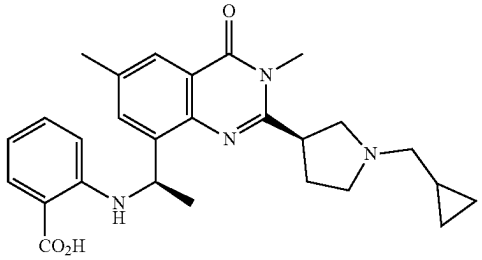
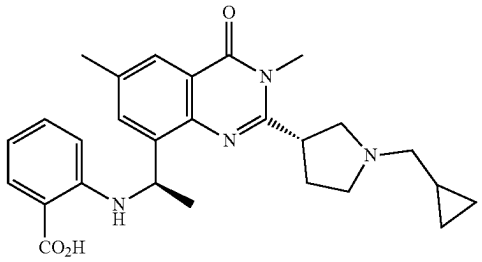
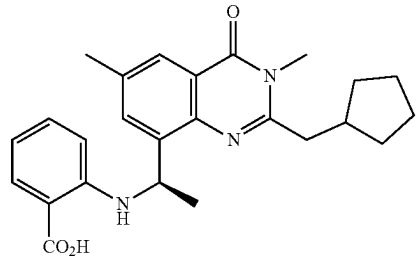
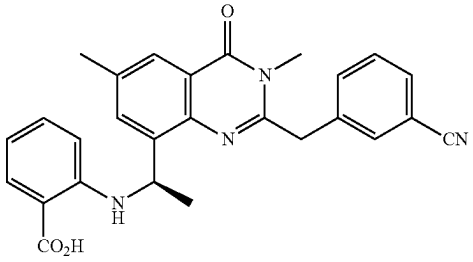
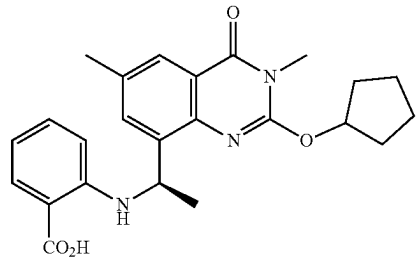

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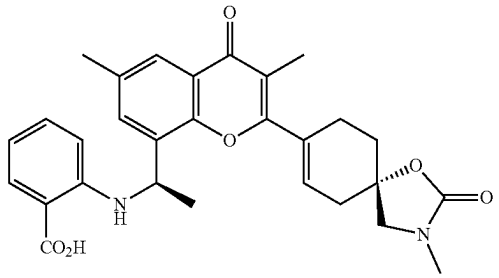
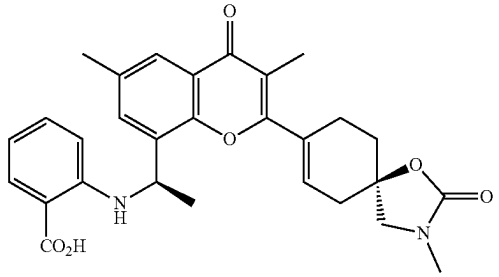
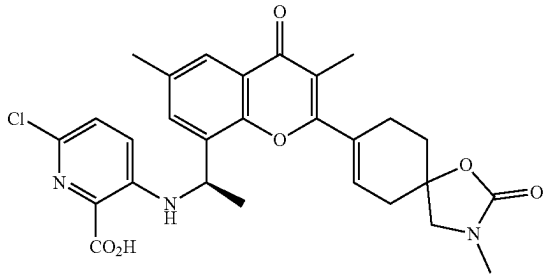
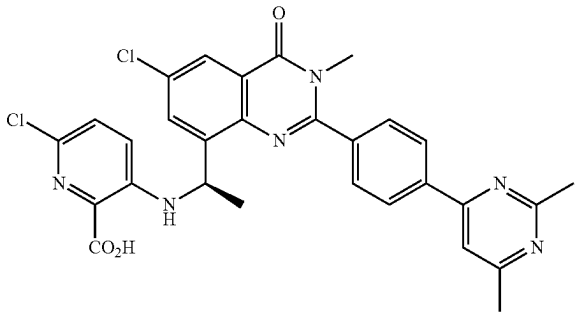
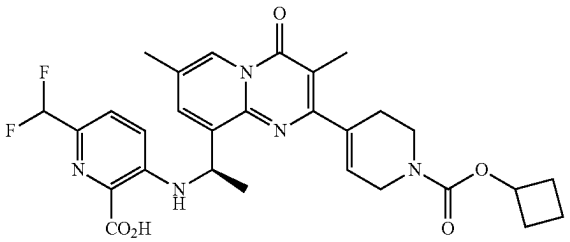

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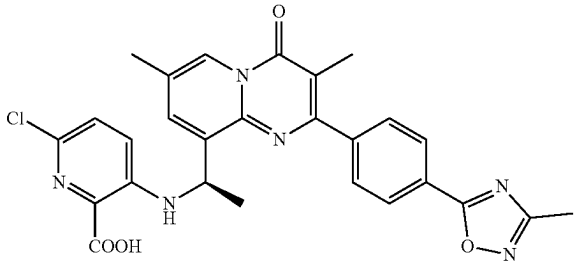
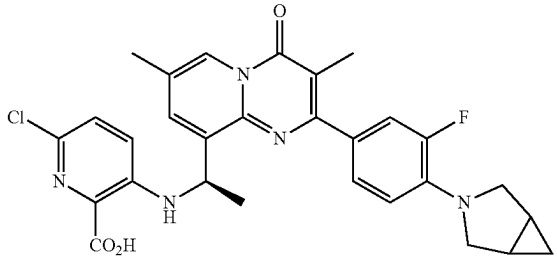
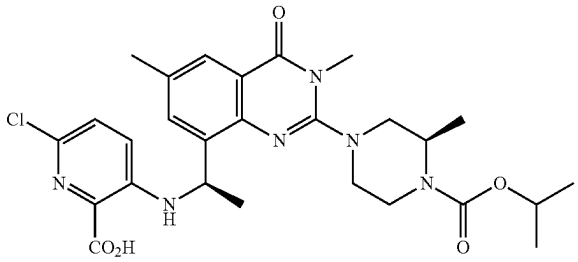
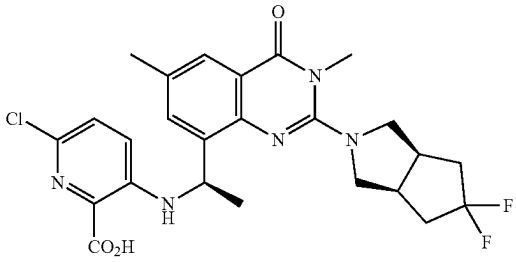
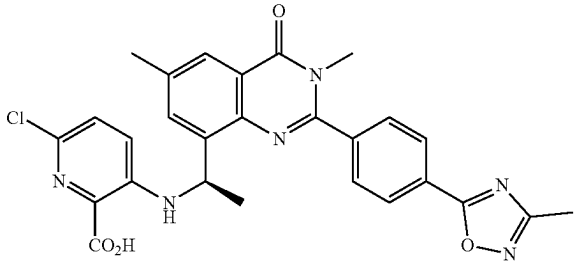

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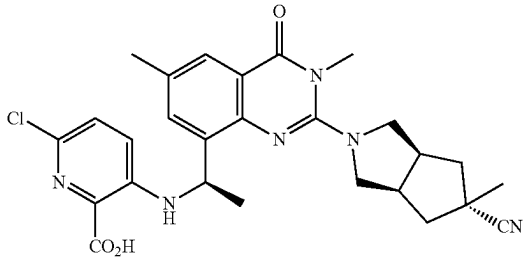
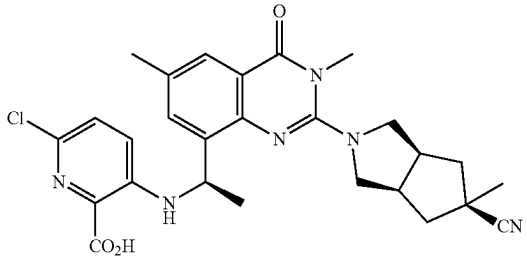
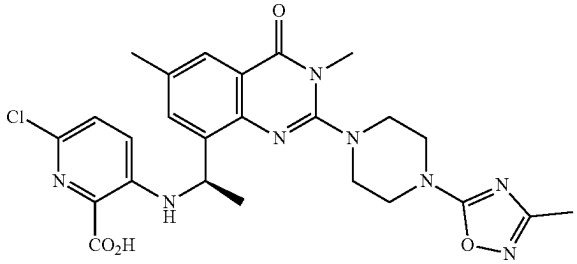
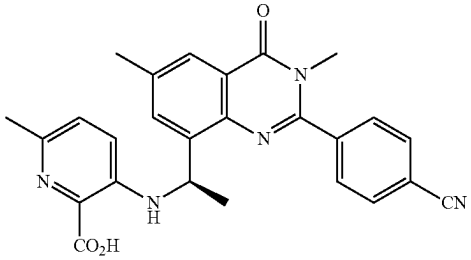
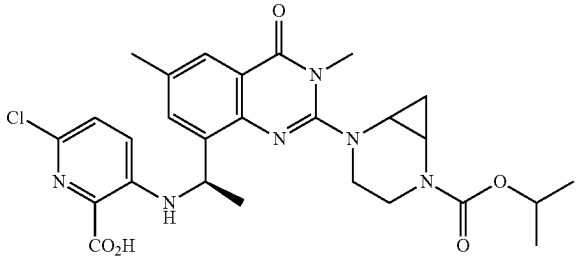

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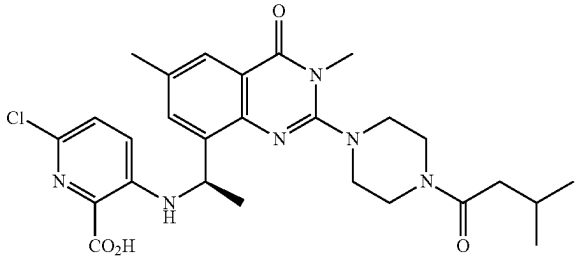
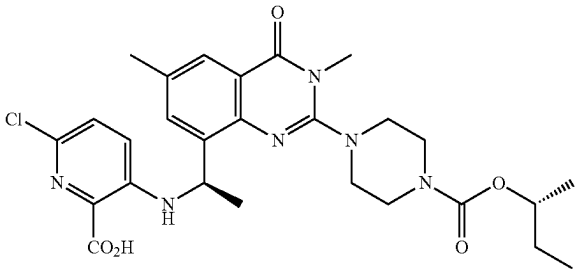
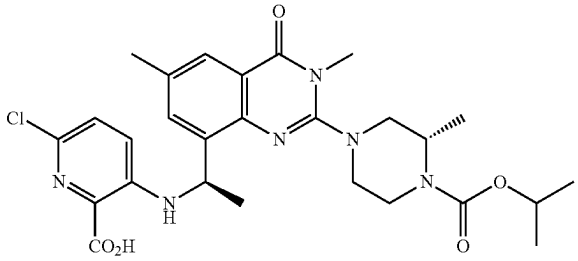
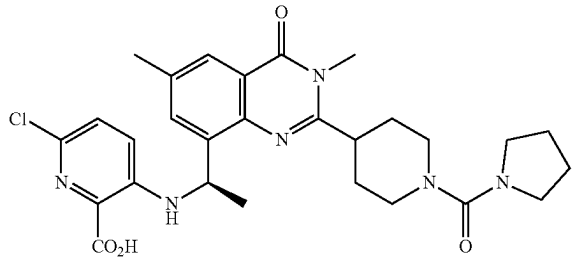
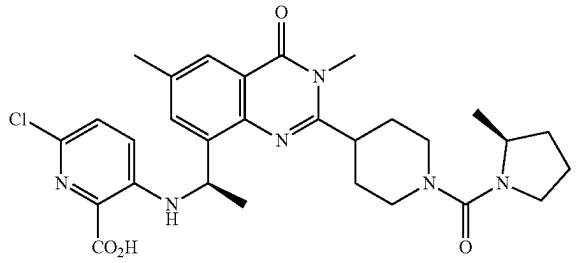

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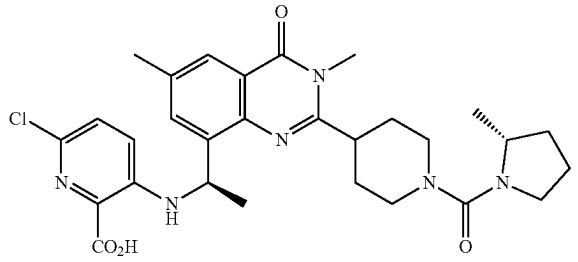
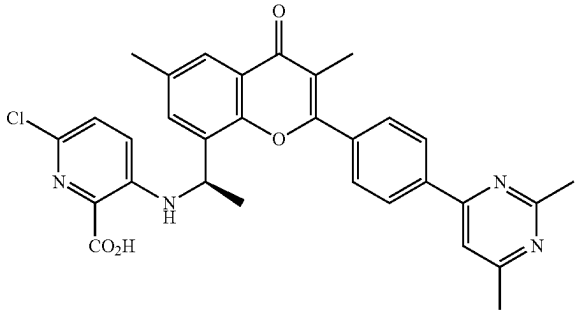
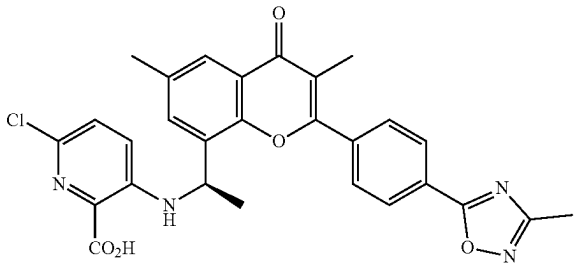
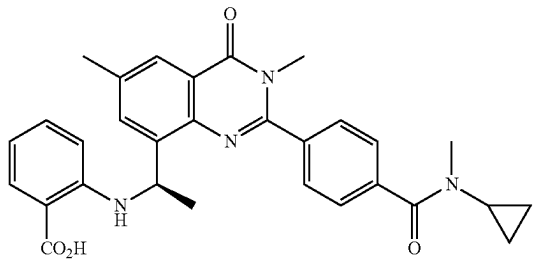
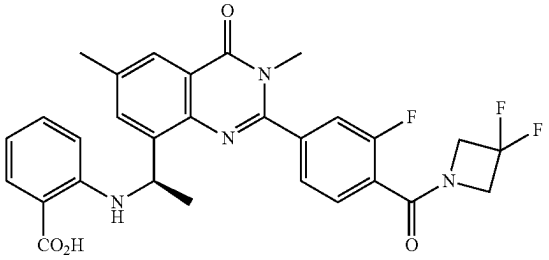

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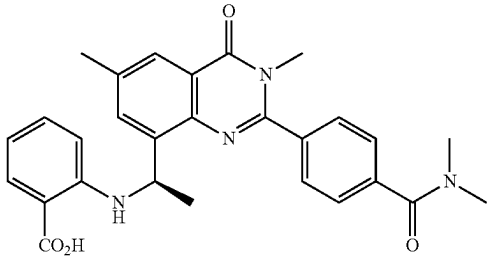
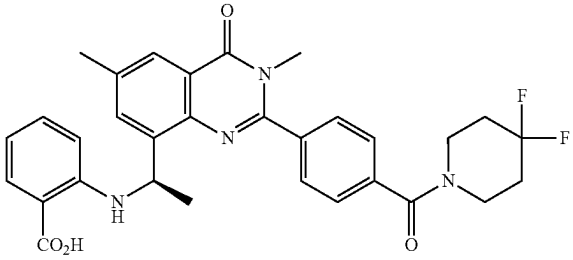
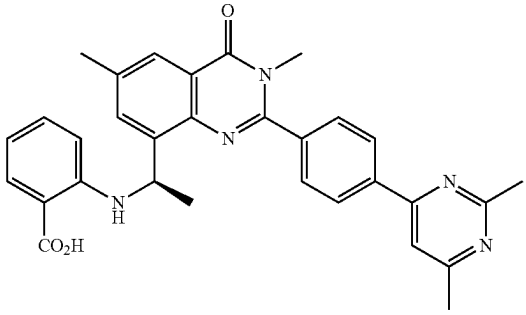
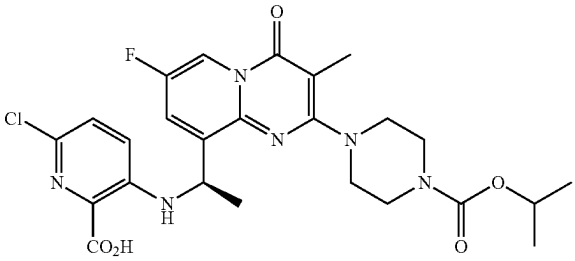
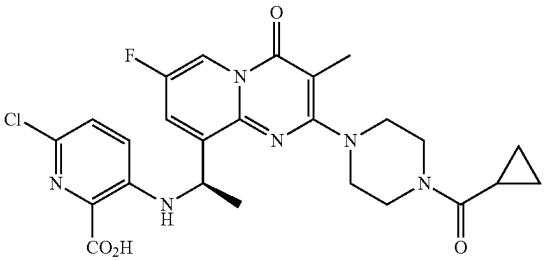

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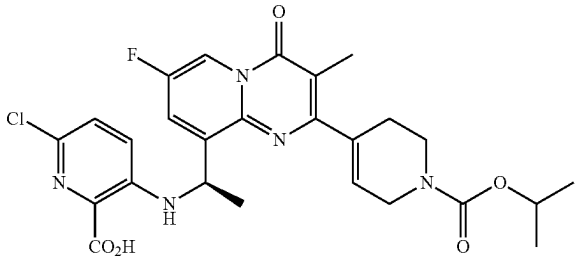
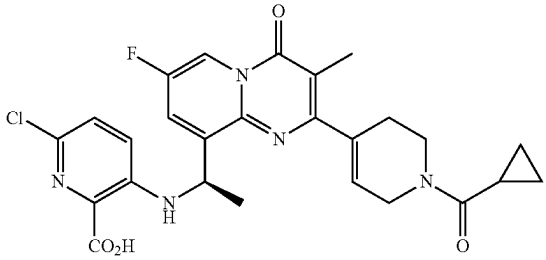
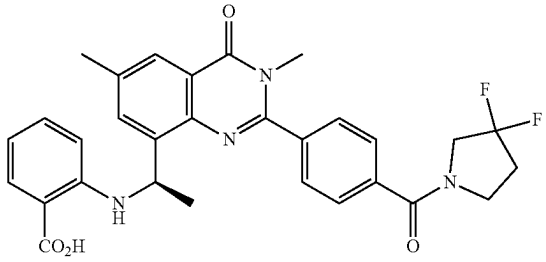
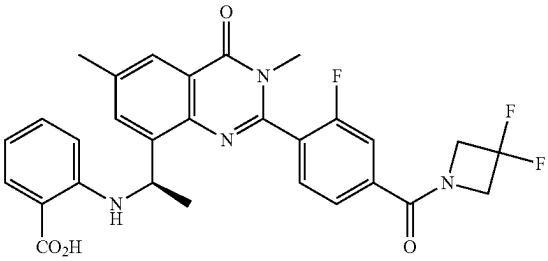
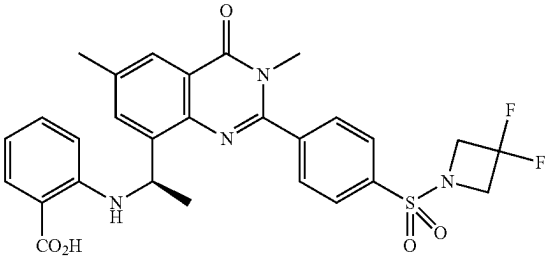

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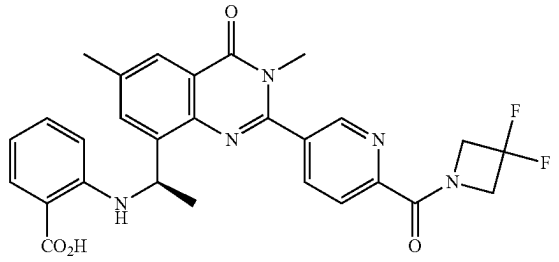
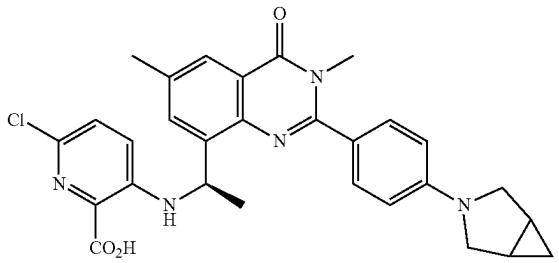
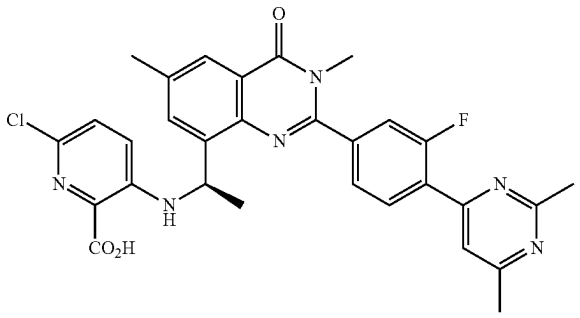
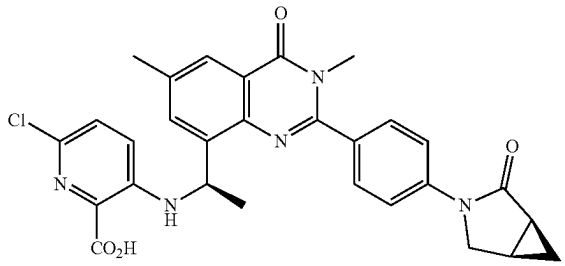
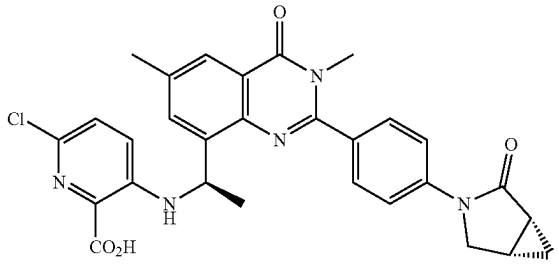

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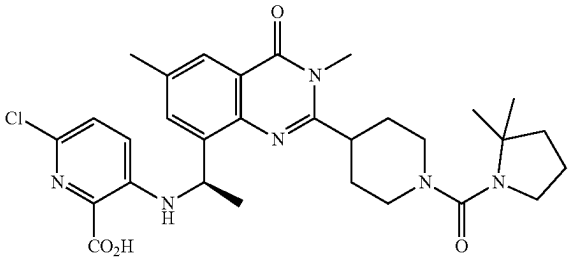
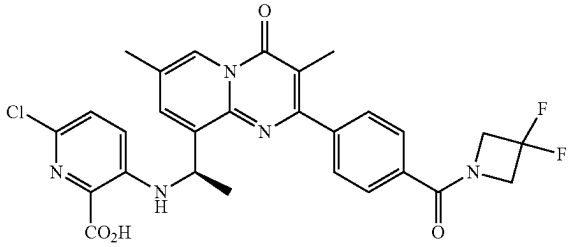
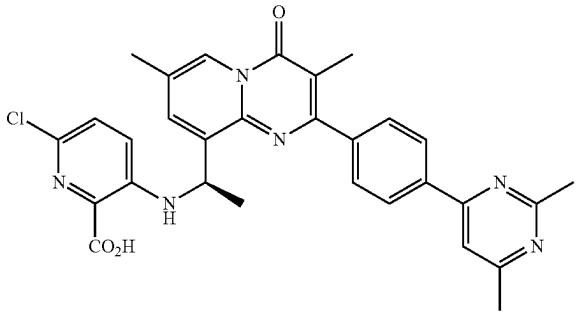
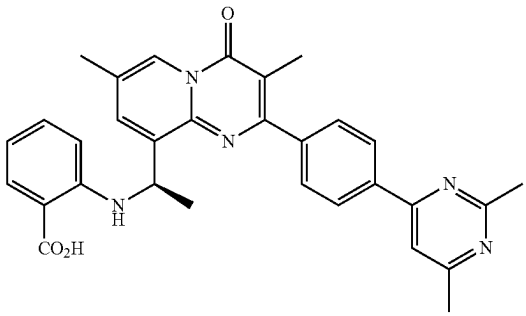
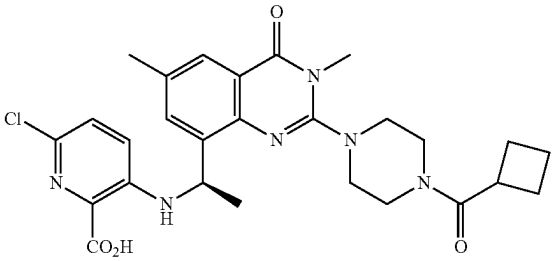

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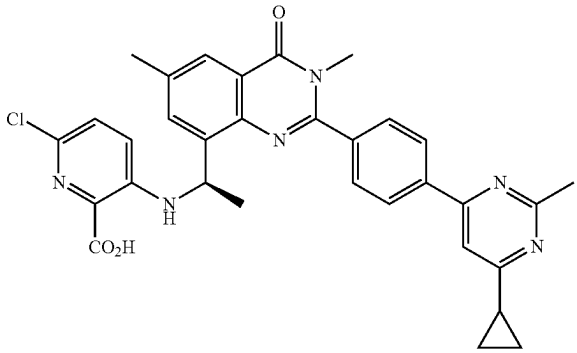
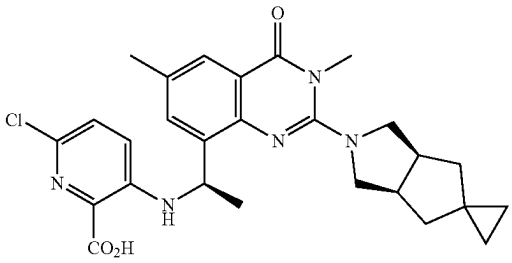
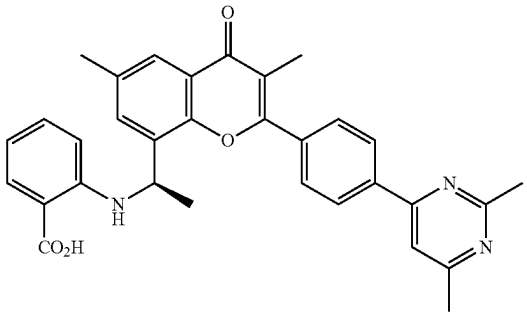
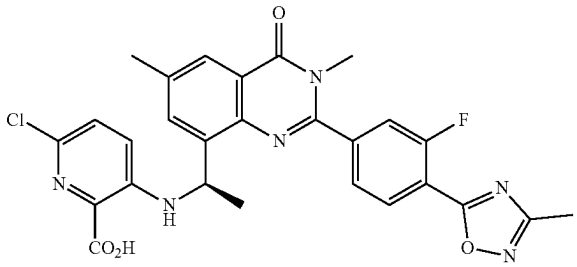
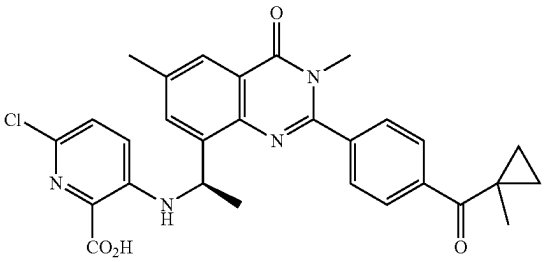

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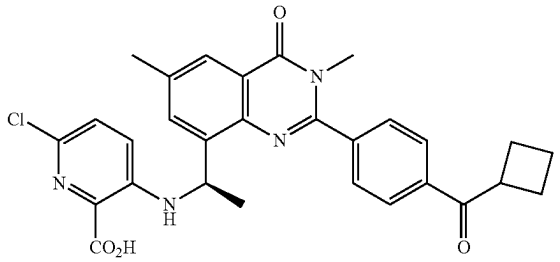
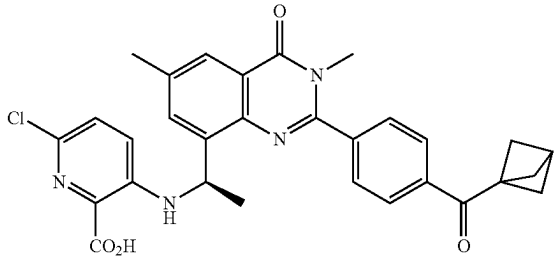
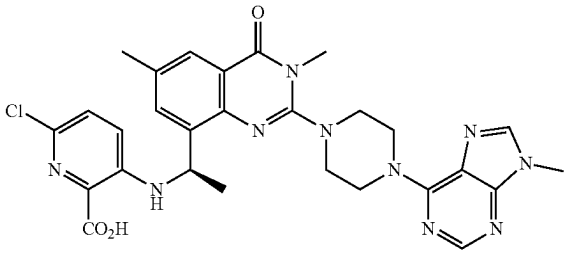
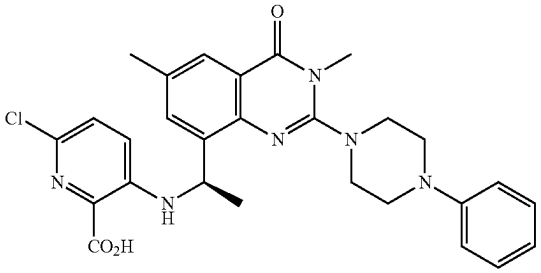
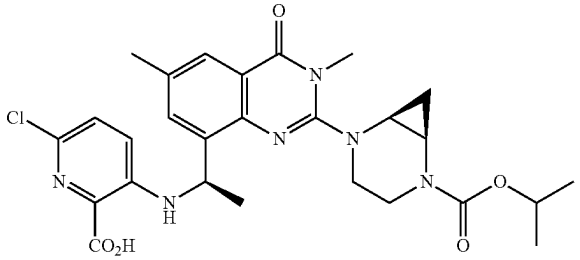

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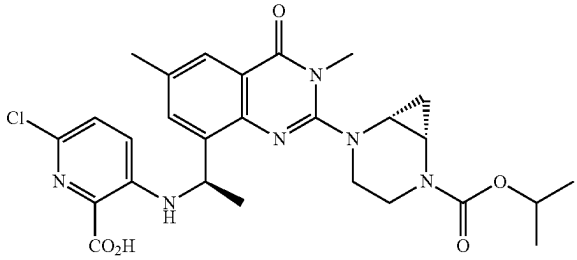
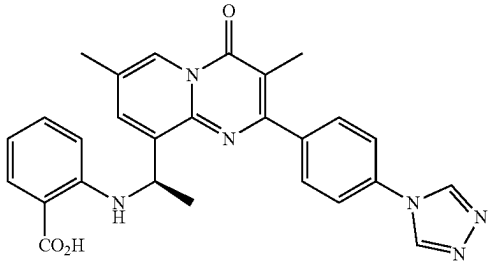
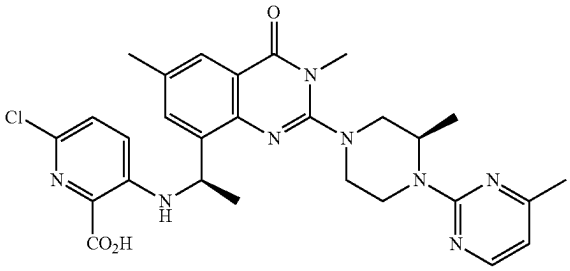
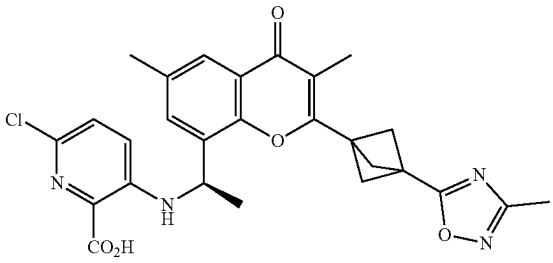
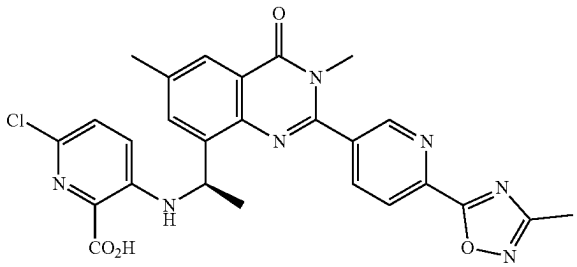

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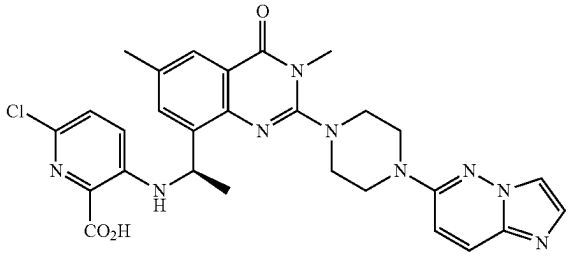
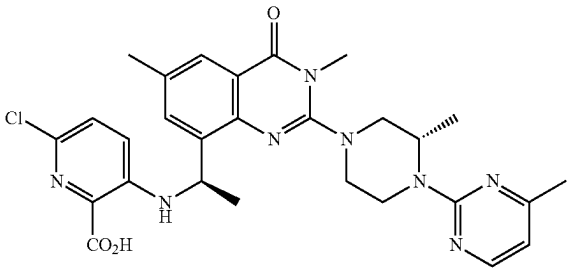
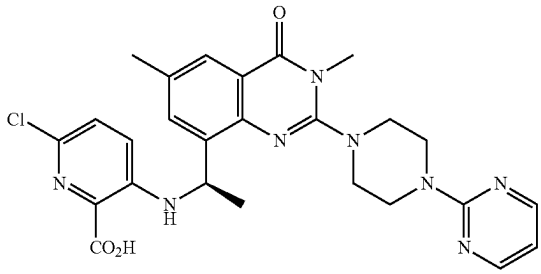
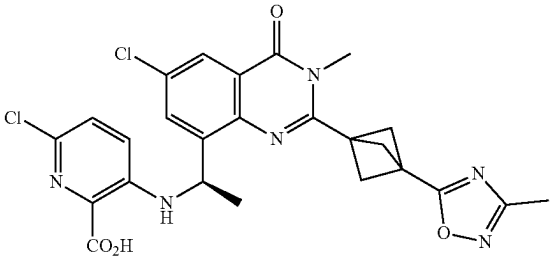
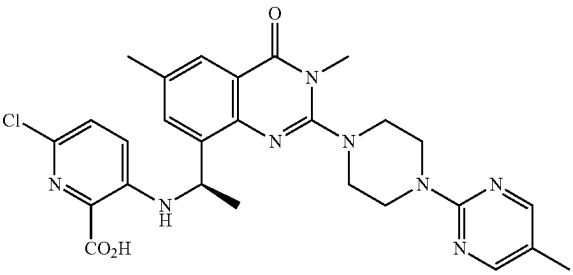

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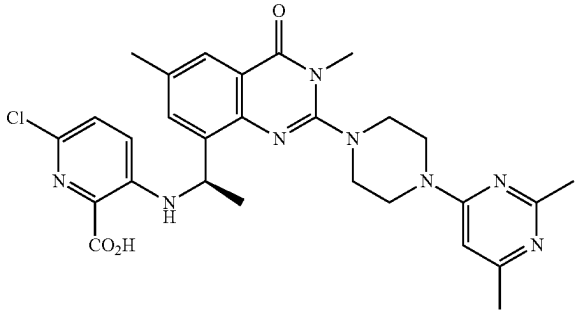
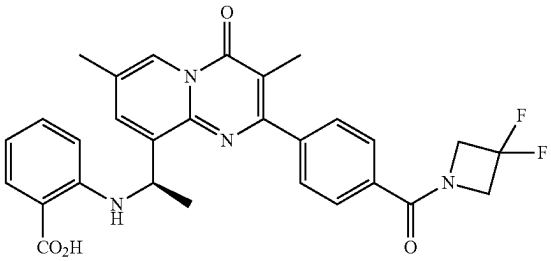
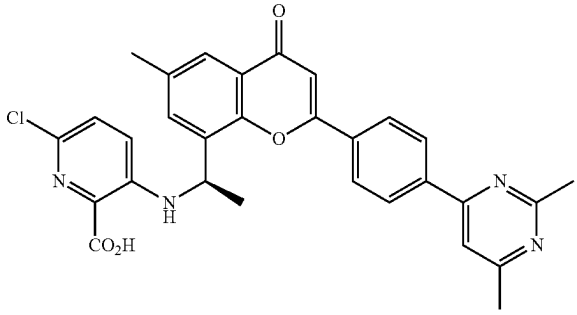
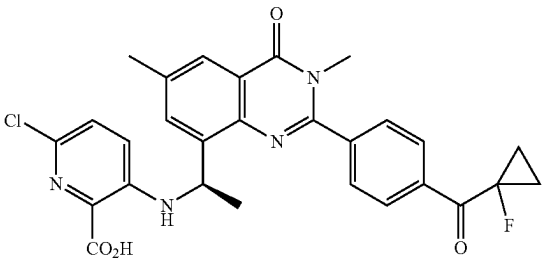
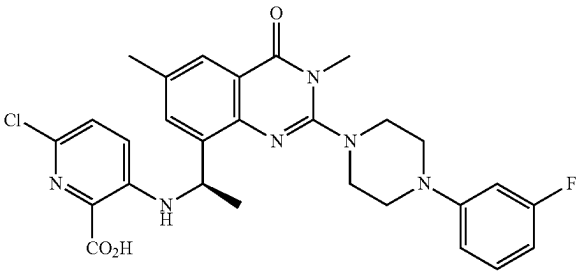

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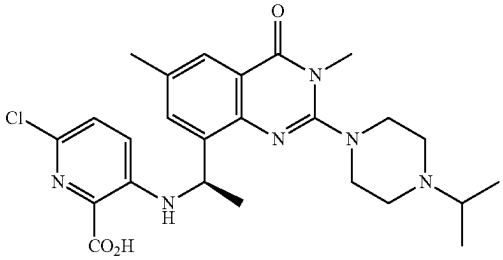
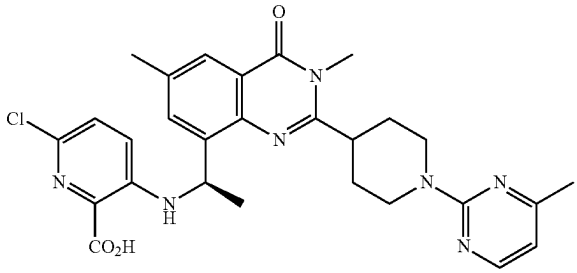
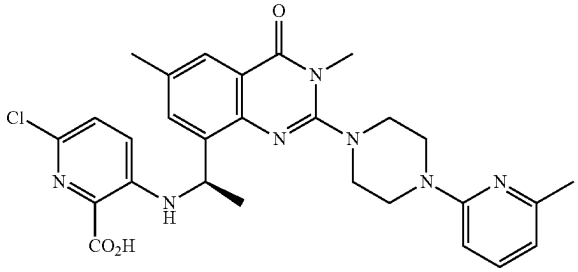
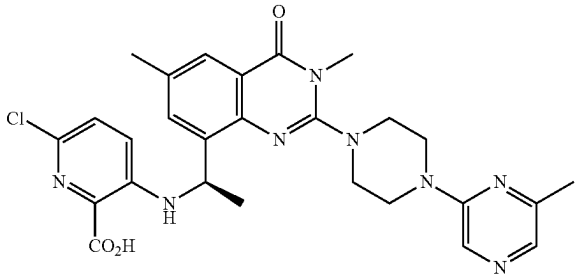
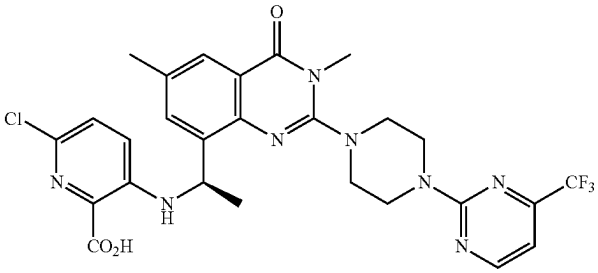

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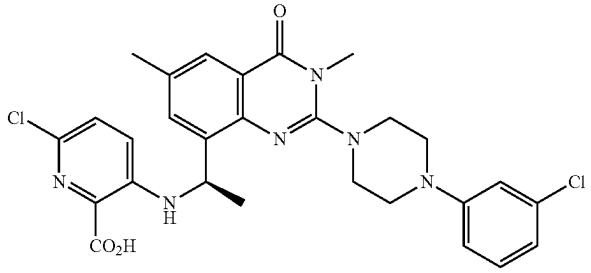
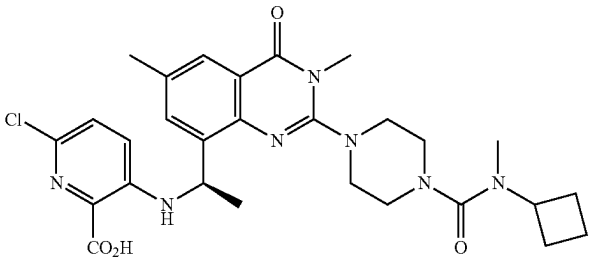
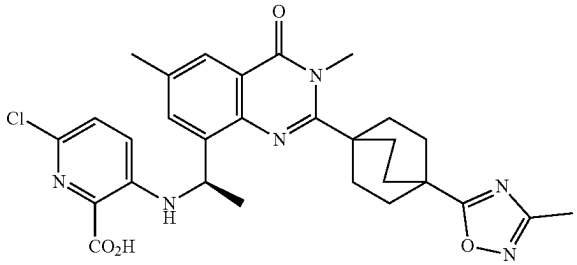
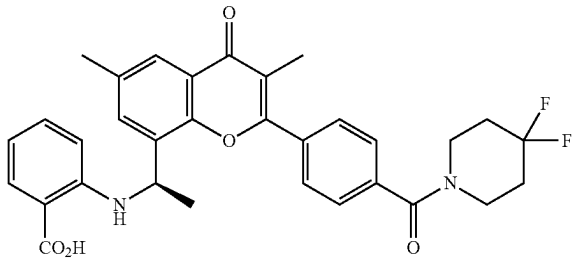
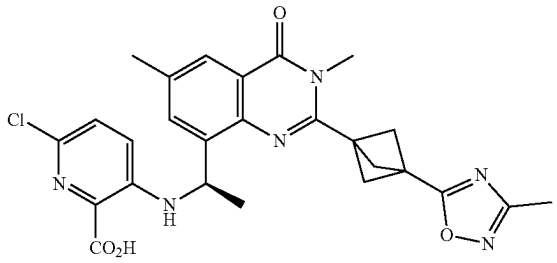

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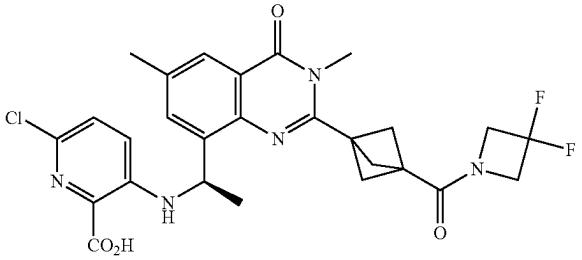
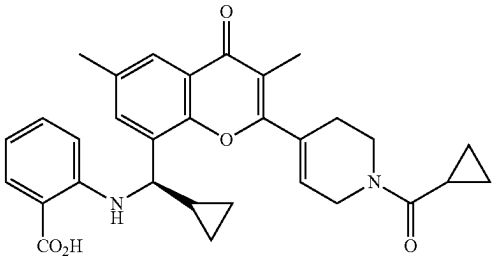
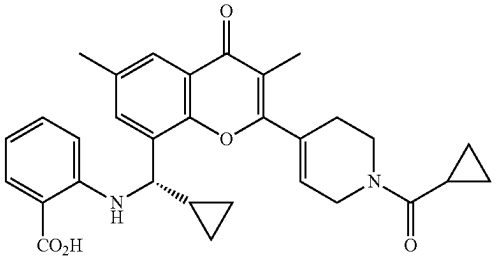
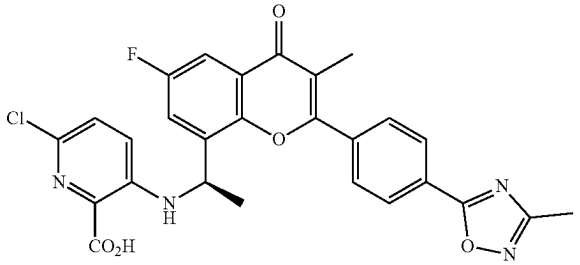
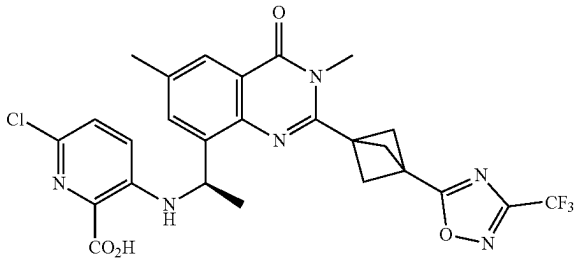

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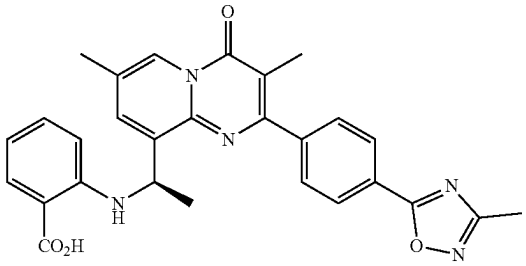
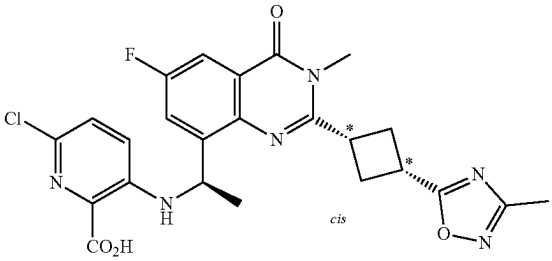
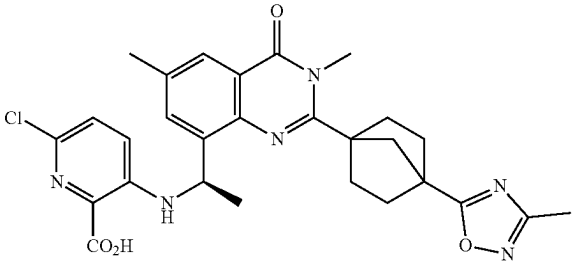
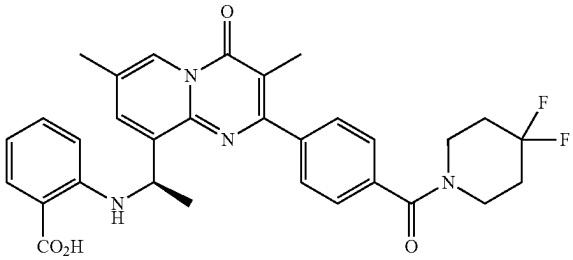
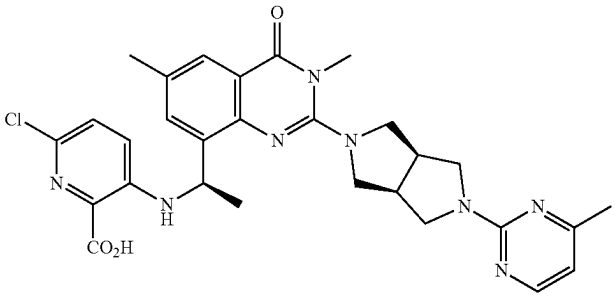

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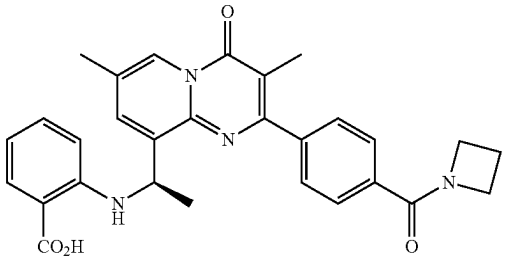
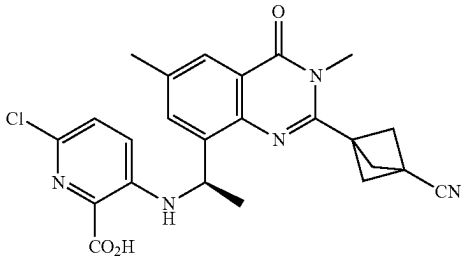
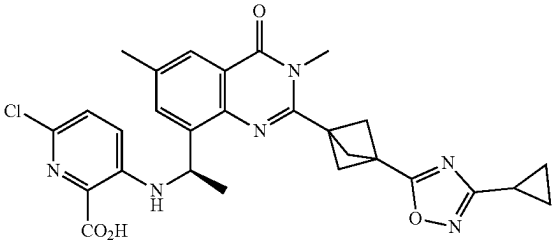
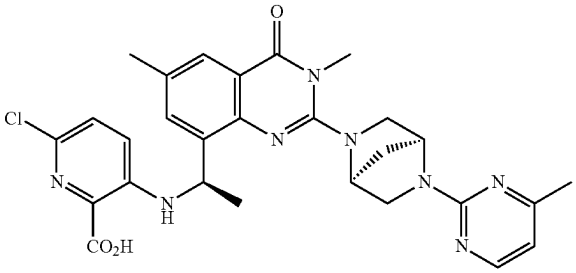
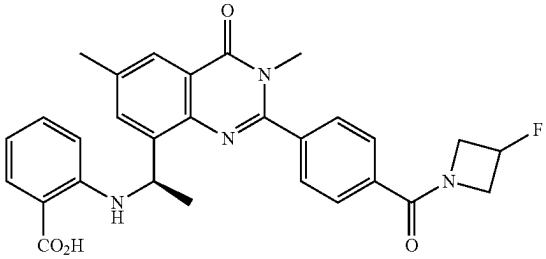

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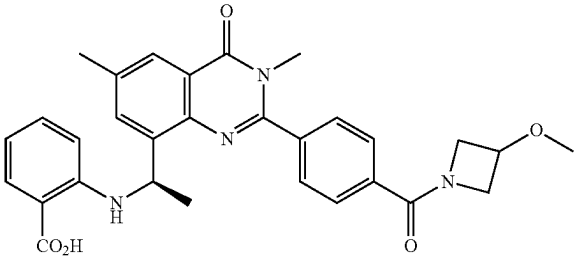
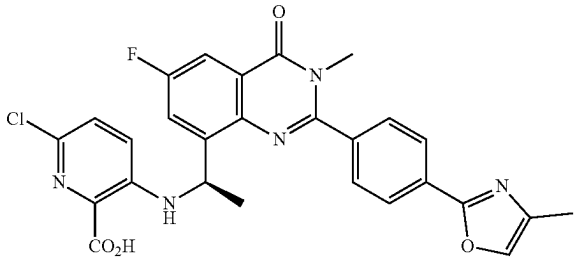
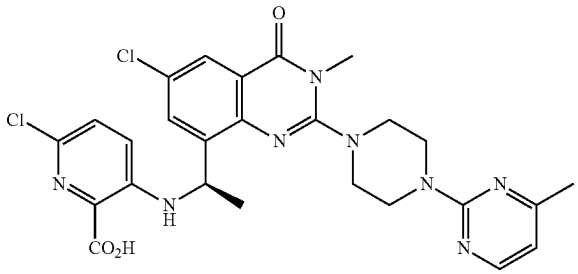
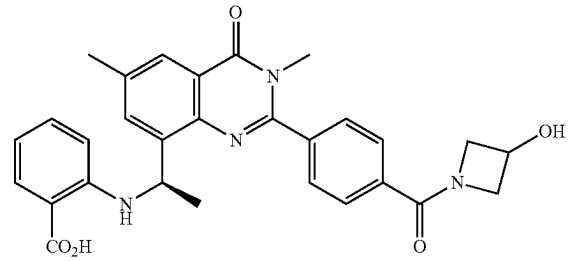
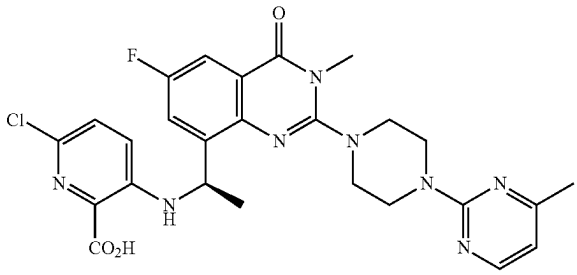

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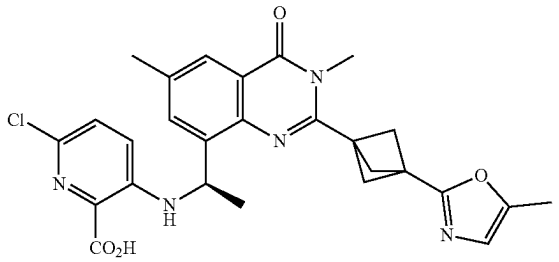
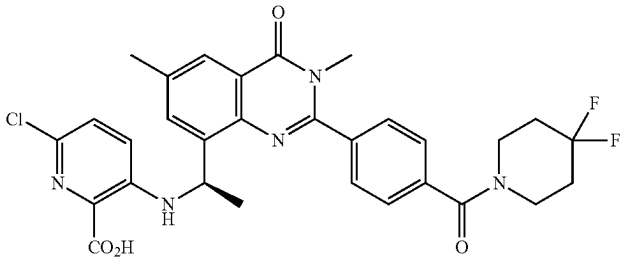
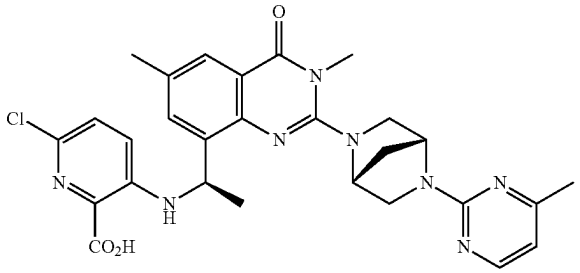
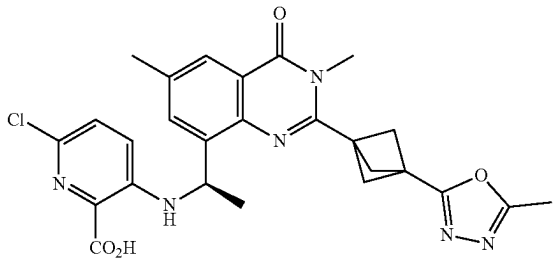
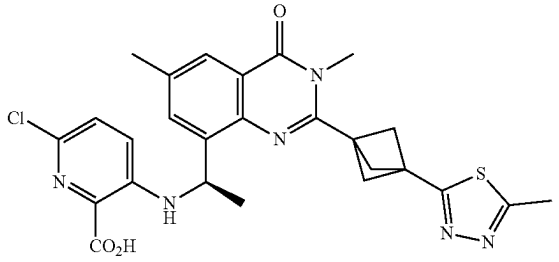

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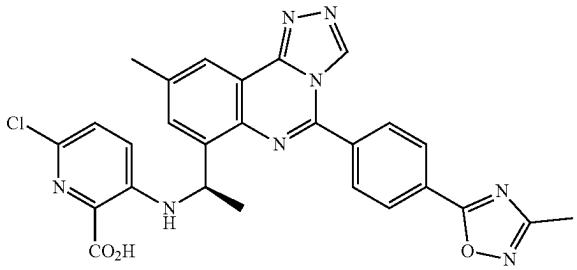
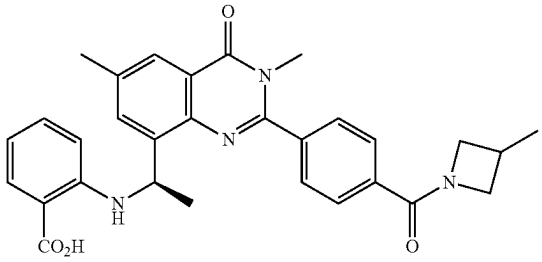
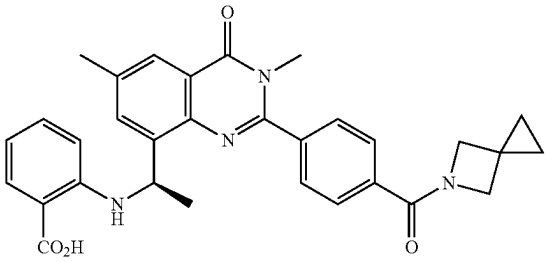
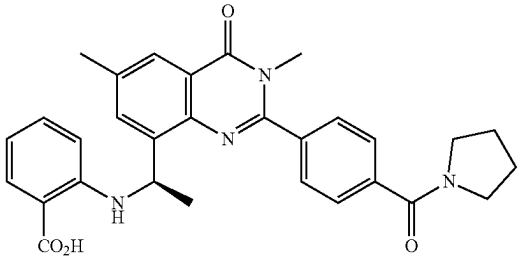
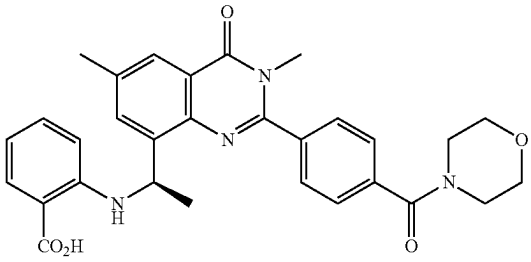

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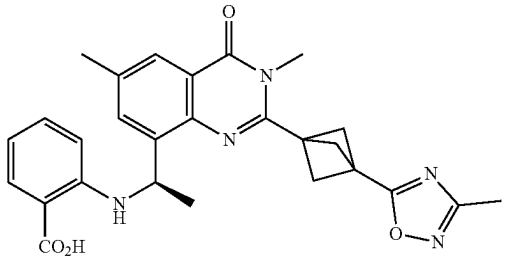
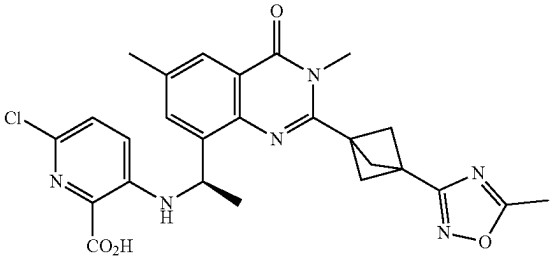
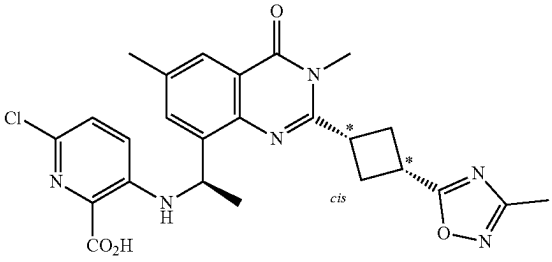
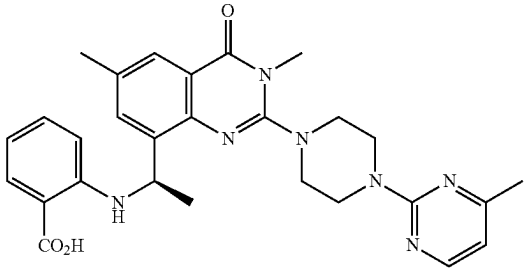
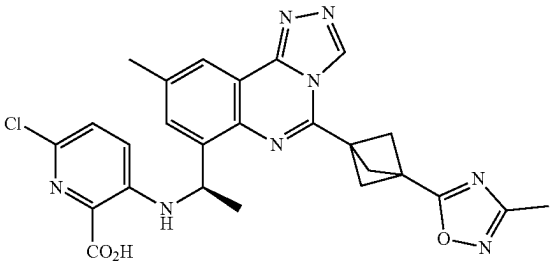

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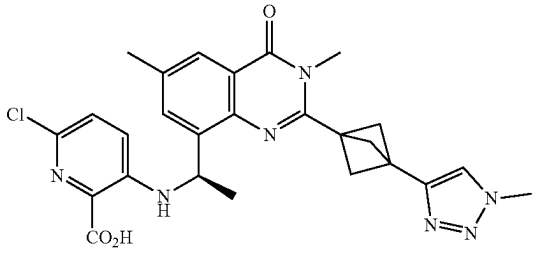
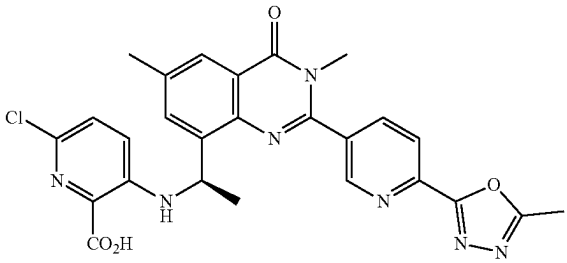
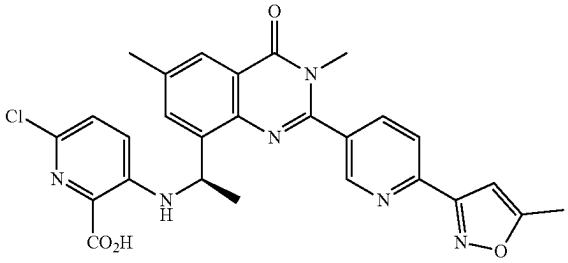
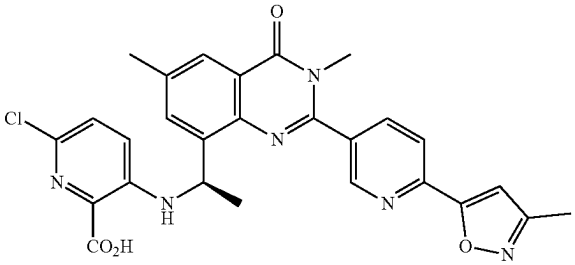
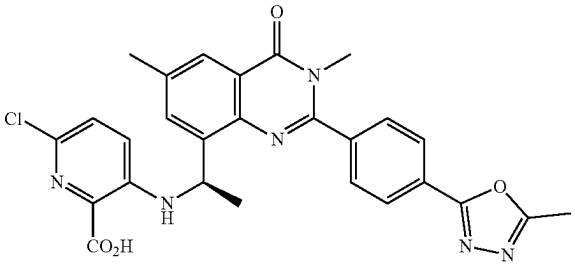

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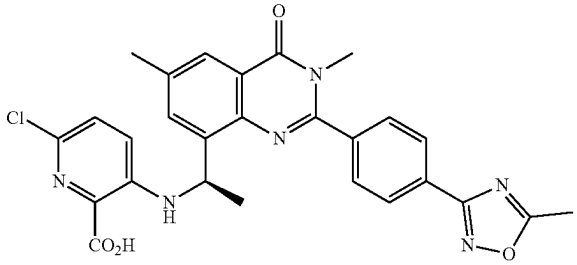
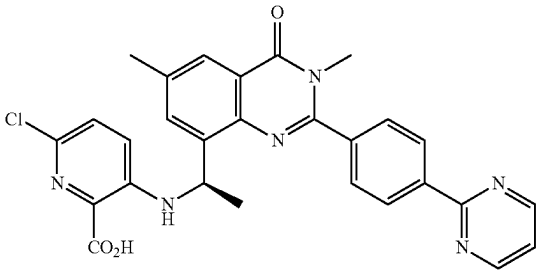
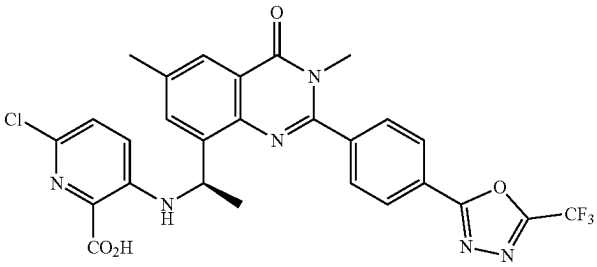
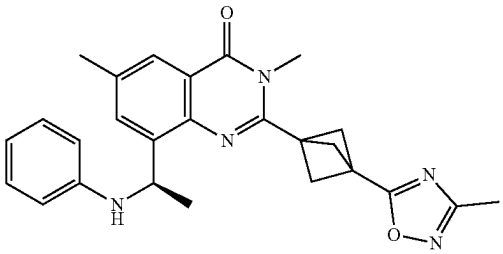
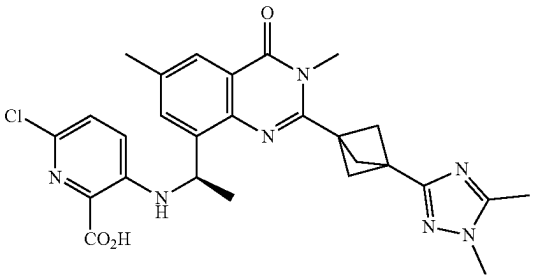

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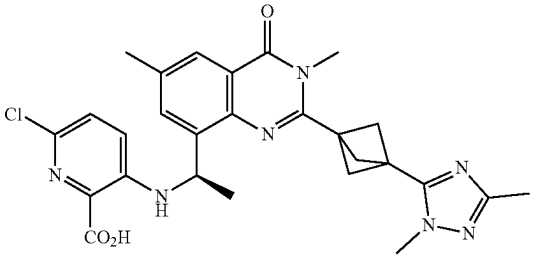
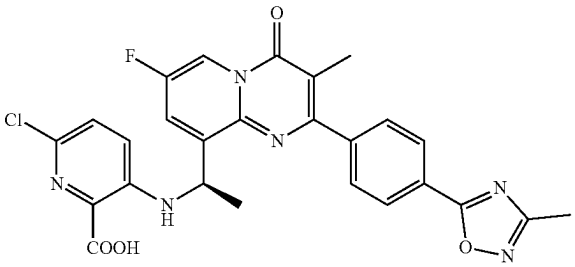
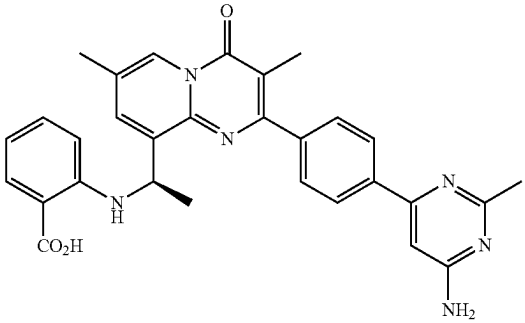
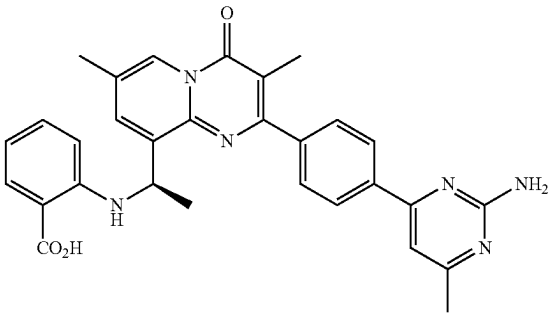
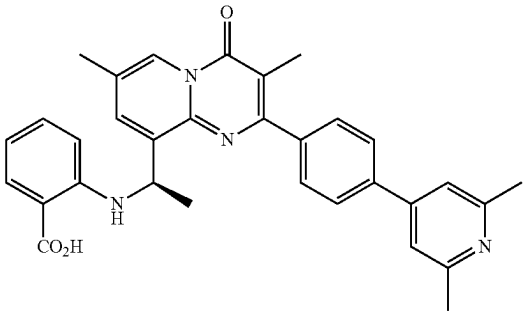

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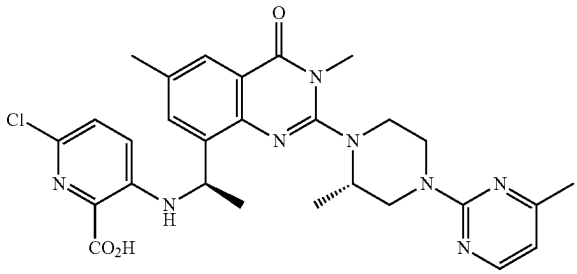
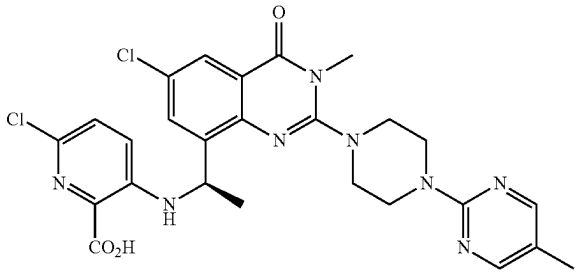
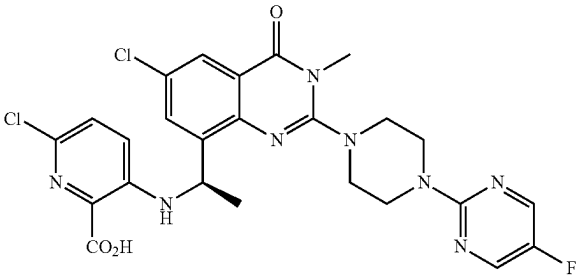
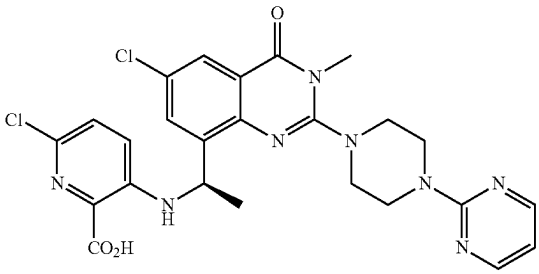
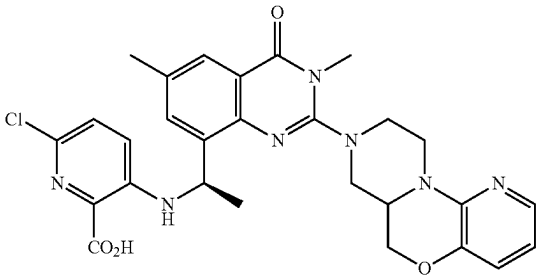

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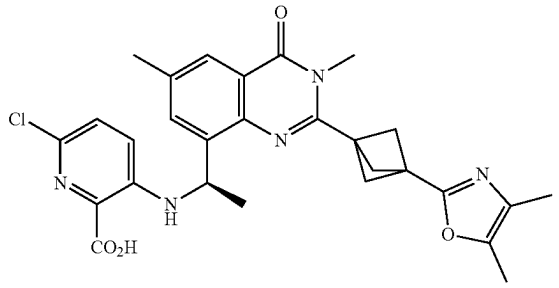
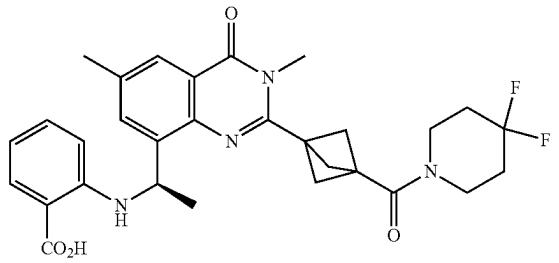
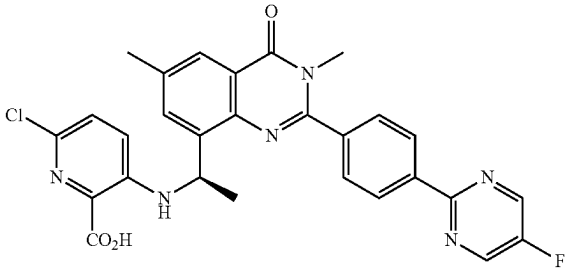
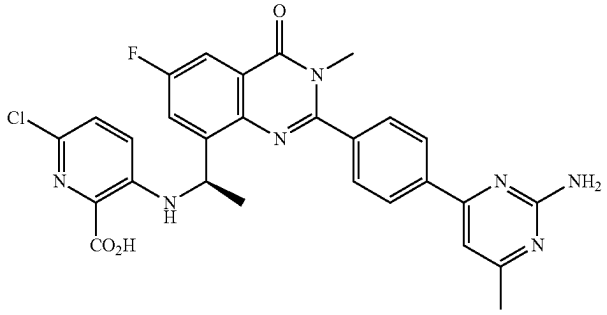
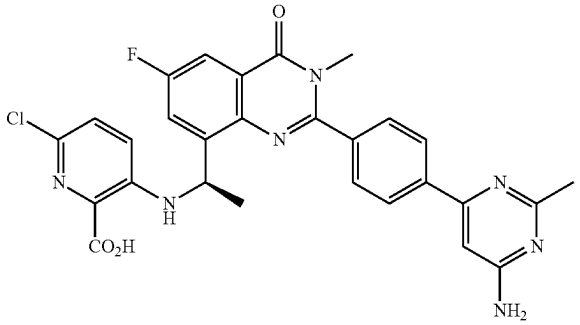

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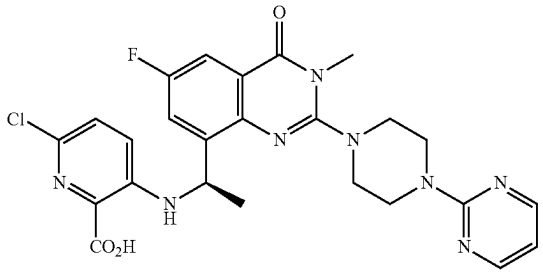
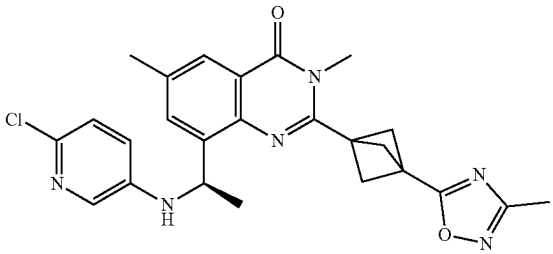
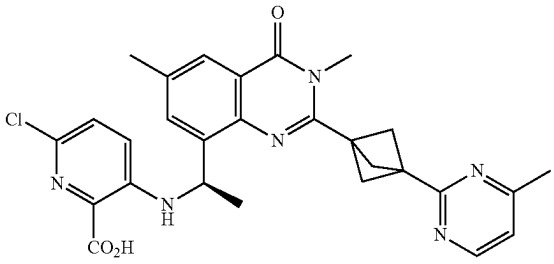
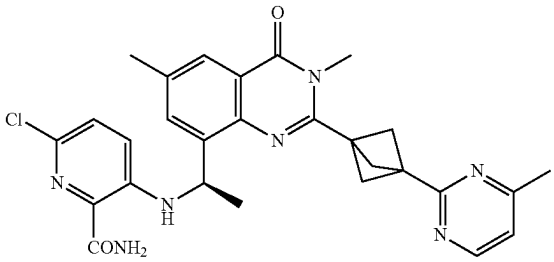
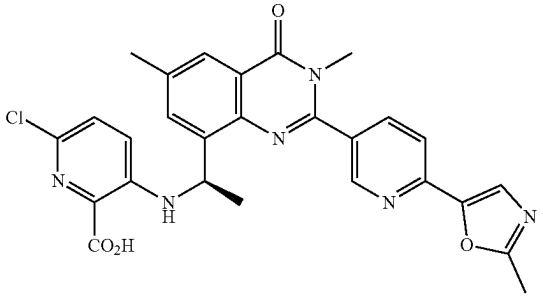

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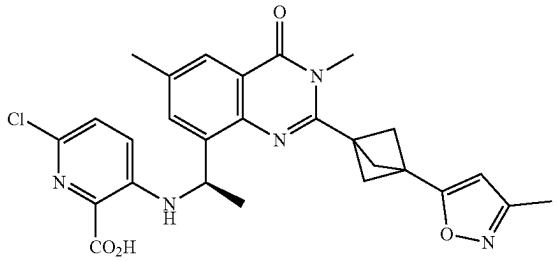
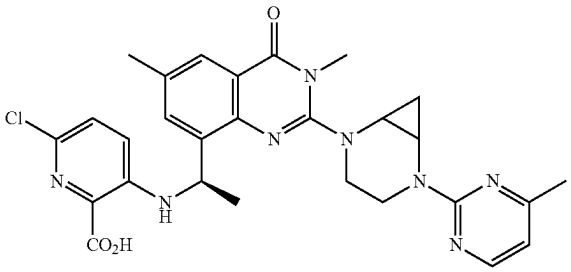
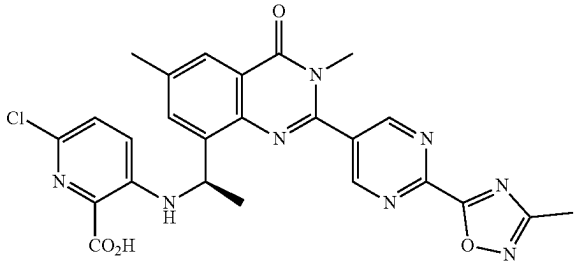
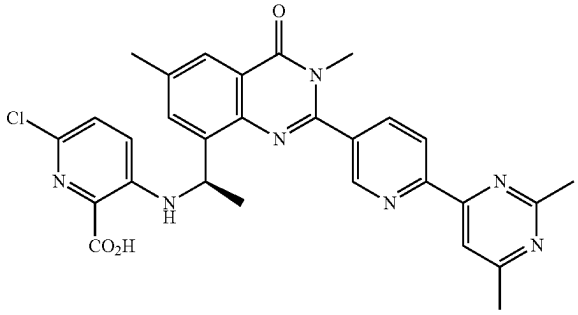
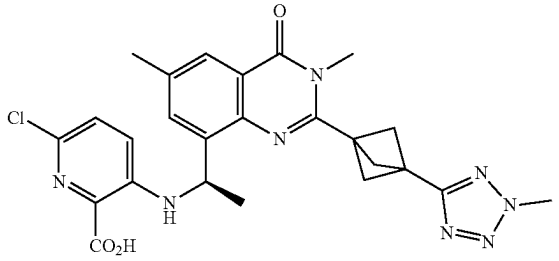

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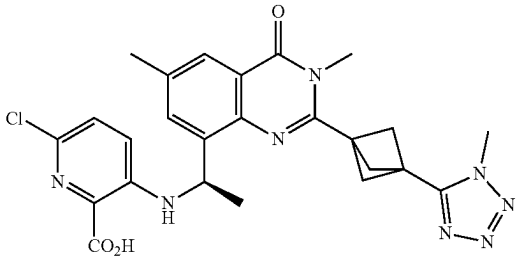
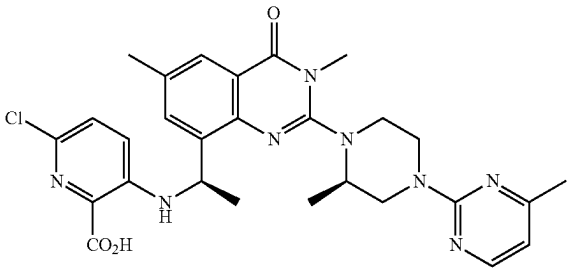
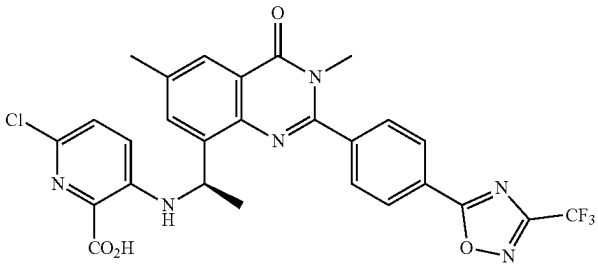
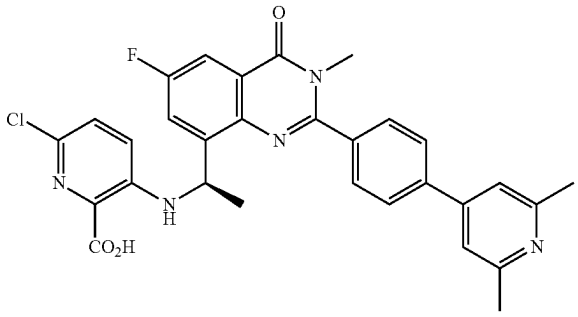
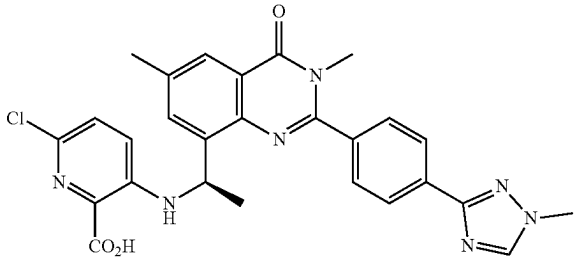

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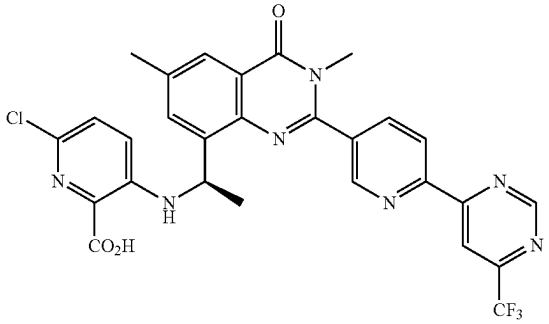
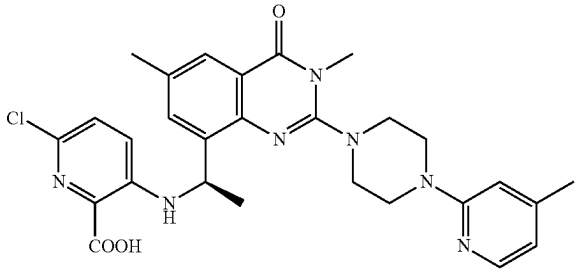
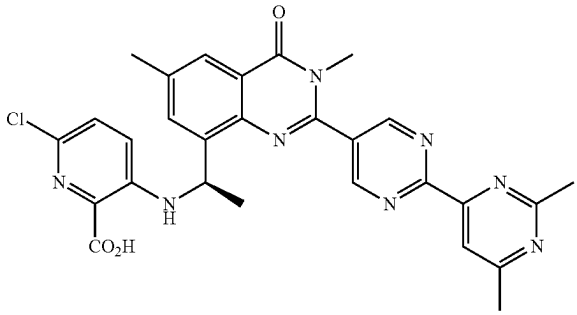
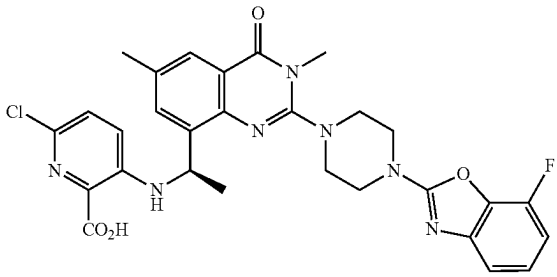
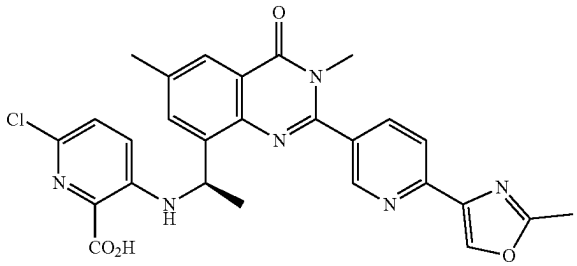

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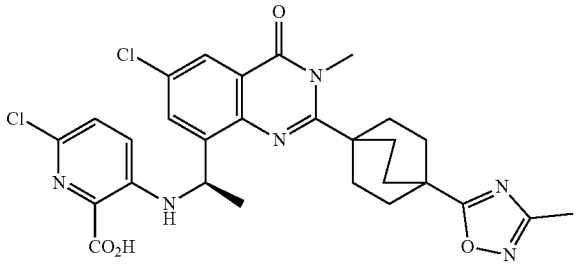
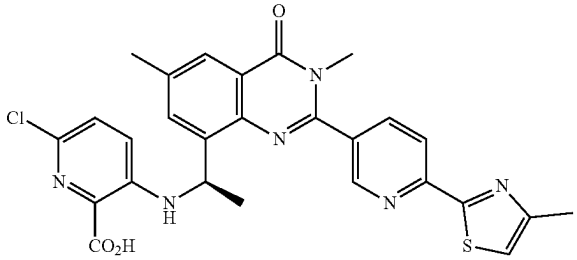
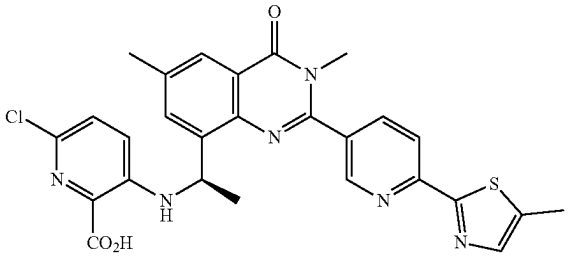
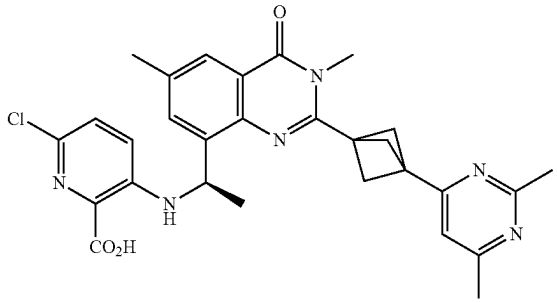
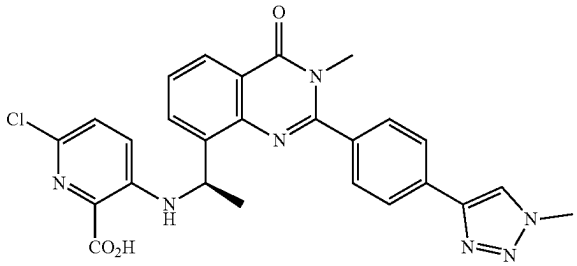

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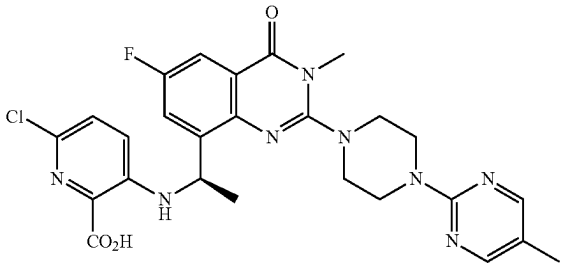
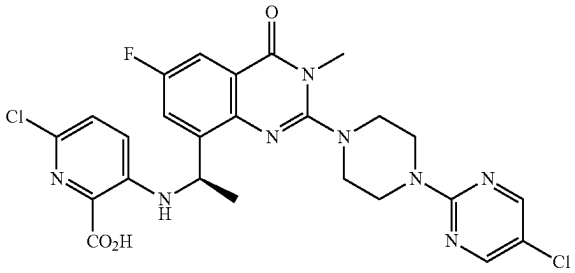
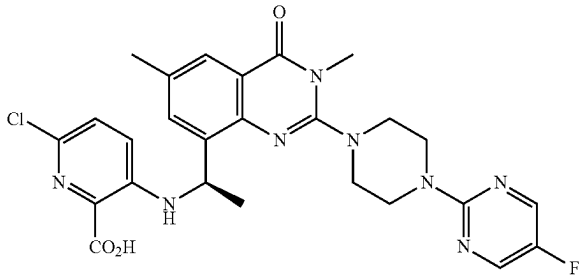
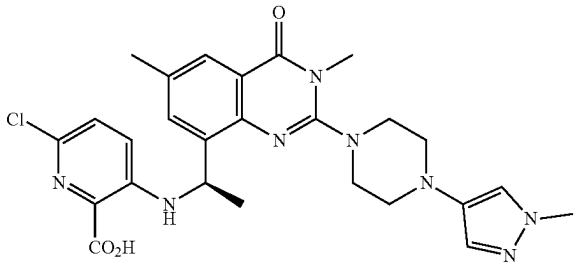
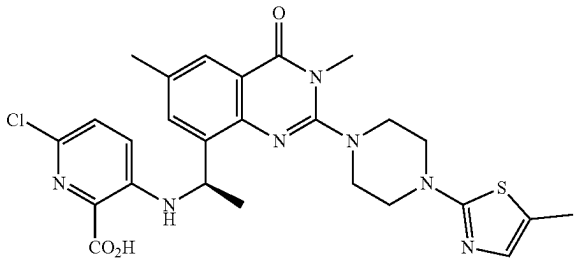

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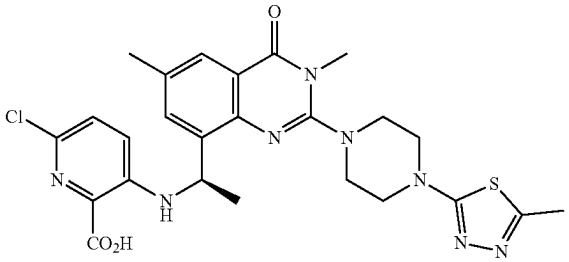
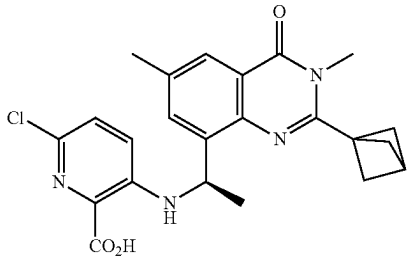
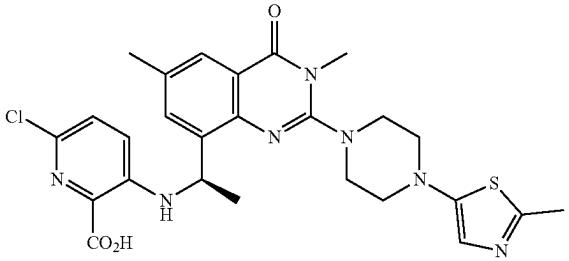
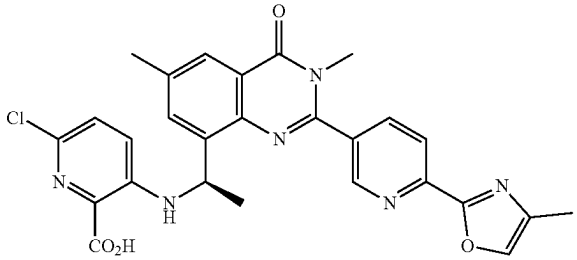
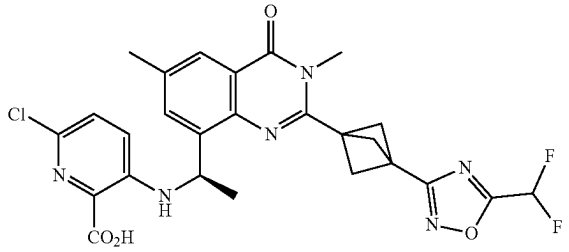

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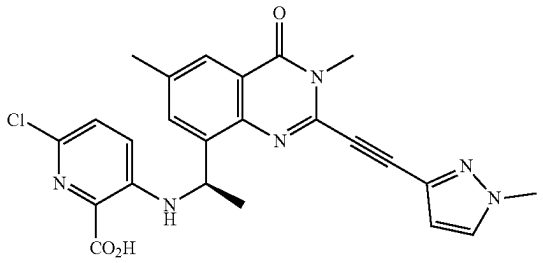
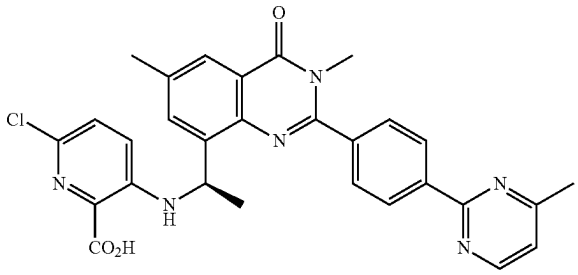
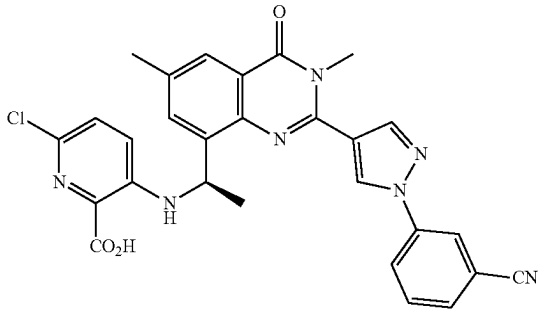
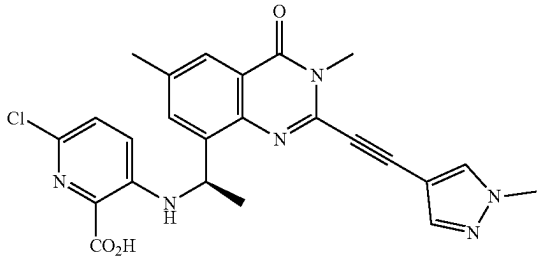
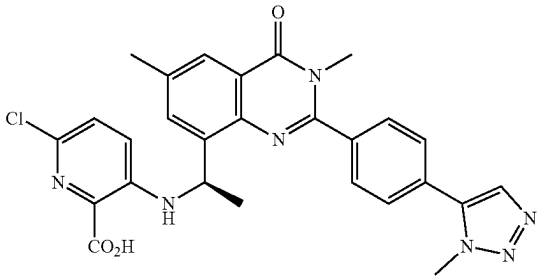

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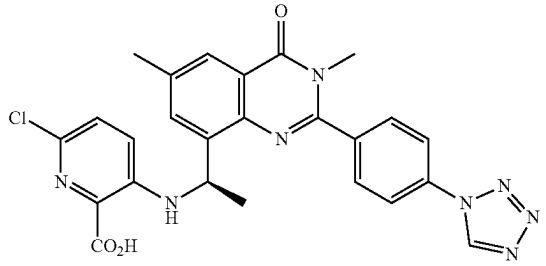
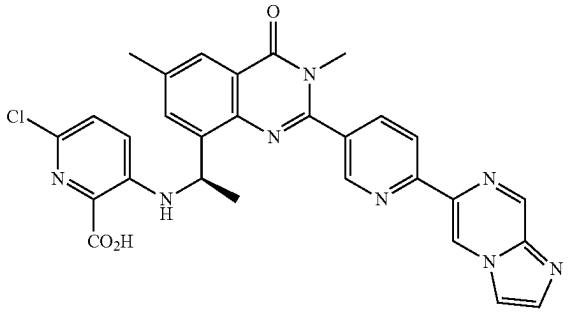
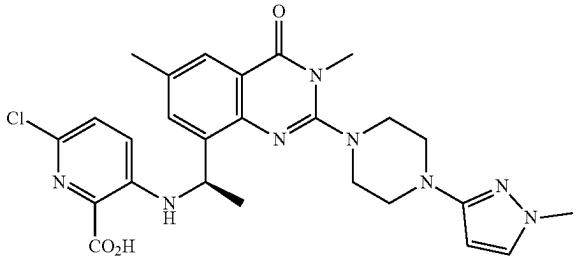
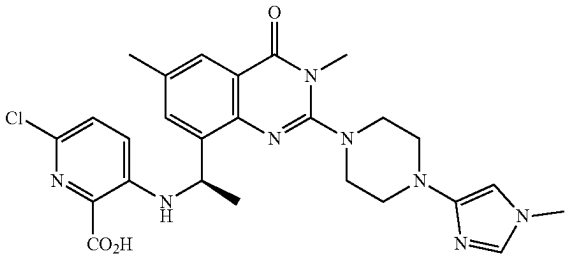
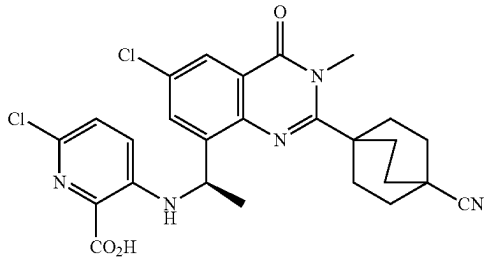

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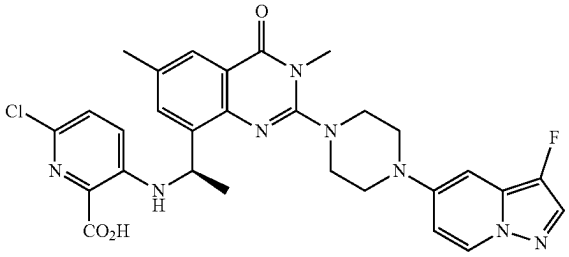
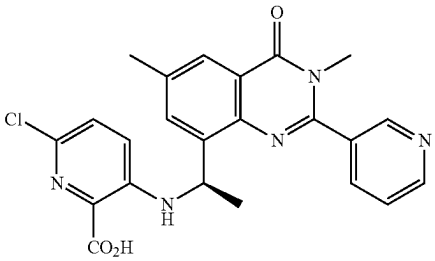
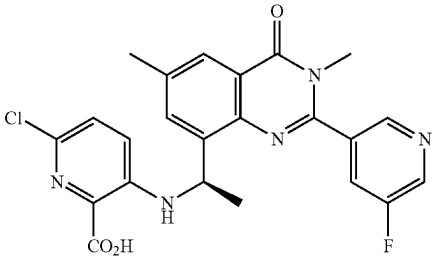
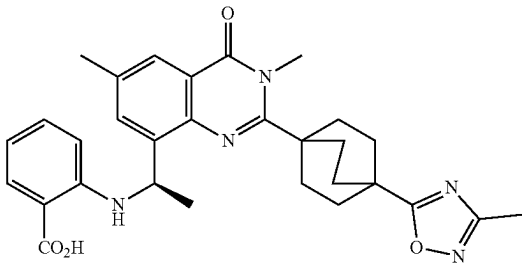
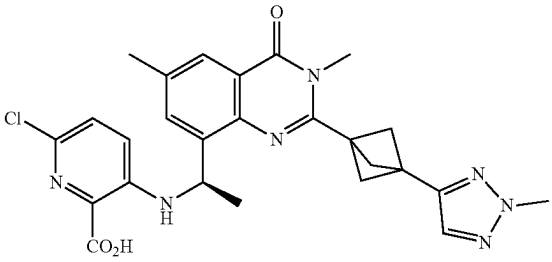

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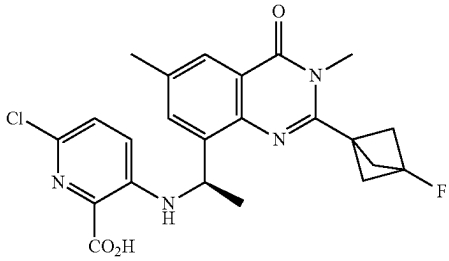
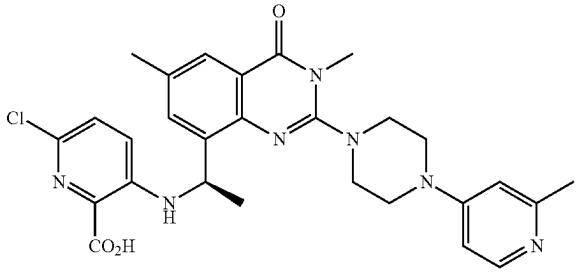
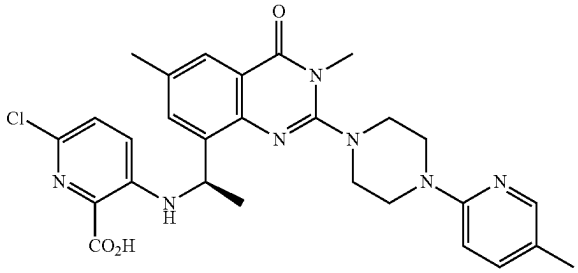
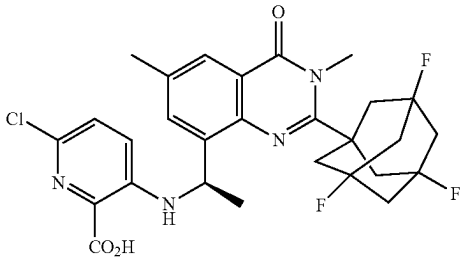
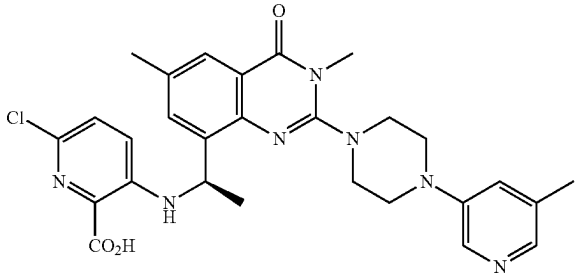

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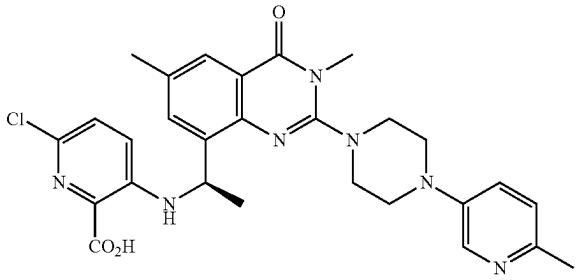
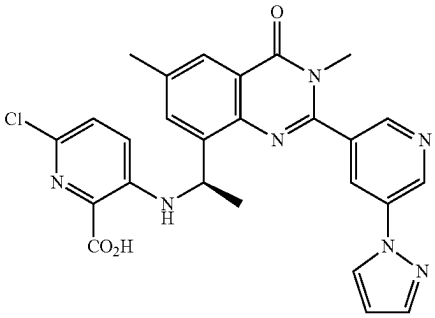
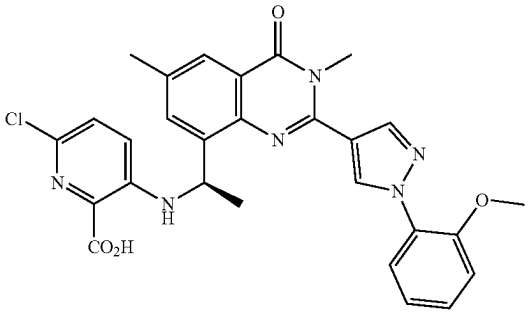
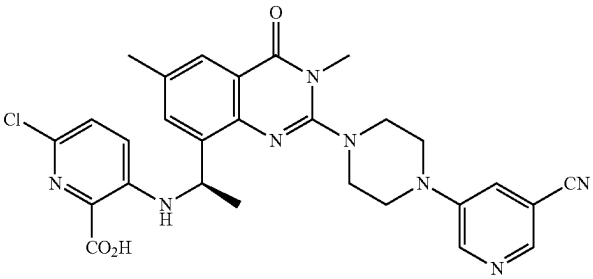
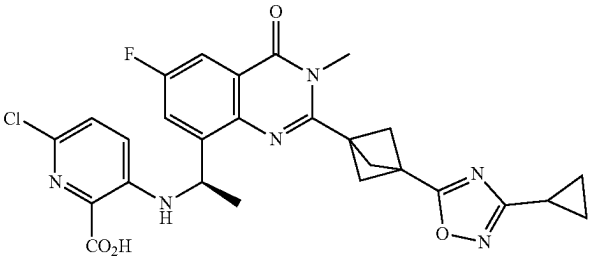

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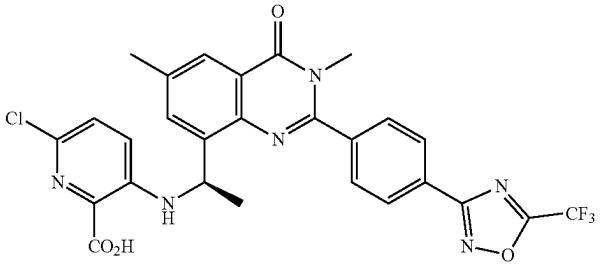
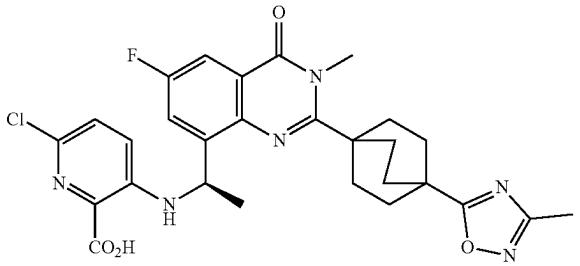
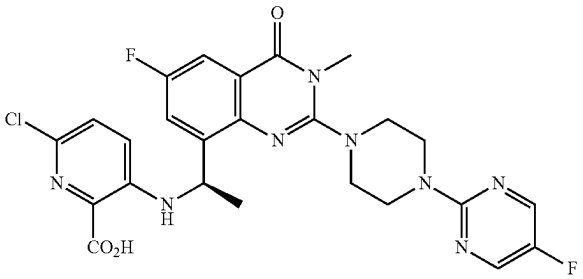
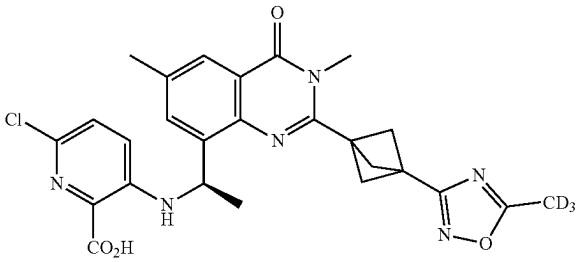
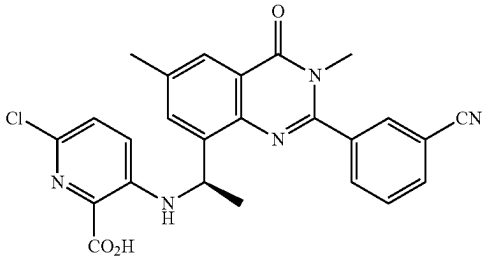

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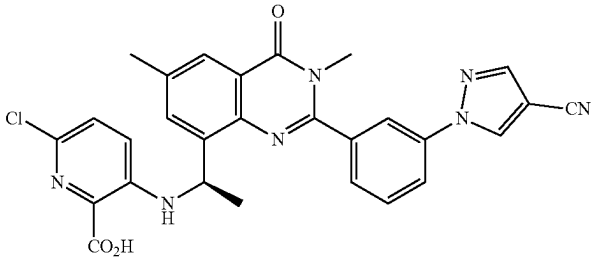
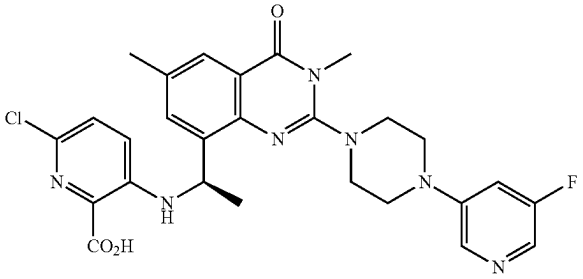
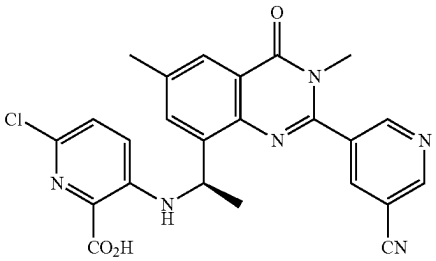
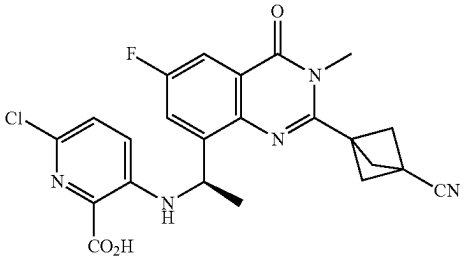
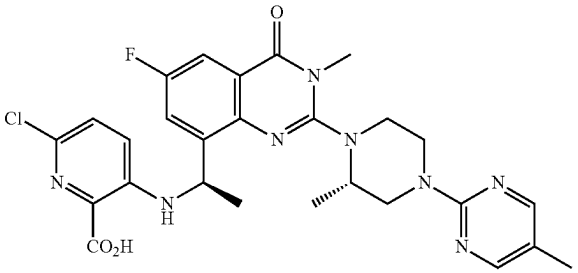

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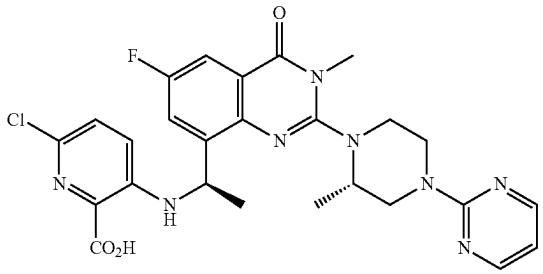
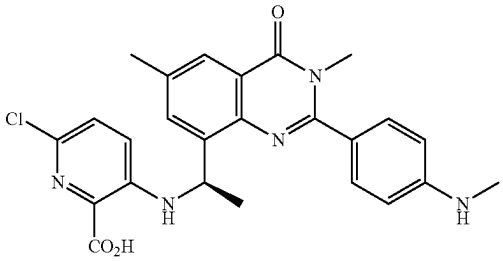
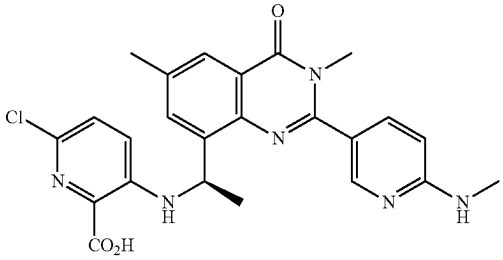
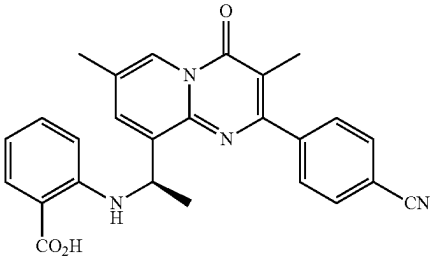
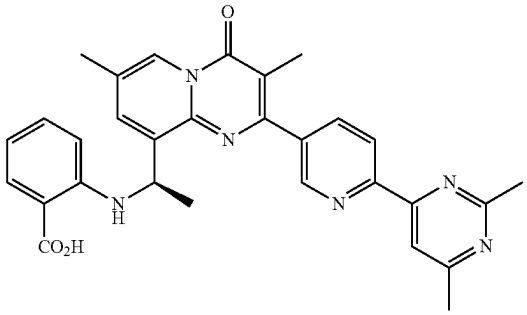

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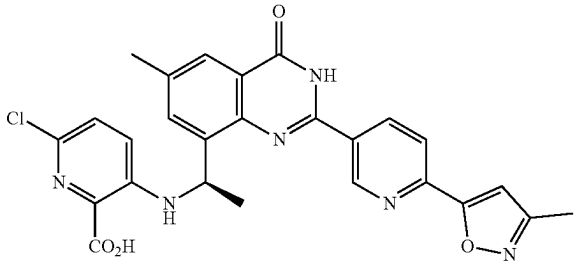
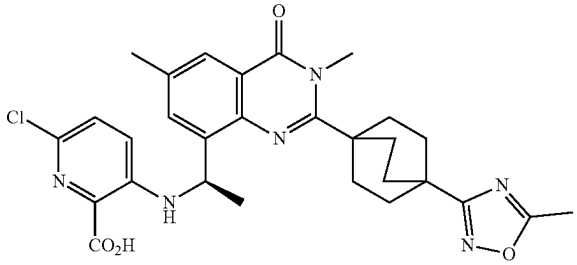
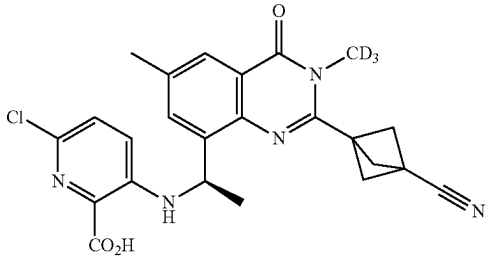
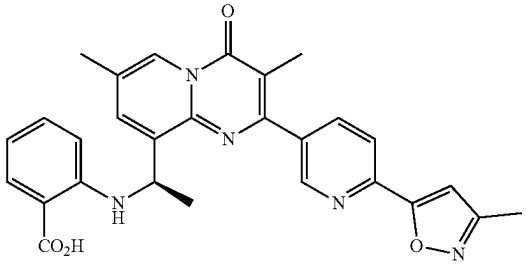
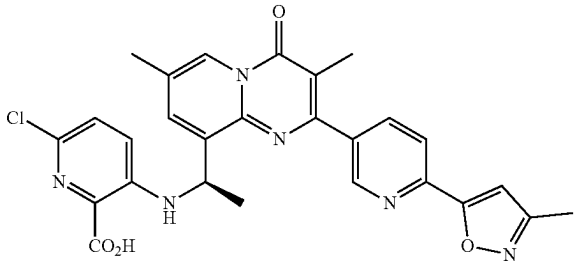

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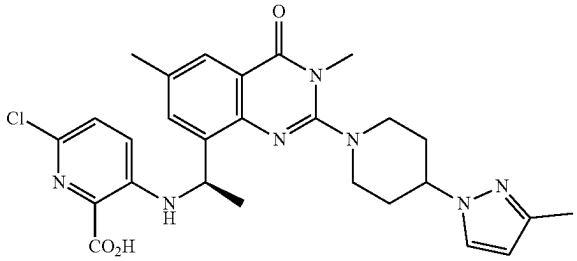
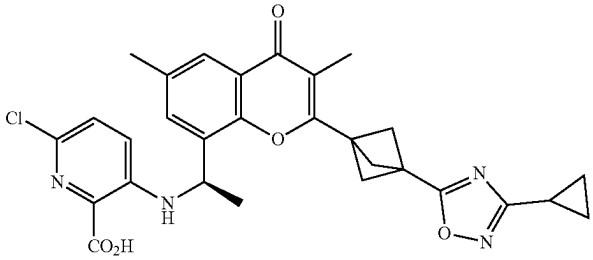
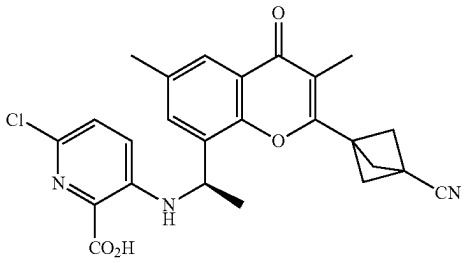
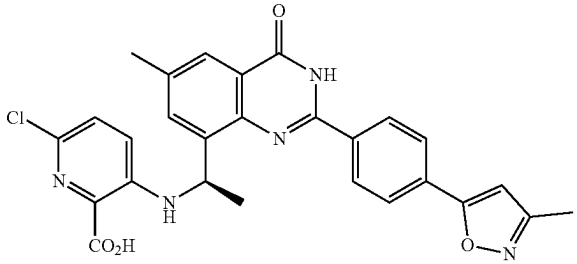
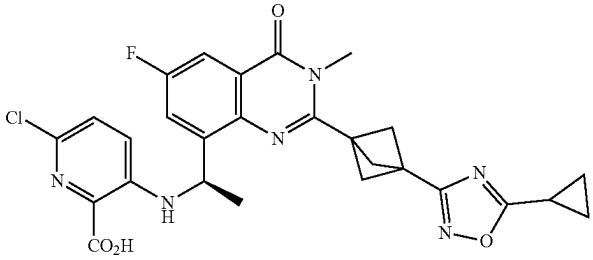

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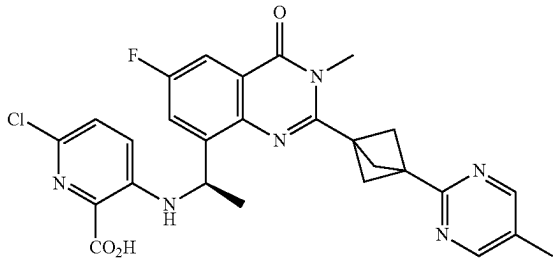
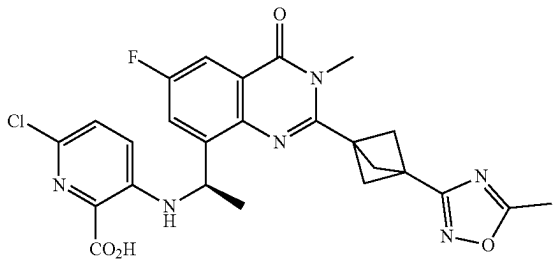
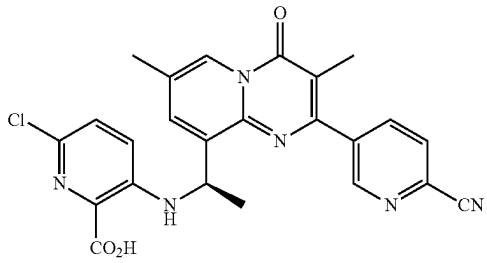
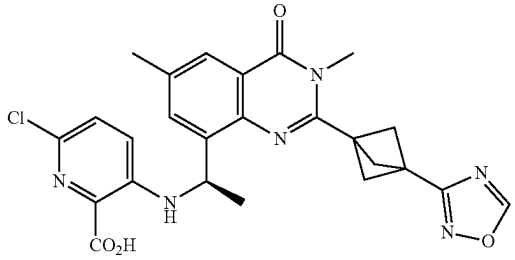
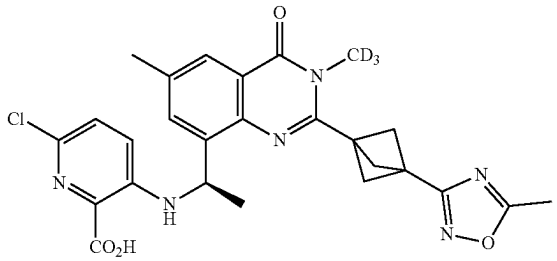

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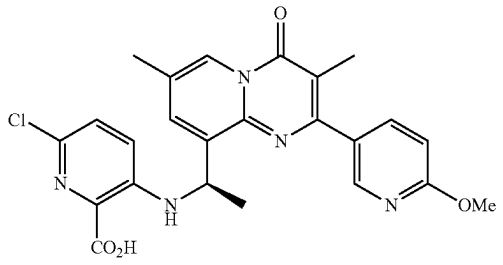
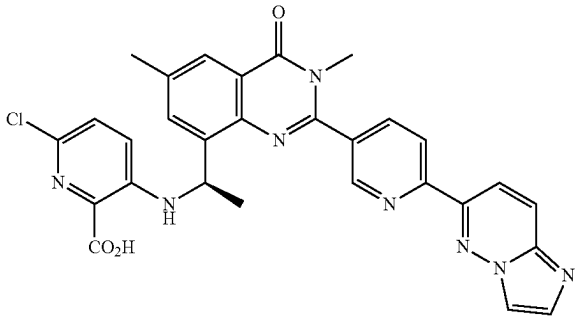
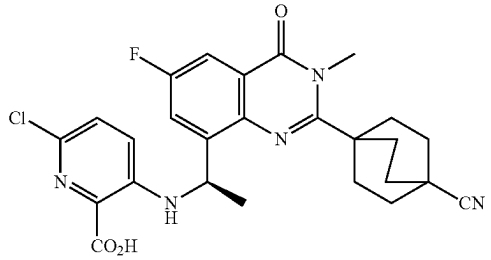
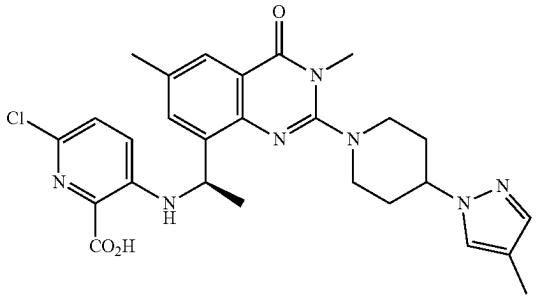
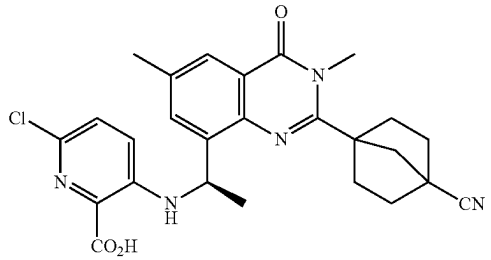

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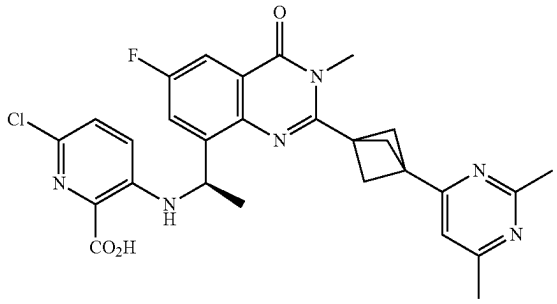
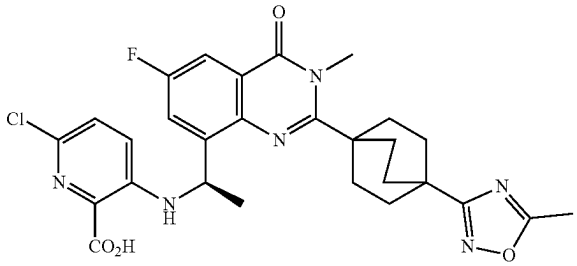
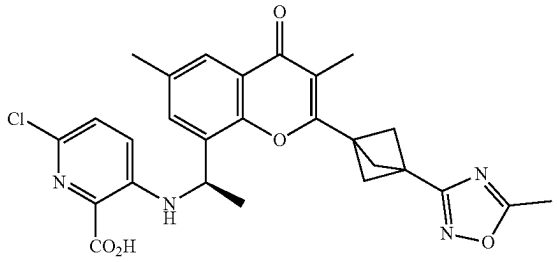
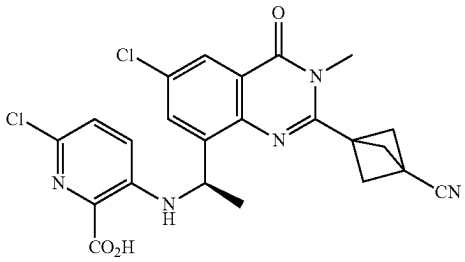
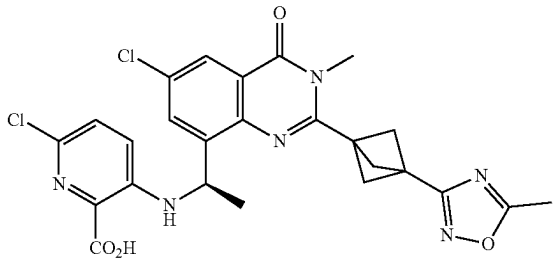

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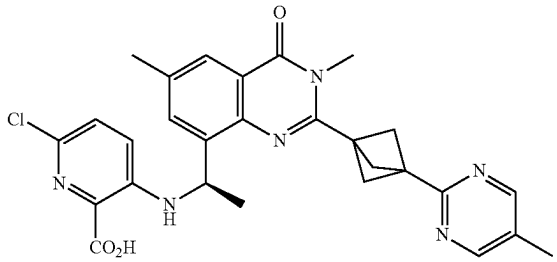
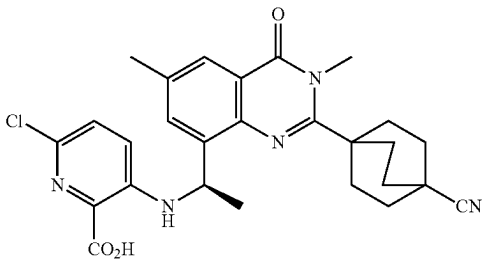
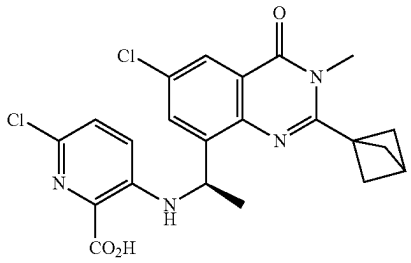
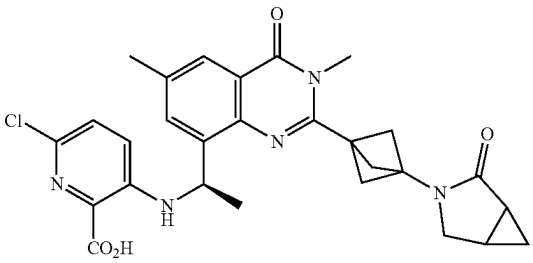
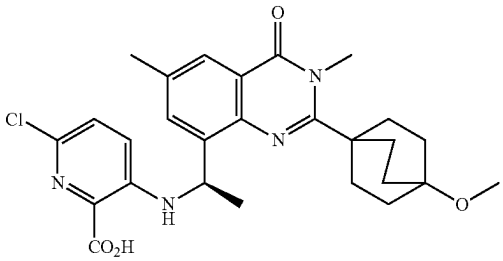

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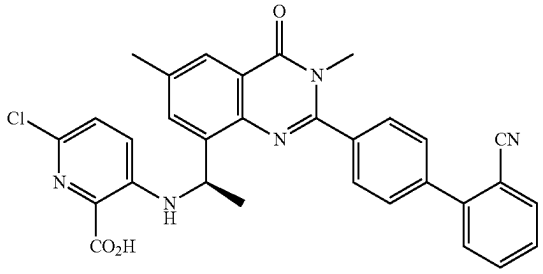
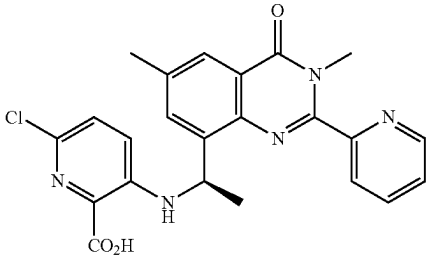
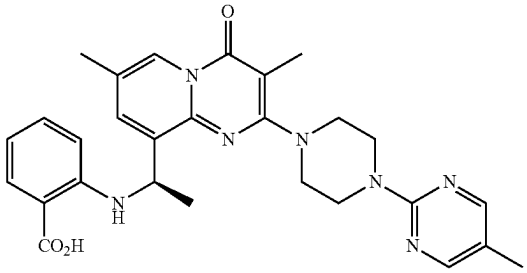
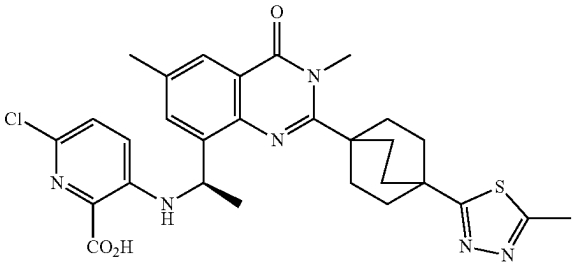
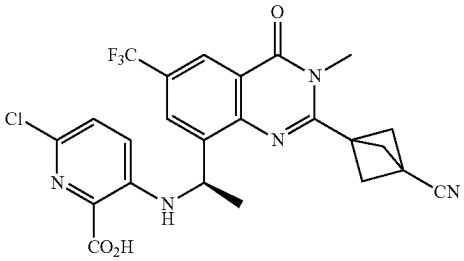

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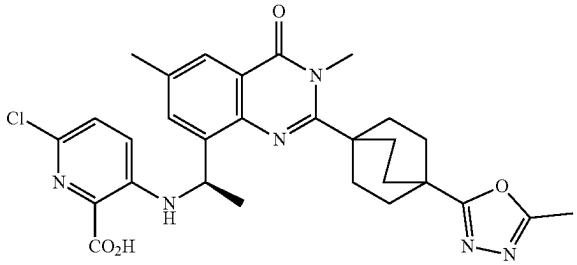
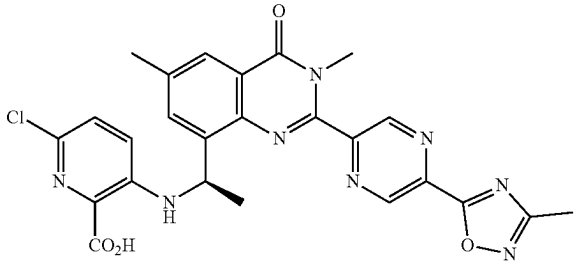
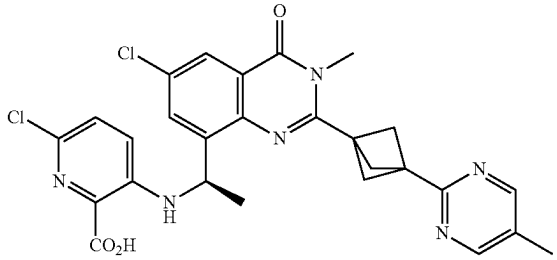
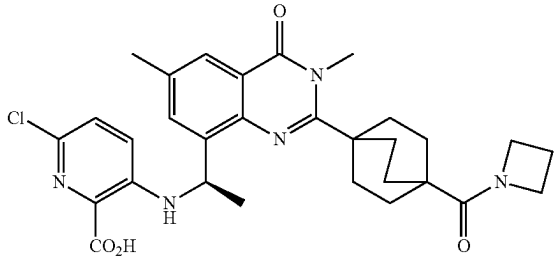
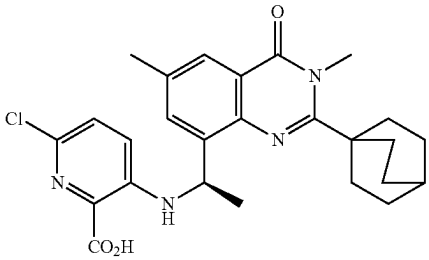

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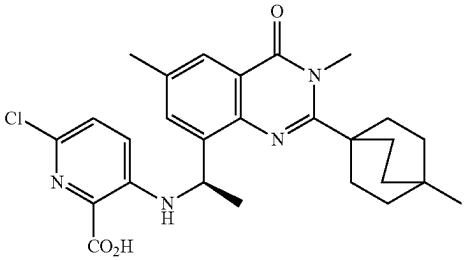
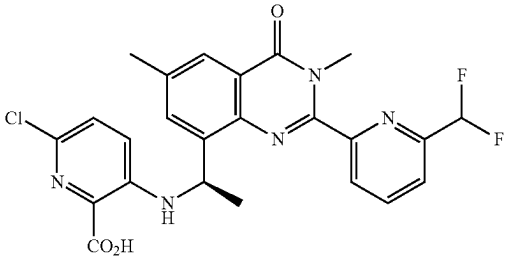
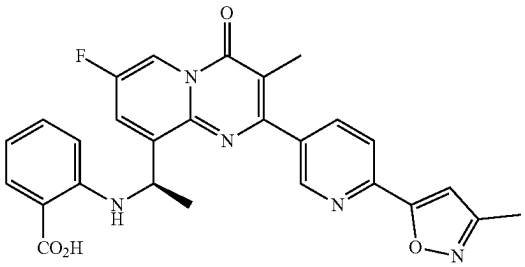
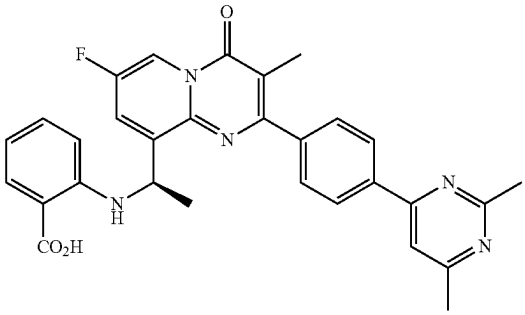
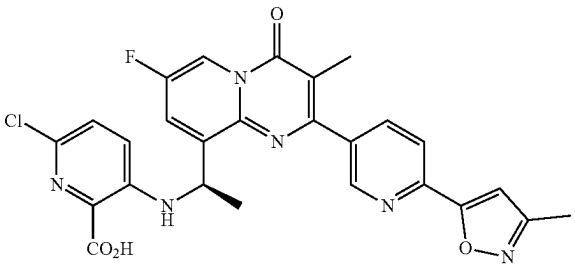

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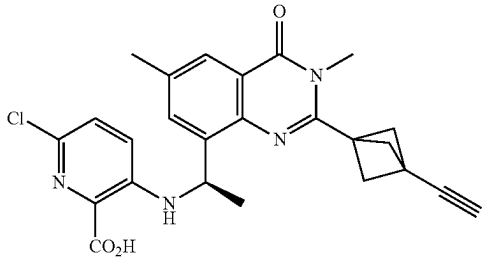
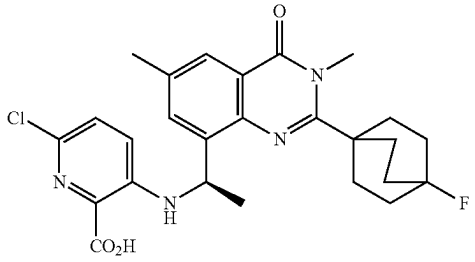
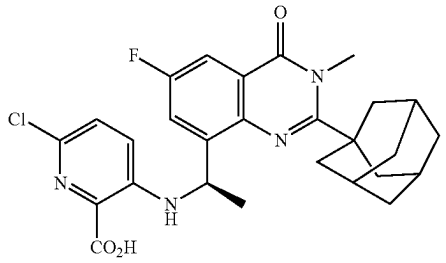
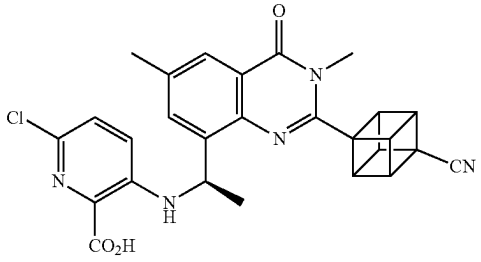
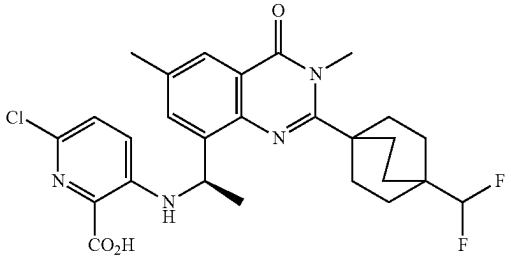

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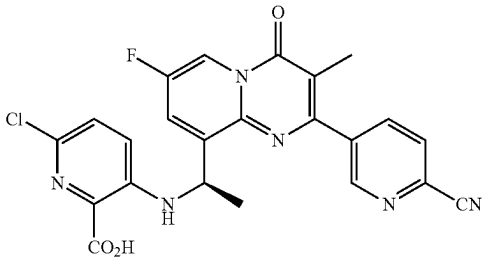
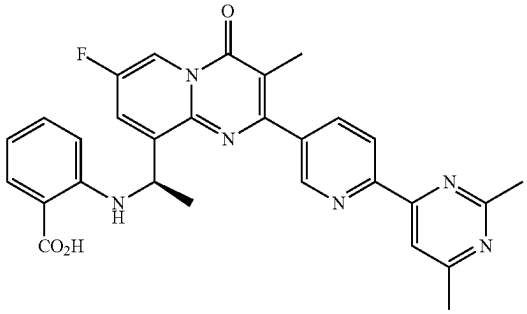
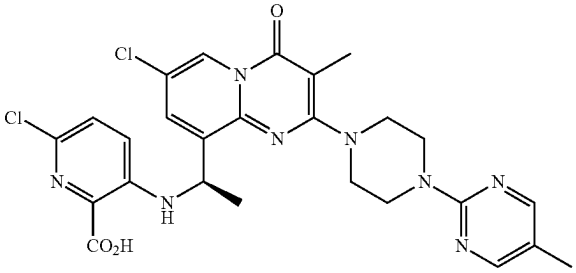
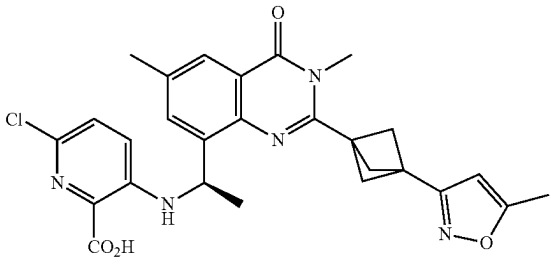
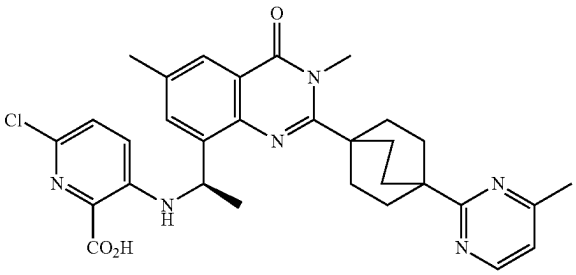

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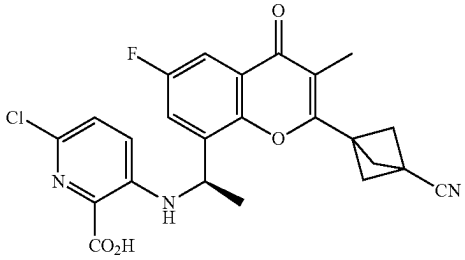
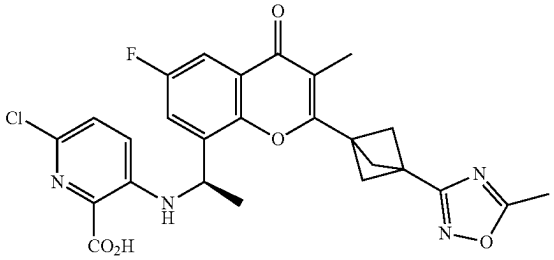
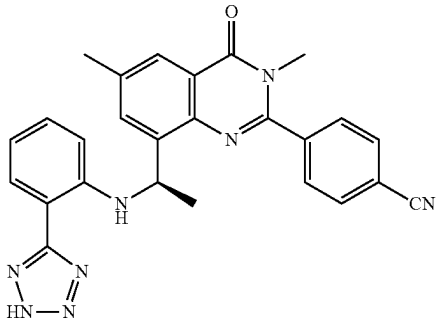
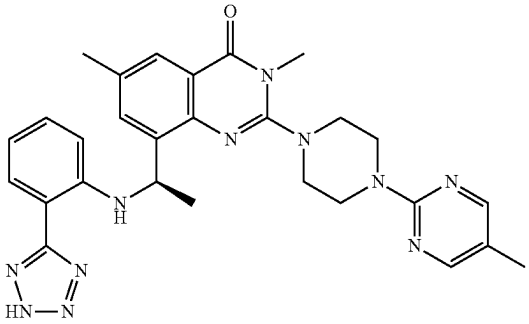
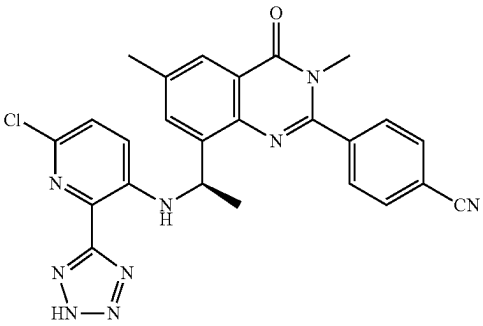

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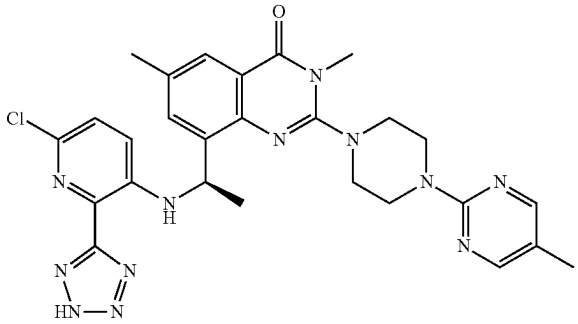
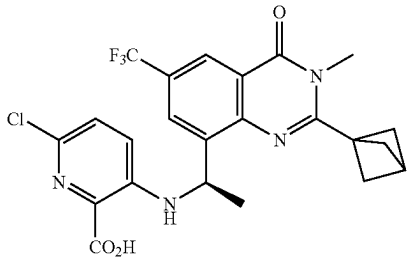
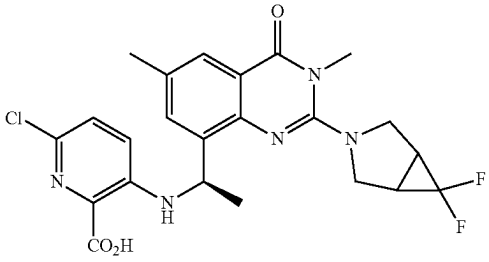
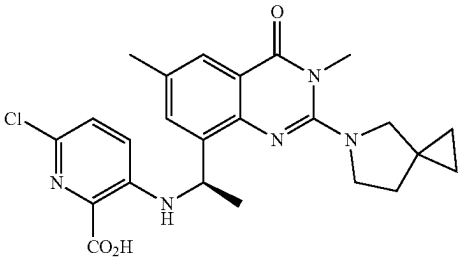
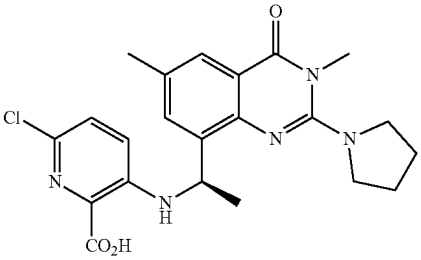

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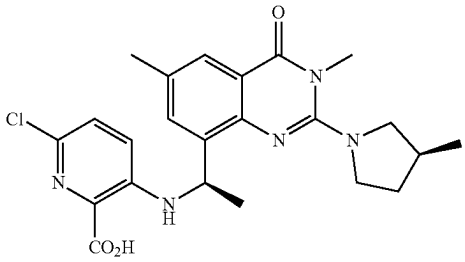
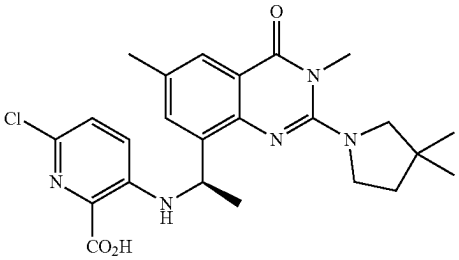
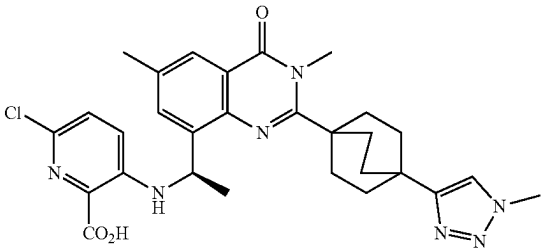
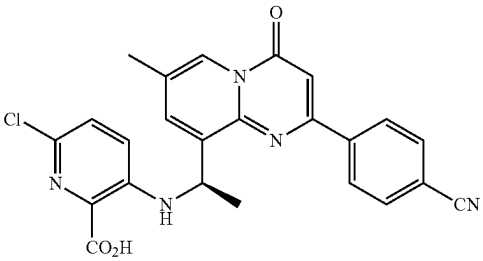
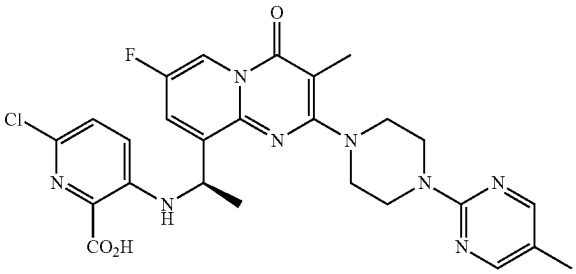

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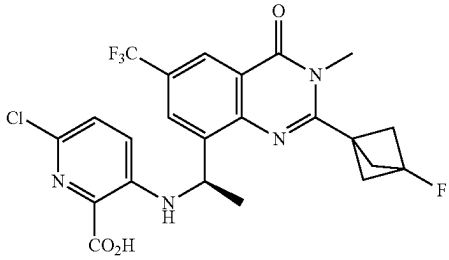
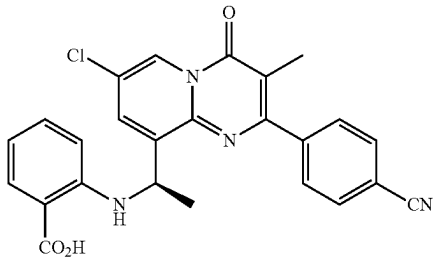
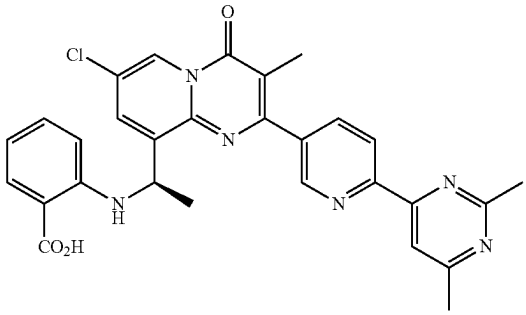
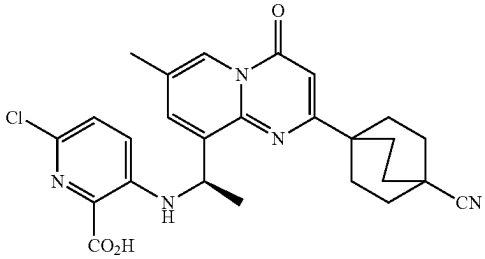
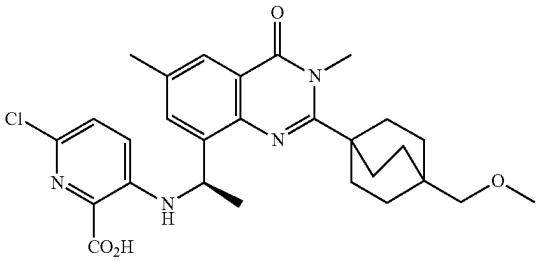

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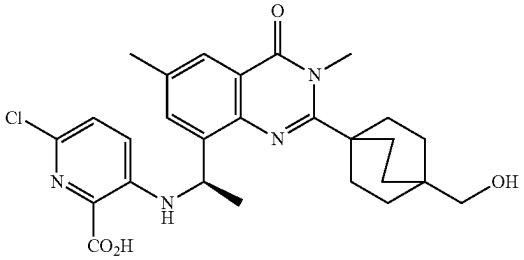
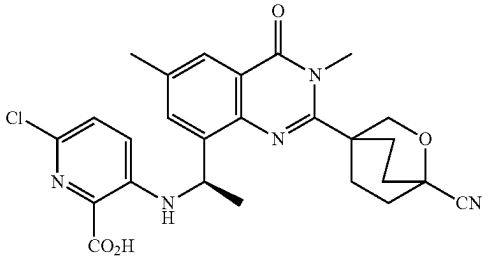
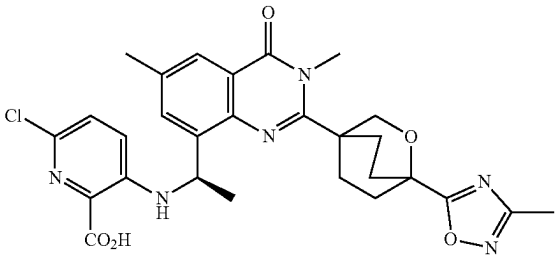
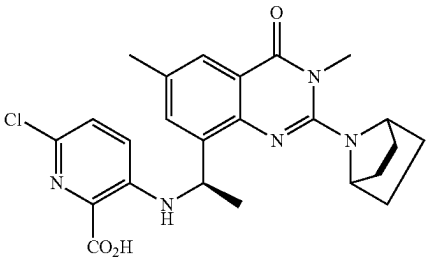
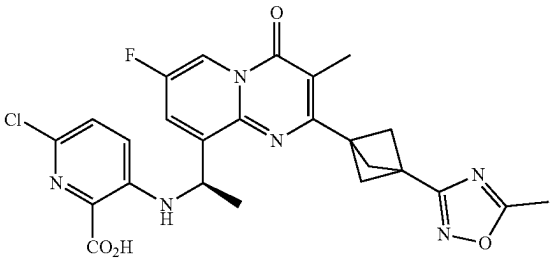

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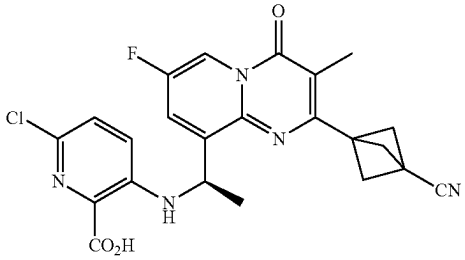
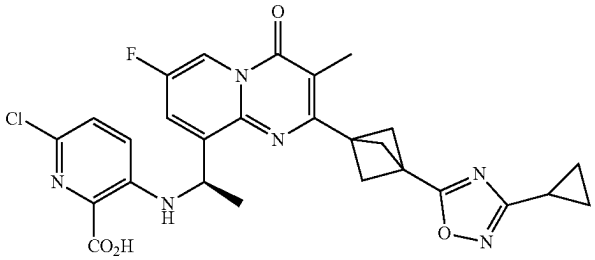
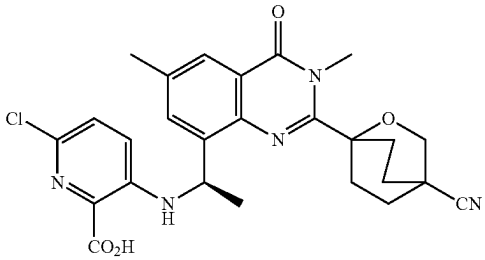
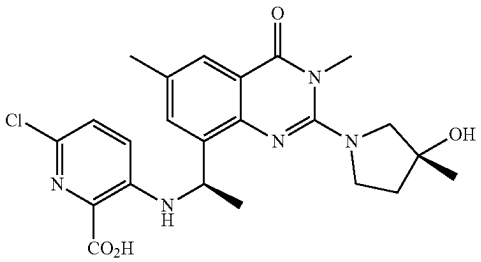
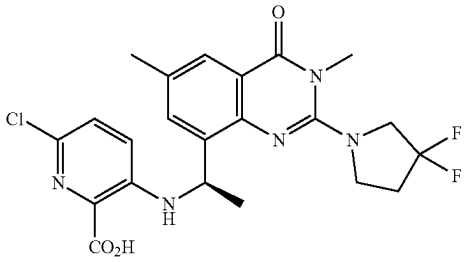

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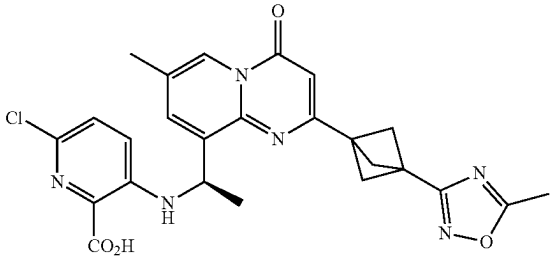
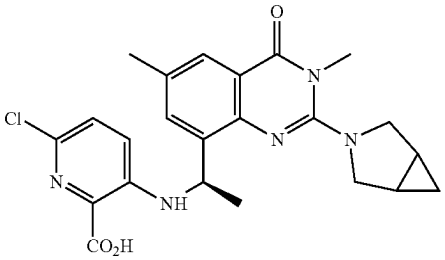
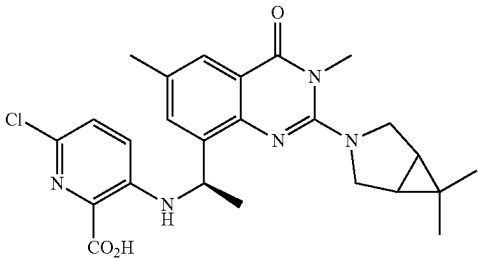
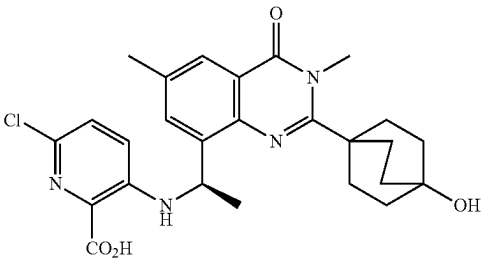
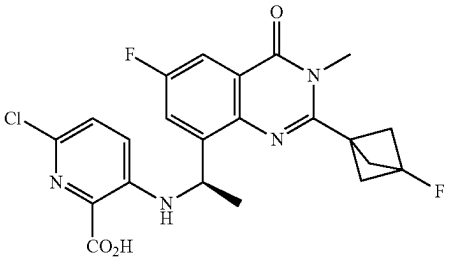

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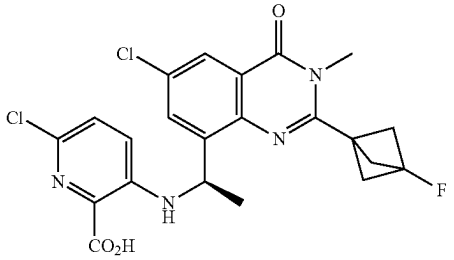
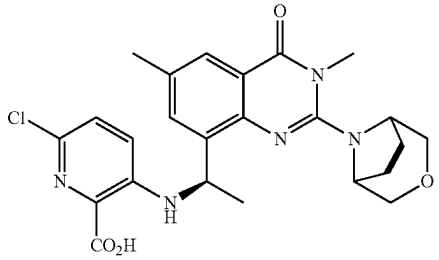
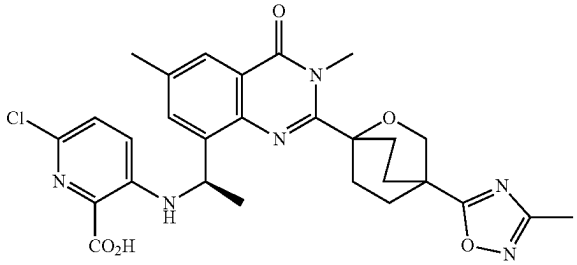
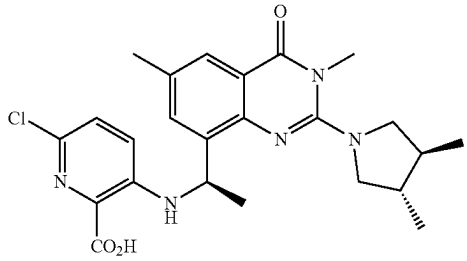
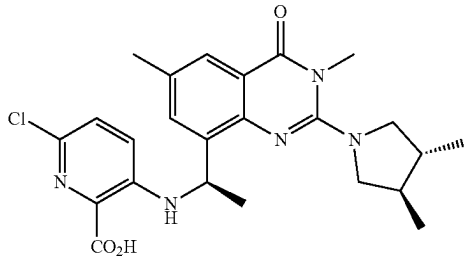

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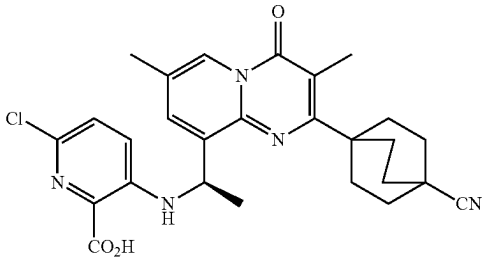
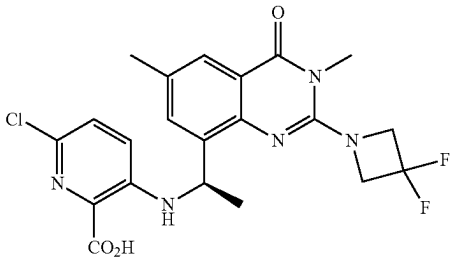
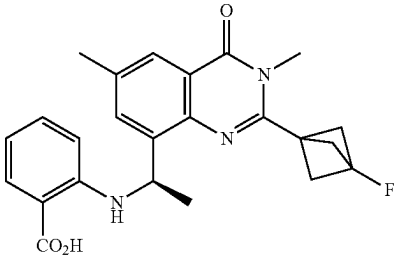
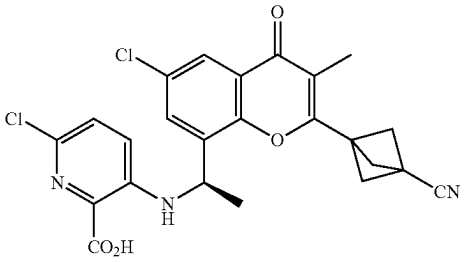
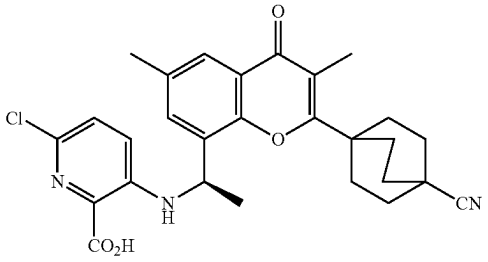

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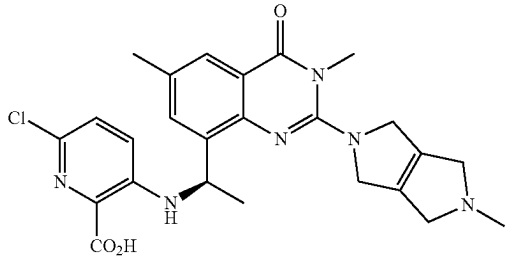
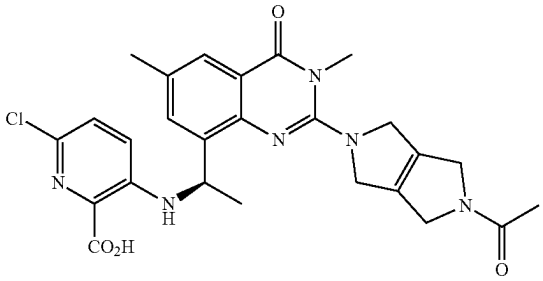
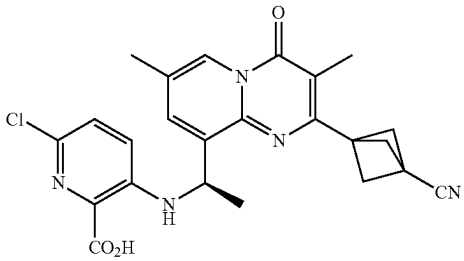
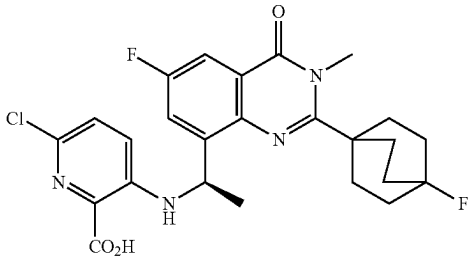
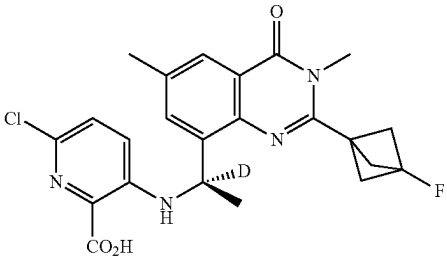

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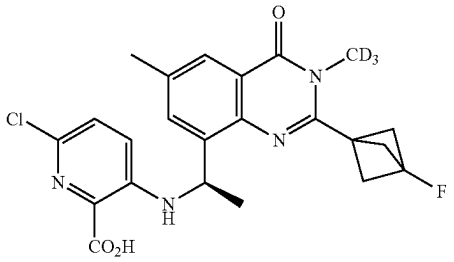
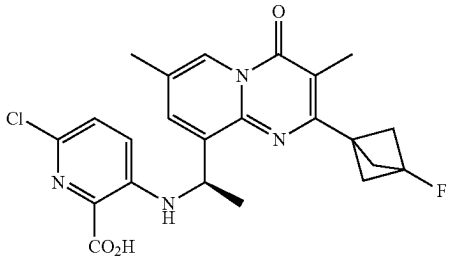
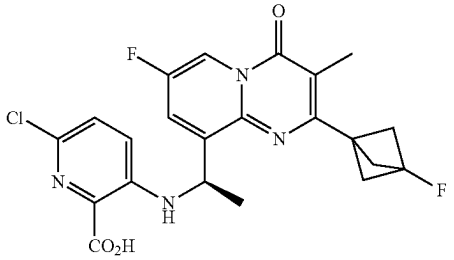
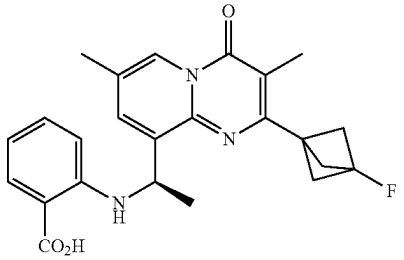
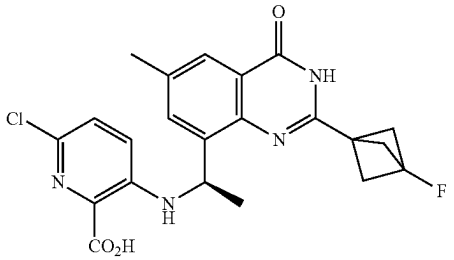

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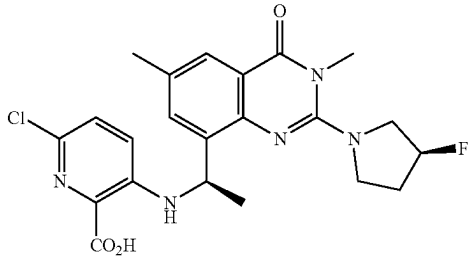
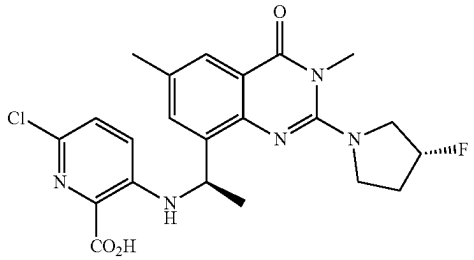
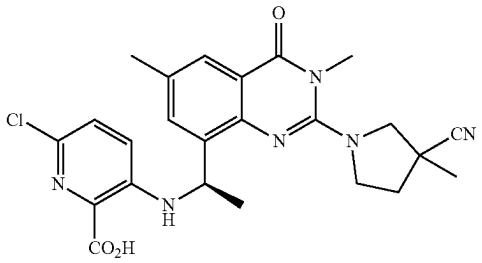
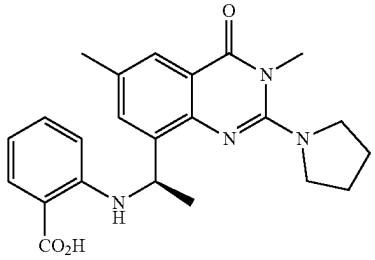
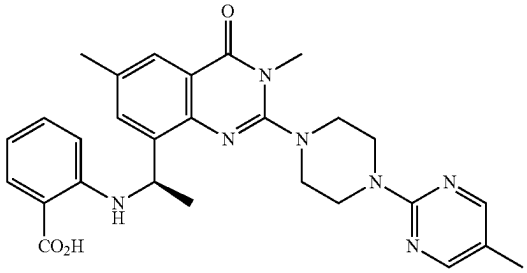

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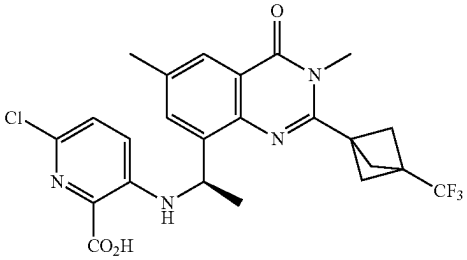
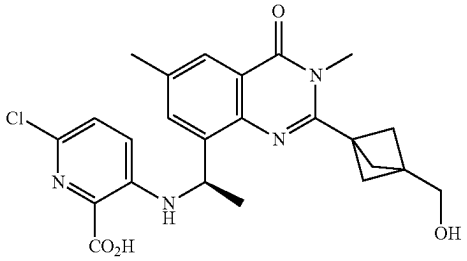
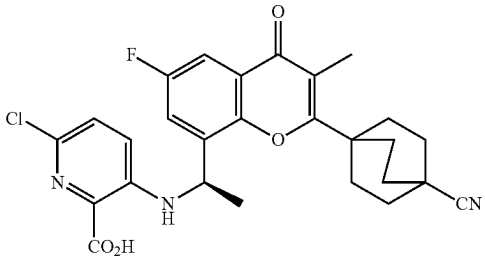
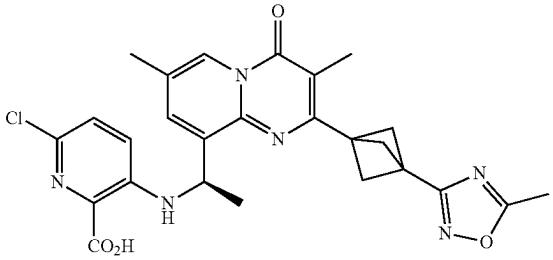
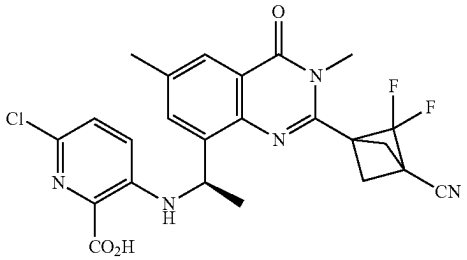

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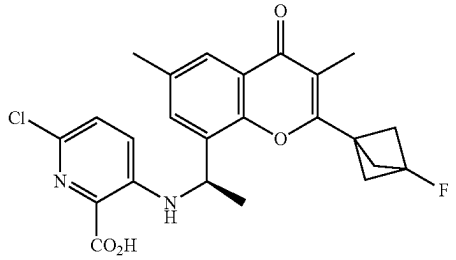
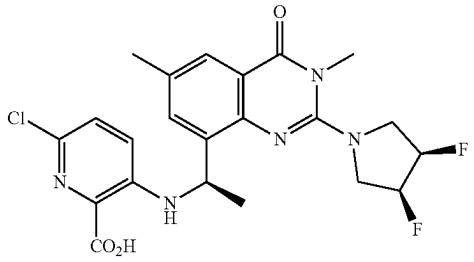
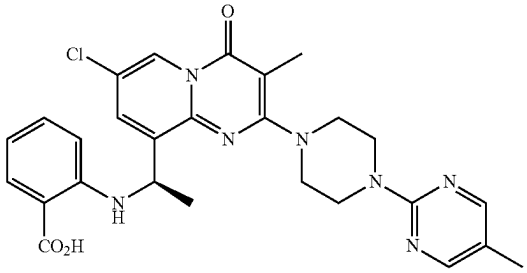
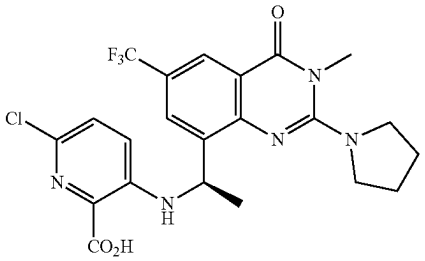
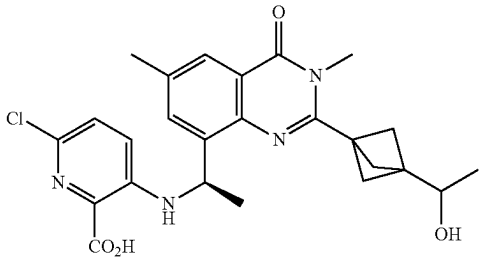

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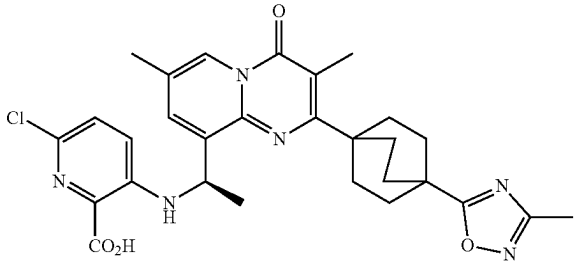
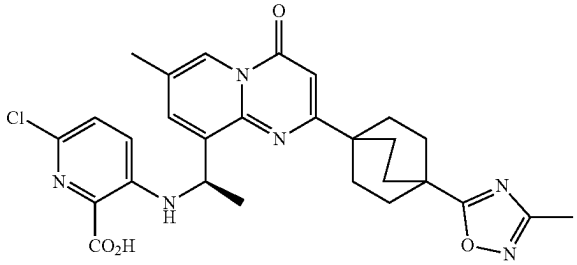
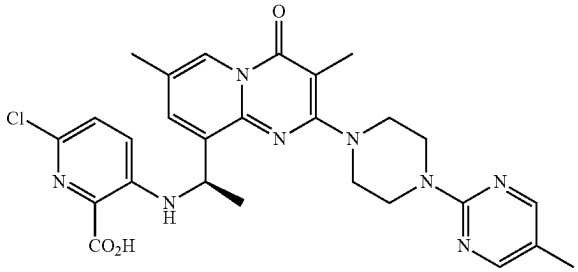
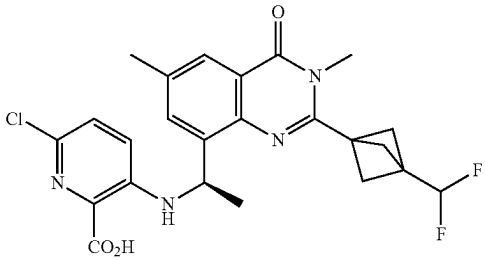
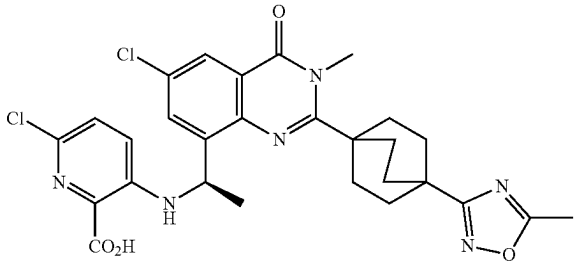

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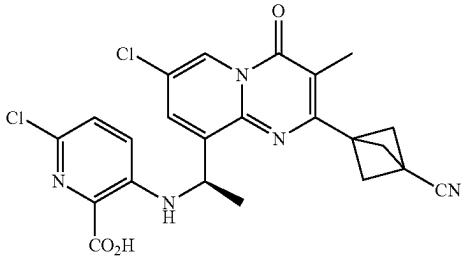
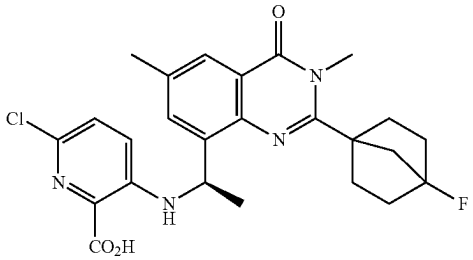
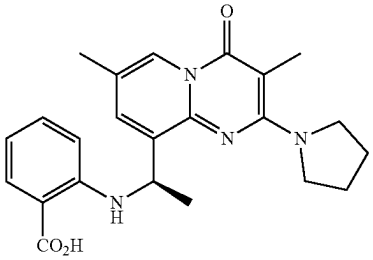
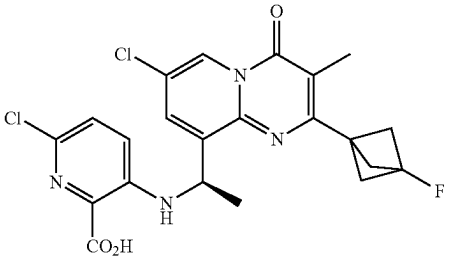
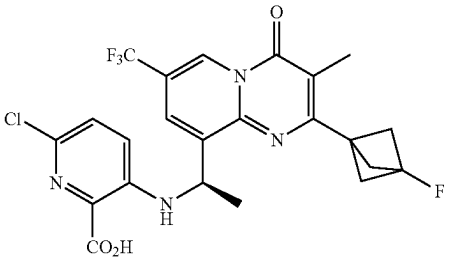

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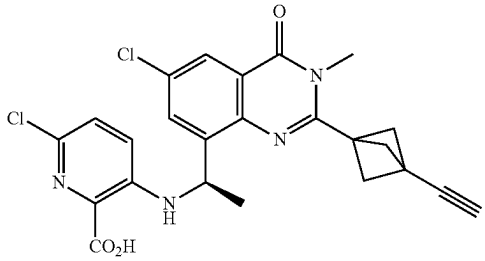
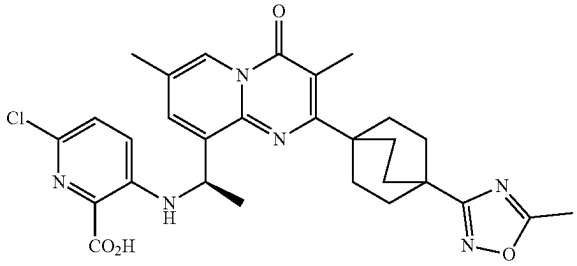
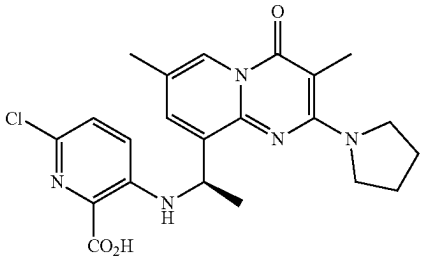
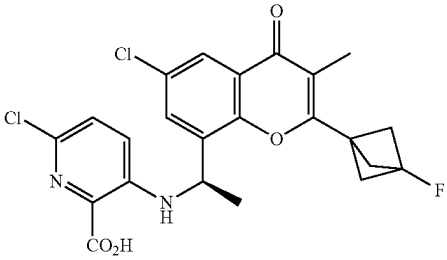
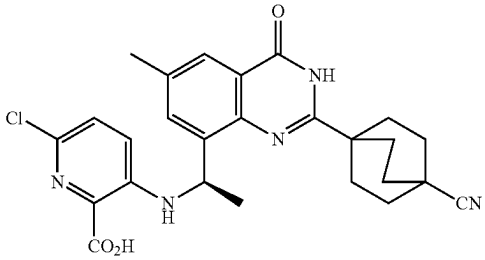

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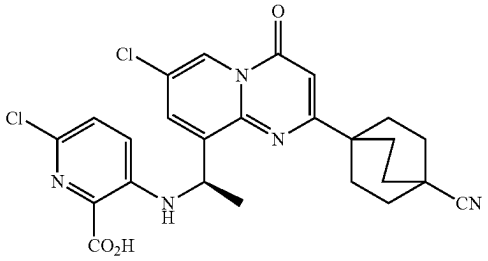
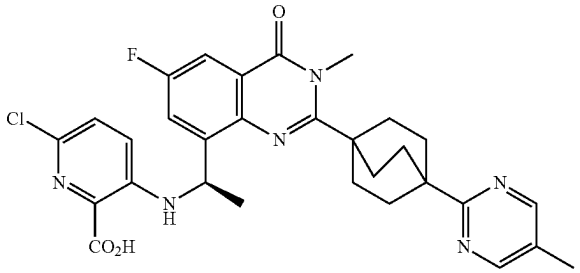
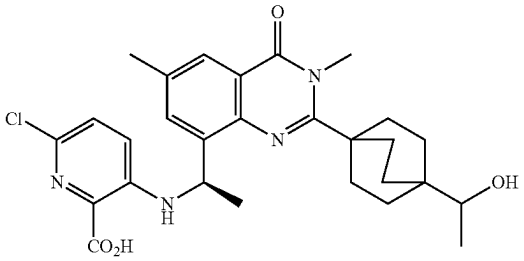
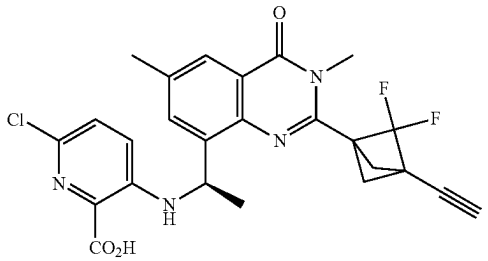
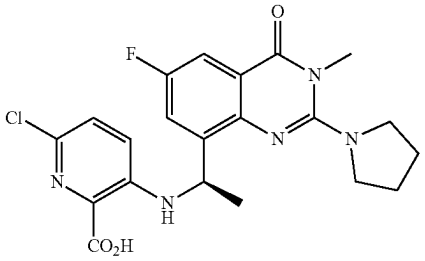

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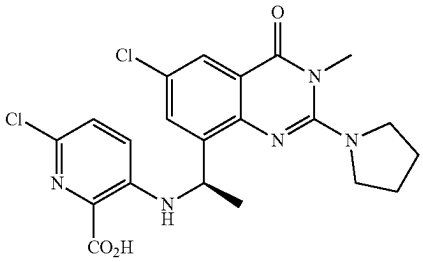
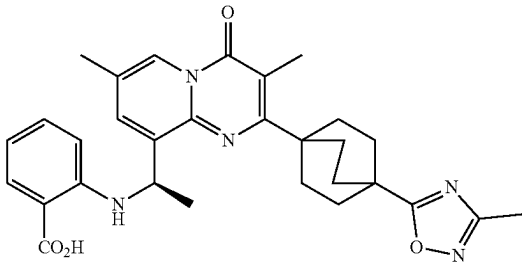
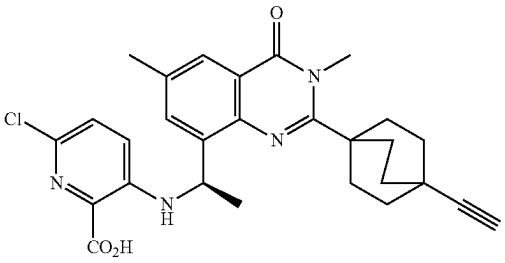
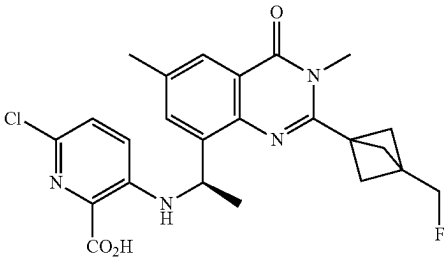
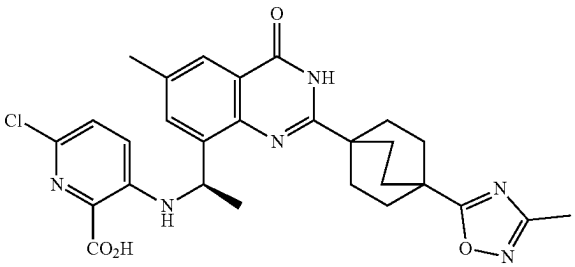

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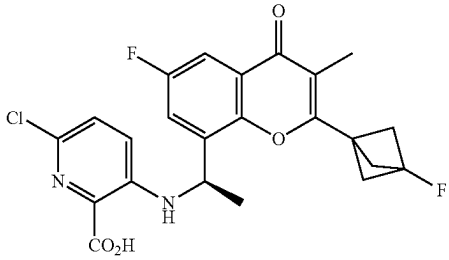
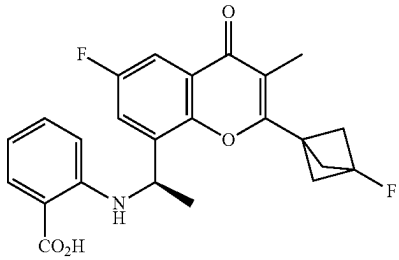
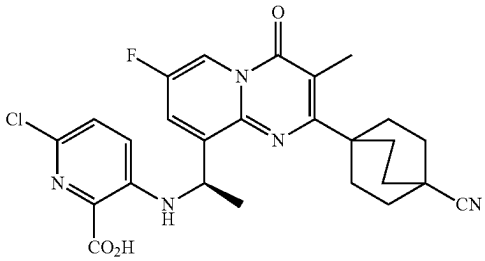
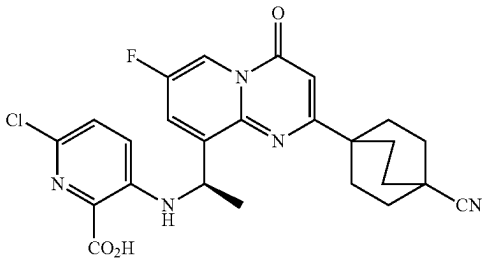
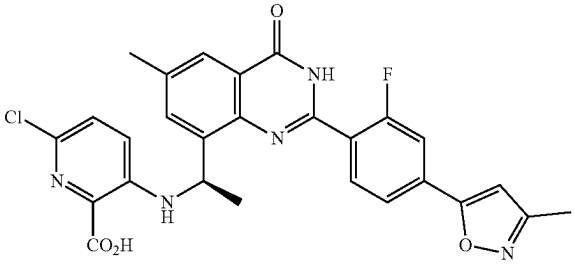

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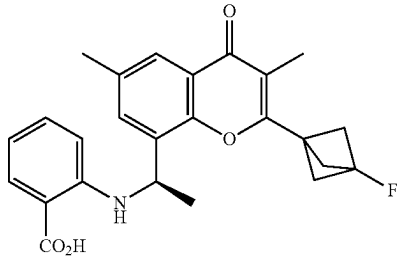
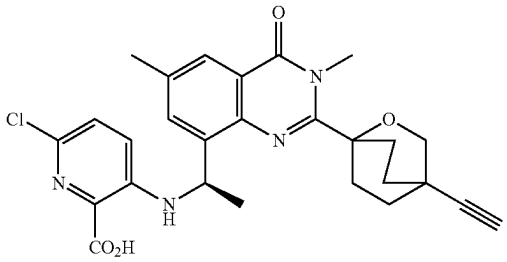
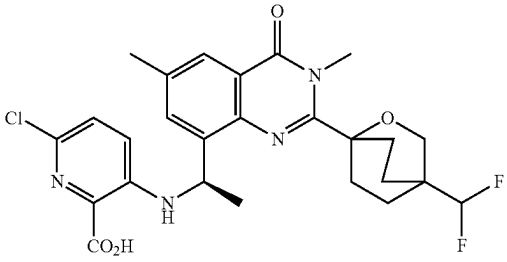
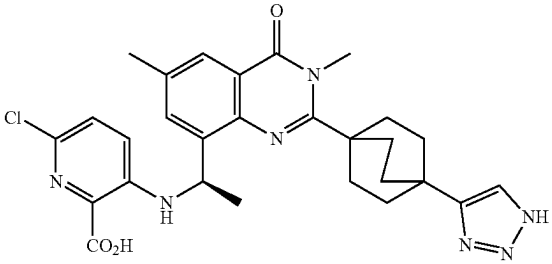
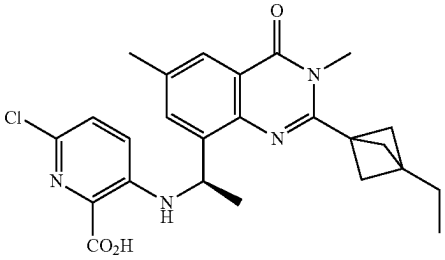

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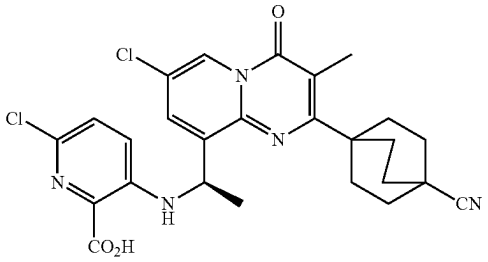
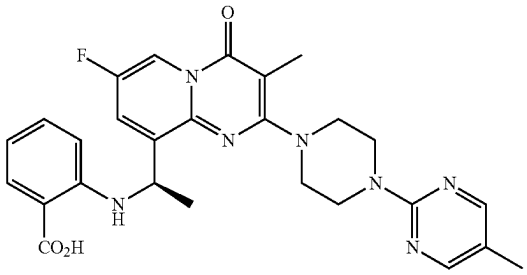
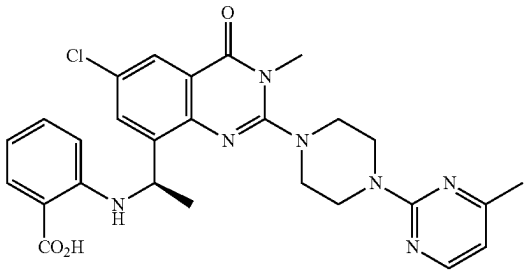
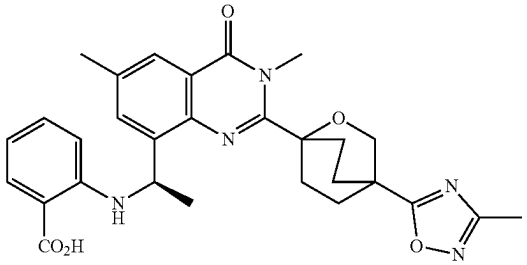
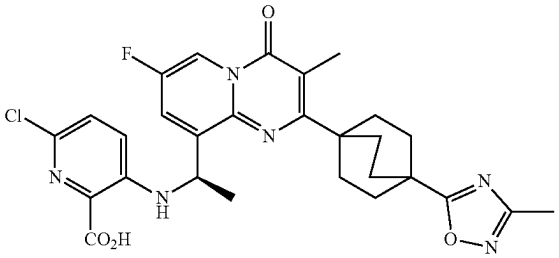

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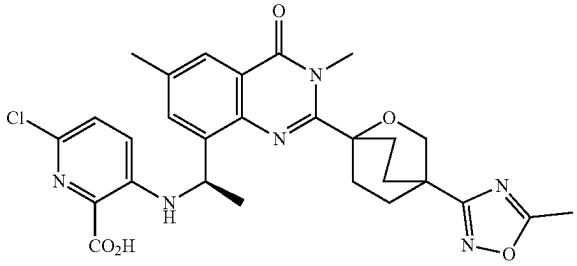
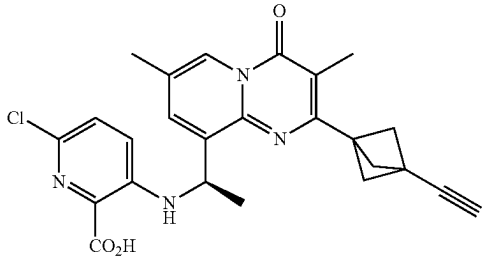
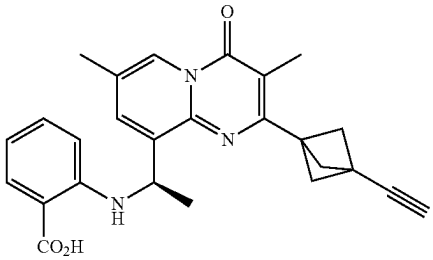
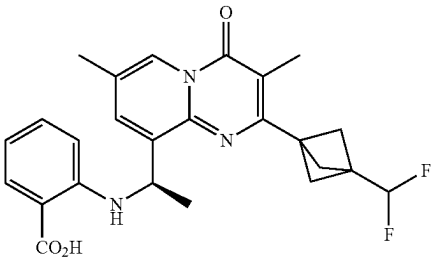
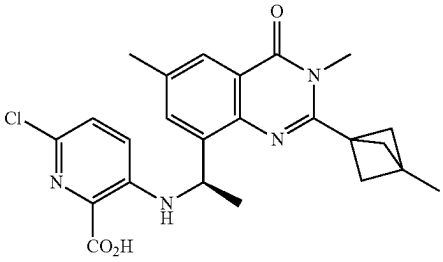

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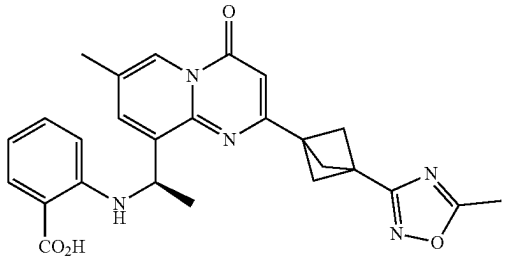
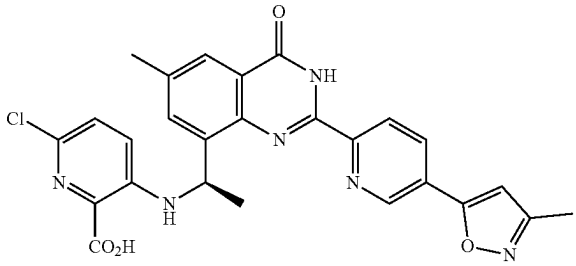
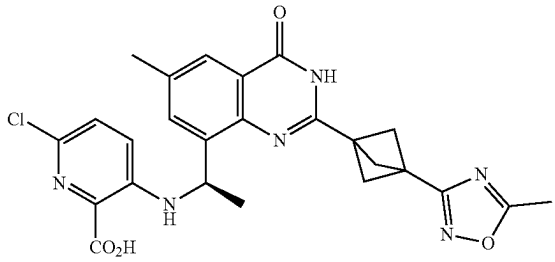
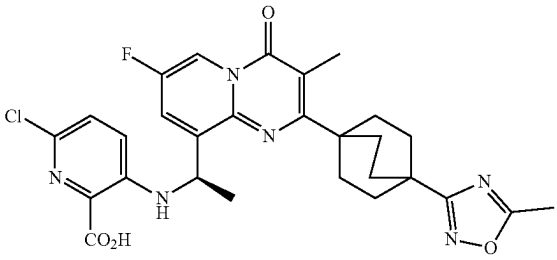
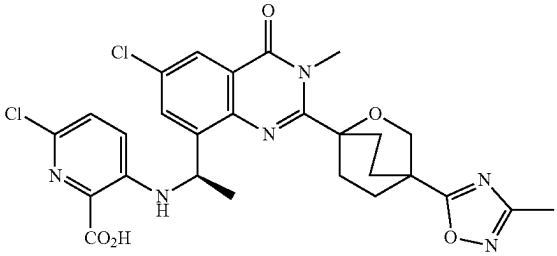

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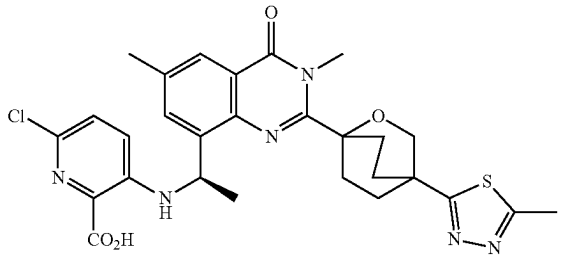
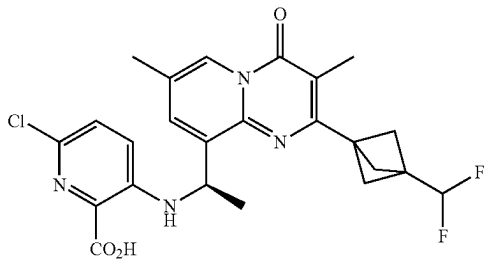
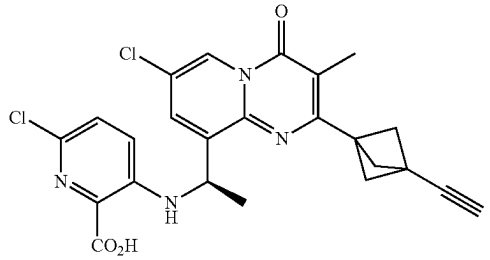
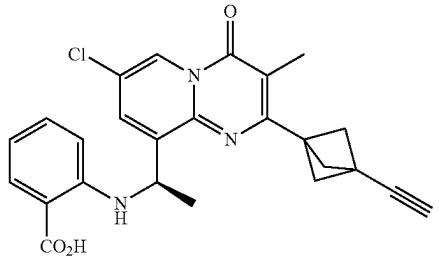
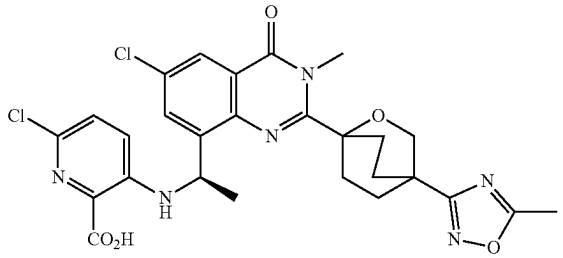

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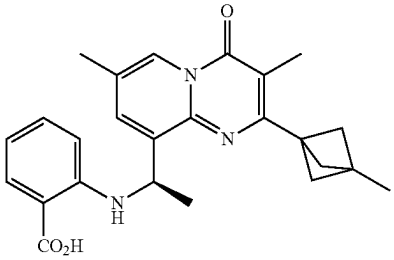
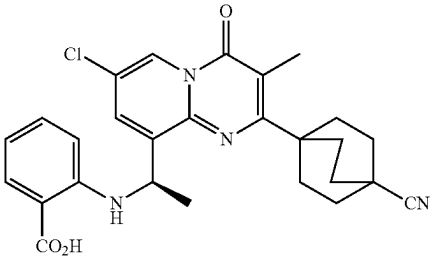
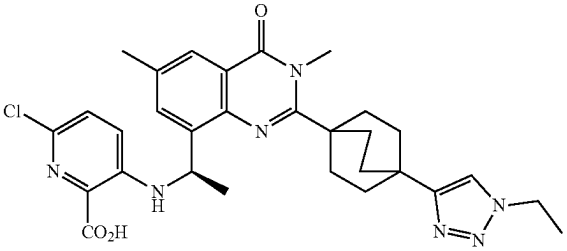
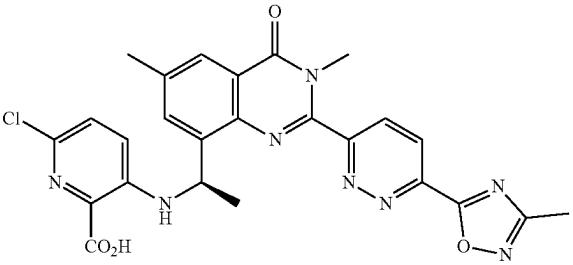
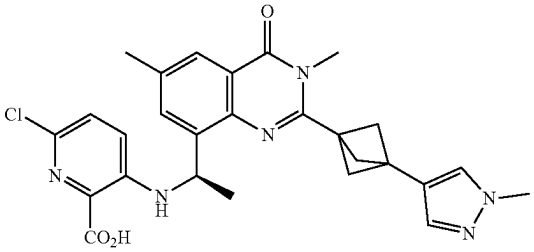

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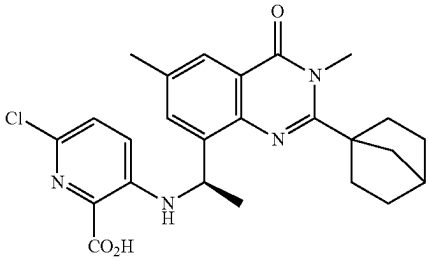
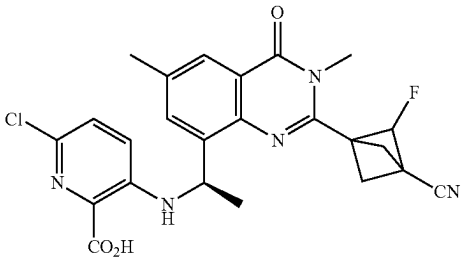
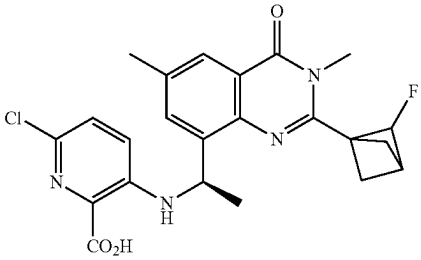
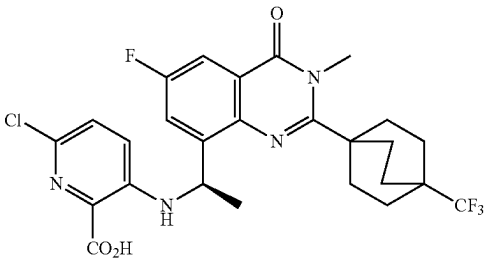
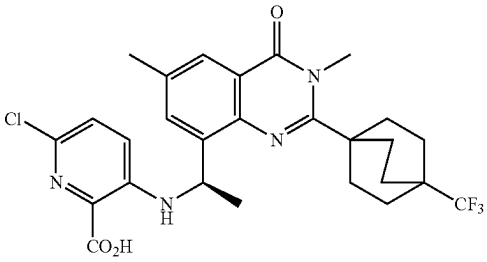

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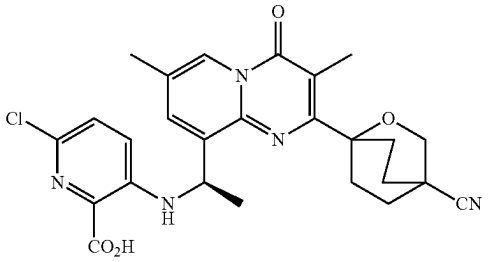
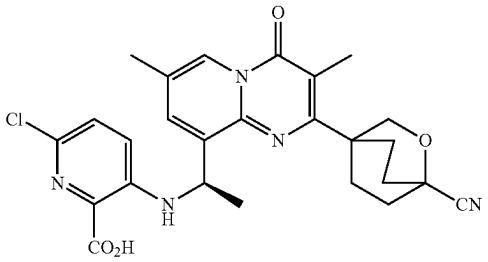
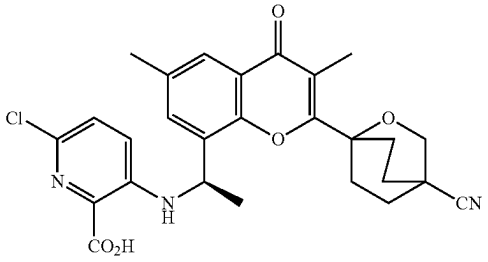
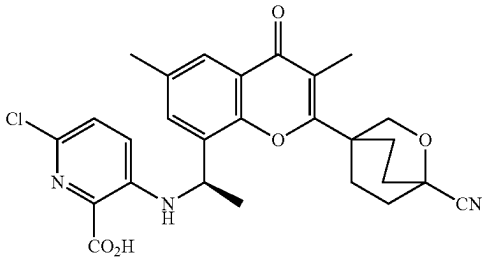
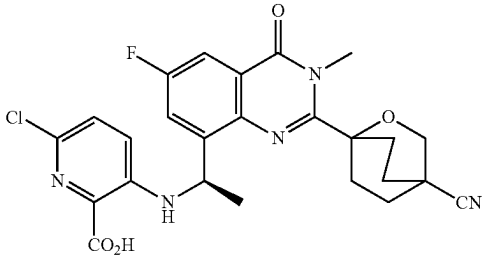

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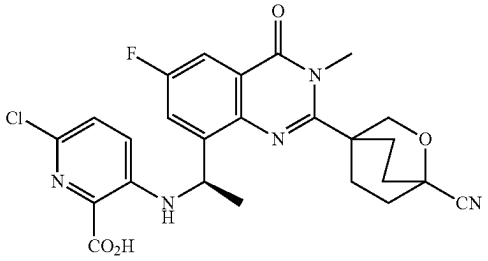
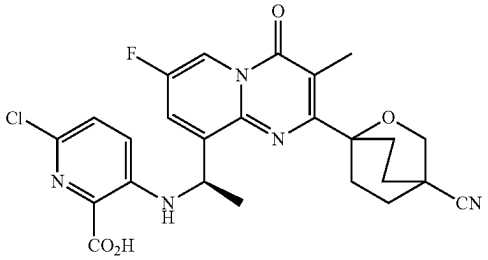
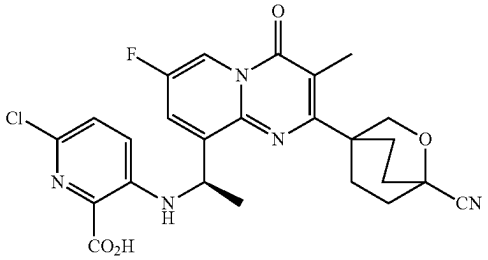
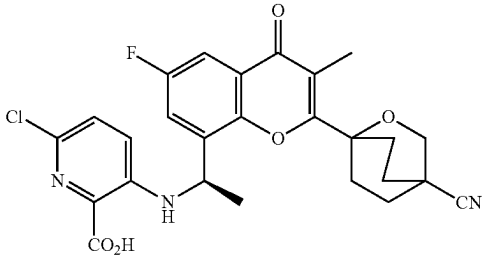
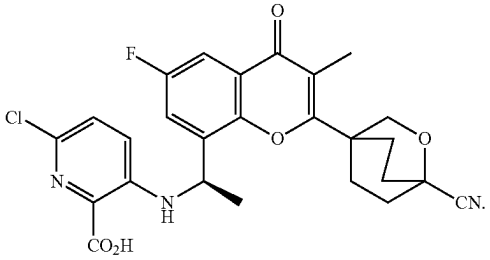






[0777] Exemplary synthesis and characterization of the above compounds are shown in Examples section. The compounds may be prepared in a racemic form, with respect to one or more of the chiral centers, which can be separated into two enantiomers, including the as-drawn enantiomer, or be prepared through chiral synthesis, in view of the present disclosure.

[0778] In some embodiments, to the extent applicable, the genus of compounds in the present disclosure also excludes any of the compounds specifically prepared and disclosed prior to this disclosure, such as those specific compounds described in WO 2021/202964.

[0779] In some embodiments, to the extent applicable, the genus of compounds in the present disclosure (such as those

defined in Embodiments B1-87 or the original claims) also excludes any of the compounds specific compounds described in WO 2023/060262 or any subgenus described in WO 2023/060262 that falls within the genus of compounds in the present disclosure.

[0780] The compounds of the present disclosure can be readily synthesized by one of ordinary skilled in the art in view of the present disclosure. Exemplified syntheses are also shown in Examples section.

[0781] As will be apparent to those having ordinary skill in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in "Protective Groups in Organic Synthesis", 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, and references cited therein. The reagents for the reactions described herein are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the reagents are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (Wiley, 7th Edition), and Larock's Comprehensive Organic Transformations (Wiley-VCH, 1999), and any of available updates as of this filing.

Pharmaceutical Compositions

[0782] Certain embodiments are directed to a pharmaceutical composition comprising one or more of the compounds of the present disclosure.

[0783] The pharmaceutical composition can optionally contain a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable excipient. Pharmaceutically acceptable excipients are known in the art. Non-limiting suitable excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, carriers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. See also Remington's The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2005; incorporated herein by reference), which discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[0784] The pharmaceutical composition can include any one or more of the compounds of the present disclosure. For example, in some embodiments, the pharmaceutical composition comprises a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof, e.g., in a therapeutically effective amount. In any of the embodiments described herein, the pharmaceutical composition can comprise a therapeutically effective amount of a compound selected from the compounds shown in Examples section, or a pharmaceutically acceptable salt thereof. In any of the embodiments described herein, the pharmaceutical composition can comprise a therapeutically effective amount of a compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof. In some preferred embodiments, compounds of the present disclosure for the pharmaceutical compositions herein are selected from those compounds that have an IC_{50} values less than 1 micromolar (preferably less than 100 nM, or less than 50 nM) when tested in the antiproliferation assay in T47D cell line according to Biological assays Example A herein. In some preferred embodiments, compounds of the present disclosure for the pharmaceutical compositions herein are selected from those compounds that have an IC_{50} values greater than 1 micromolar (preferably greater than 2 micromolar, or greater than 5 micromolar) when tested in the antiproliferation assay in SK-BR-3 cell line according to Biological assays Example A herein.

[0785] The pharmaceutical composition can also be formulated for delivery via any of the known routes of delivery, which include but are not limited to oral, parenteral, inhalation, etc.

[0786] In some embodiments, the pharmaceutical composition can be formulated for oral administration. The oral formulations can be presented in discrete units, such as capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Excipients for the preparation of

compositions for oral administration are known in the art. Non-limiting suitable excipients include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof.

[0787] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (such as intravenous injection or infusion, subcutaneous or intramuscular injection). The parenteral formulations can be, for example, an aqueous solution, a suspension, or an emulsion. Excipients for the preparation of parenteral formulations are known in the art. Non-limiting suitable excipients include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof.

[0788] In some embodiments, the pharmaceutical composition is formulated for inhalation. The inhalable formulations can be, for example, formulated as a nasal spray, dry powder, or an aerosol administrable through a metered-dose inhaler. Excipients for preparing formulations for inhalation are known in the art. Non-limiting suitable excipients include, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, and mixtures of these substances. Sprays can additionally contain propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0789] The pharmaceutical composition can include various amounts of the compounds of the present disclosure, depending on various factors such as the intended use and potency and selectivity of the compounds. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof). In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound of the present disclosure and a pharmaceutically acceptable excipient. As used herein, a therapeutically effective amount of a compound of the present disclosure is an amount effective to treat a disease or disorder as described herein, which can depend on the recipient of the treatment, the disease or disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency (e.g., for inhibiting PI3K), its rate of clearance and whether or not another drug is co-administered.

[0790] For veterinary use, a compound of the present disclosure can be administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

[0791] In some embodiments, all the necessary components for the treatment of PI3K associated diseases or disorders using a compound of the present disclosure either alone or in combination with another agent or intervention traditionally used for the treatment of such disease can be packaged into a kit. Specifically, in some embodiments, the present invention provides a kit for use in the therapeutic intervention of the disease comprising a packaged set of medicaments that include the compound disclosed herein as well as buffers and other components for preparing deliverable forms of said medicaments, and/or devices for delivering such medicaments, and/or any agents that are used in combination therapy with the compound of the present disclosure, and/or instructions for the treatment of the disease packaged with the medicaments. The instructions may be fixed in any tangible medium, such as printed paper, or a computer readable magnetic or optical medium, or instructions to reference a remote computer data source such as a world wide web page accessible via the internet.

Method of Treatment

[0792] Compounds of the present disclosure are useful as therapeutic active substances for the treatment and/or prophylaxis of diseases or disorders that are associated with the activity of phosphoinositide 3 kinase (PI3K), in particular, PI3K-alpha (PI3Ka), such as those having a H1047R mutation. Such diseases or disorders include proliferative diseases (e.g., cancer).

[0793] In some embodiments, the present disclosure provides a method of inhibiting the activity of phosphoinositide 3 kinase (PI3K), in particular, PI3K-alpha (PI3Ka), such as those having a H1047R mutation, in a cell comprising contacting a cell with an effective amount of one or more compounds of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g.,

Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof). As used herein, the term "cell" is meant to refer to a cell that is in vitro, ex vivo or in vivo. In some embodiments, an ex vivo cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an in vitro cell can be a cell in a cell culture. In some embodiments, an in vivo cell is a cell living in an organism such as a mammal. As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" the PI3K with a compound of the present disclosure includes the administration of a compound of the present disclosure to a subject, such as a human, having PI3K, as well as, for example, introducing a compound of the present disclosure into a sample containing a cellular or purified preparation containing PI3K enzyme. The term "PI3K inhibitor" such as a PI3Ka inhibitor refers to an agent capable of inhibiting the activity of PI3K.

[0794] In some embodiments, the present disclosure provides a method of treating a disease associated with activity or expression, including abnormal activity and/or overexpression, of PI3K in a subject in need thereof, the method comprising administering to the subject an effective amount of one or more compounds of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof). Examples of diseases can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of PI3K enzyme, such as over expression or abnormal activity. A PI3K-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating PI3K enzyme activity. Examples of PI3K associated diseases include various cancer described herein. In any of the embodiments described herein, unless specified or otherwise contrary, the PI3K enzyme can be a PI3Ka enzyme, such as those having a H1047R mutation. Examples of PI3K associated cancer include breast, endometrial, gastric, colorectal, ovarian, cervical, head-and-neck, liver, lung, prostate cancers. Examples of PI3K associated diseases also include CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS). In some embodiments, the disease of disorder associated with PI3K is a cancer (e.g., described herein, such as breast, endometrial, gastric, colorectal, ovarian, cervical, head-and-neck, liver, lung, prostate cancers, leukemia, lymphoma, sarcoma and melanoma. In some embodiments, the disease or disorder associated with PI3K includes, but is not limited to, CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS), endometrial cancer, breast cancer, esophageal squamous-cell cancer, cervical squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma, soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma, adrenocortical carcinoma, renal non-clear-cell carcinoma, renal clear-cell carcinoma, germ-cell carcinoma, thymic tumor, pheochromocytoma, miscellanea. Additional diseases or disorders associated with PI3K are described herein and also include those described in WO 2021/202964.

[0795] In some embodiments, the present disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of one or more compounds of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof) or a therapeutically effective amount of a pharmaceutical composition described herein. In some embodiments, the cancer is associated with PI3K, such as PI3Ka, for example, those having H1047R mutation. In some embodiments, the cancer is breast, endometrial, gastric, colorectal, ovarian, cervical, head-and-neck, liver, lung, prostate cancers. Additional cancer suitable to be treated include those described herein.

[0796] In some embodiments, the cancer is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, aids-related cancers, aids-related lymphoma, anal cancer, astrocytoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain tumors, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, cancer of unknown primary, cardiac (heart) tumors, atypical teratoid/rhabdoid tumor, primary CNS lymphoma, cervical cancer, cholangiocarcinoma, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colorectal cancer, craniopharyngioma, cutaneous t-cell lymphoma, mycosis fungoides, Sezary syndrome, ductal carcinoma in situ (DCIS), embryonal tumors,

medulloblastoma, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, fallopian tube cancer, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, malignant gastrointestinal stromal tumors (GIST), germ cell tumors, gestational trophoblastic disease, hairy cell leukemia, head and neck cancer, hepatocellular cancer, Langerhans cell histiocytosis, Hodgkin lymphoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, laryngeal cancer, leukemia, liver cancer, lung cancer, lymphoma, male breast cancer, intraocular melanoma, Merkel cell carcinoma, malignant mesothelioma, metastatic cancer, metastatic squamous neck cancer, midline tract carcinoma with nut gene changes, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasms, myelodysplastic syndromes, myelodysplastic neoplasms, myeloproliferative neoplasms, chronic myeloproliferative neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, lip and oral cavity cancer, oropharyngeal cancer, malignant fibrous histiocytoma of bone, ovarian cancer, pancreatic cancer, pancreatic neuroendocrine tumors (islet cell tumors), papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, plasma cell neoplasm, multiple myeloma, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, recurrent cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, childhood vascular tumors, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma of the skin, testicular cancer, oropharyngeal cancer, hypopharyngeal cancer, thymoma, thymic carcinoma, thyroid cancer, tracheobronchial tumors, transitional cell cancer of the renal pelvis and ureter, urethral cancer, uterine sarcoma, vaginal cancer, vascular tumors, vulvar cancer, and Wilms tumor.

[0797] In some embodiments, the cancer is Endometrial cancer, Breast cancer, Oesophageal squamous-cell cancer, Cervical squamous-cell carcinoma, Cervical adenocarcinoma, Colorectal adenocarcinoma, Bladder Urothelial Carcinoma, Glioblastoma, Ovarian cancer, Non-small-cell Lung cancer, Esophagogastric cancer, Nerve-sheath tumor, Head and neck squamous-cell carcinoma, Melanoma, Esophagogastric adenocarcinoma, Soft-tissue sarcoma, Prostate cancer, Fibrolamellar carcinoma, Hepatocellular carcinoma, Diffuse glioma, Colorectal cancer, Pancreatic cancer, Cholangiocarcinoma, B-cell lymphoma, Mesothelioma, Adrenocortical carcinoma, Renal non-clear-cell carcinoma, Renal clear-cell carcinoma, Germ-cell carcinoma, Thymic tumor, Pheochromocytoma, Miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, or encapsulated glioma.

[0798] In some embodiments, the cancer is a breast cancer, a prostate cancer, or a brain cancer. In some embodiments, the cancer is a breast cancer. In some embodiments, the cancer is a prostate cancer. In some embodiments, the cancer is a brain cancer.

[0799] In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is ductal carcinoma in situ (DCIS). In some embodiments, the breast cancer is invasive ductal carcinoma. In some embodiments, the breast cancer is triple negative breast cancer. In some embodiments, the breast cancer is medullary carcinoma. In some embodiments, the breast cancer is tubular carcinoma. In some embodiments, the breast cancer is mucinous carcinoma. In some embodiments, the breast cancer is Paget disease of the breast or nipple. In some embodiments, the breast cancer is inflammatory breast cancer (IBC).

[0800] In some embodiments, the prostate cancer is an adenocarcinoma. In some embodiments, the prostate cancer is a small cell carcinoma. In some embodiments, the prostate cancer is a neuroendocrine tumor. In some embodiments, the prostate cancer is a transitional cell carcinoma. In some embodiments, the prostate cancer is a sarcoma.

[0801] In some embodiments, the brain cancer is an acoustic neuroma. In some embodiments, the brain cancer is an astrocytoma. In some embodiments, the brain cancer is a brain metastasis. In some embodiments, the brain cancer is choroid plexus carcinoma. In some embodiments, the brain cancer is craniopharyngioma. In some embodiments, the brain cancer is an embryonal tumor. In some embodiments, the brain cancer is an ependymoma. In some embodiments, the brain cancer is a glioblastoma. In some embodiments, the brain cancer is a glioma. In some embodiments, the brain cancer is a medulloblastoma. In some embodiments, the brain cancer is a meningioma. In some embodiments, the brain cancer is an oligodendroglioma. In some embodiments, the brain cancer is a pediatric brain tumor. In some embodiments, the brain cancer is a pineoblastoma. In some embodiments, the brain cancer is a pituitary tumor.

[0802] In some embodiments, the cancer is endometrial cancer, head and neck cancer, or a sarcoma.

[0803] In some embodiments, the cancer is endometrial cancer. In some embodiments the cancer is head and neck cancer. In some embodiments, the cancer is a sarcoma.

[0804] In some embodiments, the sarcoma is soft tissue sarcoma, osteosarcoma, chondrosarcoma, Ewing sarcoma, hemangioendothelioma, angiosarcoma, fibrosarcoma, myxofibrosarcoma, chordoma, adamantinoma, liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, synovial sarcoma, or malignant solitary fibrous tumor.

[0805] In some embodiments, the sarcoma is soft tissue sarcoma. In some embodiments the soft tissue sarcoma is liposarcoma, atypical lipomatous tumor, dermatofibrosarcoma protuberans, malignant solitary fibrous tumor, inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma, fibrosarcoma, myxofibrosarcoma, low-grade fibromyxoid sarcoma, giant cell tumor of soft tissues, leiomyosarcoma, malignant glomus tumor, rhabdomyosarcoma, hemangioendothelioma, angiosarcoma of soft tissue, extraskeletal osteosarcoma, gastrointestinal stromal tumor, malignant gastrointestinal stromal tumor (GIST), malignant peripheral nerve sheath tumor, malignant Triton tumor, malignant granular cell tumor, malignant ossifying fibromyxoid tumor, stromal sarcoma, myoepithelial carcinoma, malignant phosphaturic mesenchymal tumor, synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft tissue, extraskeletal myxoid chondrosarcoma, extraskeletal Ewing sarcoma, desmoplastic small round cell tumor, extrarenal rhabdoid tumor, perivascular epithelioid cell tumor, intimal sarcoma, undifferentiated spindle cell sarcoma, undifferentiated pleomorphic sarcoma,

undifferentiated round cell sarcoma, undifferentiated epithelioid sarcoma, or undifferentiated sarcoma, not otherwise specified.

[0806] In some embodiments, the present disclosure provides a method of treating a disease or disorder in a subject, the method comprising administering to the subject a therapeutically effective amount of one or more compounds of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof) or a therapeutically effective amount of a pharmaceutical composition described herein, wherein the disease or disorder is selected from CLOVES syndrome (congenial lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS), breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer. In some embodiments, the disease or disorder is leukemia, lymphoma, or sarcoma.

[0807] In some preferred embodiments, compounds of the present disclosure for the methods herein are selected from those compounds that have an IC_{50} values less than 1 micromolar (preferably less than 100 nM, or less than 50 nM) when tested in the antiproliferation assay in T47D breast cancer cell line with PI3KCA-H1047R mutation according to Biological assays Example A herein. In some preferred embodiments, compounds of the present disclosure for the methods herein are selected from those compounds that have an IC_{50} values greater than 1 micromolar (preferably greater than 2 micromolar, or greater than 5 micromolar) when tested in the antiproliferation assay in SK-BR-3 breast cancer cell line with no PI3KCA mutation according to Biological assays Example A herein.

[0808] Compounds of the present disclosure can be used as a monotherapy or in a combination therapy. In some embodiments, the combination therapy includes treating the subject with a targeted therapeutic agent, chemotherapeutic agent, therapeutic antibody, radiation, cell therapy, and/or immunotherapy. In some embodiments, compounds of the present disclosure can also be co-administered with an additional pharmaceutically active compound, either concurrently or sequentially in any order, to a subject in need thereof. In some embodiments, the combination therapy includes treating the subject with one or more additional therapies such as chemotherapeutics or other anti-cancer agents.

[0809] Combination therapy also can include the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and/or non-drug therapies (e.g., surgery or radiation treatment.)

[0810] The administering herein is not limited to any particular route of administration. For example, in some embodiments, the administering can be orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally or parenterally. In some embodiments, the administering is orally.

[0811] Dosing regimen including doses can vary and can be adjusted, which can depend on the recipient of the treatment, the disease or disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

Definitions

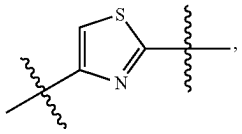
[0812] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof.

[0813] It is also meant to be understood that a specific embodiment of a variable moiety herein can be the same or different as another specific embodiment having the same identifier.

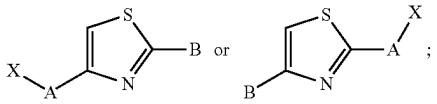
[0814] The present disclosure encompasses all combinations of the aspects and/or embodiments of the disclosure herein. It is understood that any and all embodiments of the present disclosure may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiments is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

[0815] Suitable atoms or groups for the variables herein are independently selected. The definitions of the variables can be combined. Using Formula I as an example, any of the definitions of one of W, Q, Z, L^1, L^2, R^1, R^2, R^4, R^5, R^6, R^7, R^8, and R^9 in Formula I can be combined with any of the definitions of the others of W, Q, Z, L^1, L^2, R^1, R^2, R^4, R^5, R^6, R^7, R^8, and R^9 in Formula I. Such combination is contemplated and within the scope of the present disclosure. Non-limiting useful groups for the variables in compounds of Formula A, B, C, D, E, or F, or a subformula thereof, as applicable, include any of the respective groups, individually or in any combination, as shown in Examples section or in the specific compounds described in Table A herein.

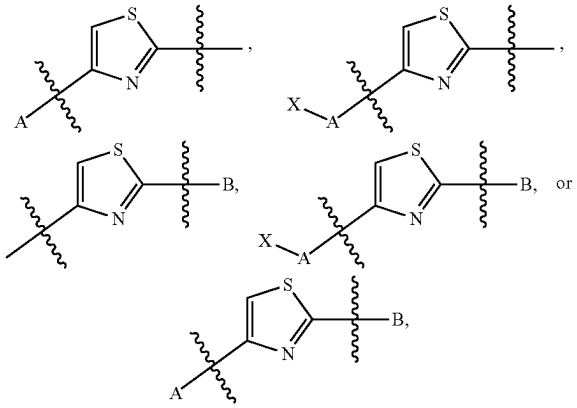
[0816] The symbol, ∿, when displayed perpendicular to (or otherwise crossing) a bond, indicates the point at which the displayed moiety is attached to the remainder of the molecule. It should be noted that for a divalent structure (or multivalent structure), the immediately connected group or groups or appropriate variable(s) shown in a formula may be shown in the divalent structure (or multivalent structure) beyond the symbol, ∿, to indicate direction of attachment. When the immediately connected group(s) or variable is not shown for either of the two attaching points of a divalent structure, it should mean that either direction of attachment to the remainder of the molecule is allowed, unless otherwise specified or obviously contrary from context. Using a structure of "X-A-G-B" to illustrate, for example, if G is defined as



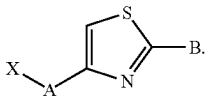
i.e., the immediately connected group(s) or variable(s) is not shown, then the structure of "X-A-G-B" can be either



on the other hand, if G is defined as



then the structure of "X-A-G-B" should be understood as



[0817] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics,* 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry,* 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis,* 3rd Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents described herein.

[0818] Compounds of the present disclosure can comprise one or more asymmetric centers and/or axial chirality, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer, atropisomer, or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those having ordinary skill in the art, including chiral high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen et al., Tetrahedron 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers including racemic mixtures. In embodiments herein, unless otherwise obviously contrary from context, when a stereochemistry is specifically drawn, it should be understood that with respect to that particular chiral center or axial chirality, the compound can exist predominantly as the as-drawn stereoisomer, such as with less than 20%, less than 10%, less than 5%, less than 10%, by weight, by HPLC or SFC area, or both, or with a non-detectable amount of the other stereoisomer(s). For example, in some embodiments, with respect to the particular chiral center or axial chirality as drawn, the compound can exist predominantly as the as-drawn stereoisomer, with an enantiomeric excess ("ee") of greater than 50%, such as 80% ee or higher, 90% ee or higher, 95% ee or higher, 98% ee or higher, 99% ee or higher. The presence and/or amounts of stereoisomers can be determined by those having ordinary skill in the art in view of the present disclosure, including through the use of chiral HPLC or SFC.

[0819] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6}" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6}.

[0820] As used herein, the term "compound(s) of the present disclosure" or "compound(s) of the present invention" refers to any of the compounds described herein according to Formula A (e.g., Formula I, I-1, I-1-a, I-1-b, I-1-c, I-1-d, I-1-e, I-1-x, I-1-y, I-1-a-1, I-1-a-1R, I-1-a-1 S, I-1-a-2, I-1-a-2-a, I-1-a-2-b, I-1-a-2-c, I-1-a-2-d, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, I-1-a-3-f, I-1-a-3, I-1-a-4, or I-1-a-5), Formula B (e.g., Formula II, II-1, II-2, II-3, II-1-a, II-2-a, II-3-a, II-1-b, II-2-b, or II-3-b), Formula C (e.g., Formula III, III-1, III-1-a, III-1-b, III-1-a-1, III-1-a-2, III-1-a-2-a, III-1-a-2-b, III-1-a-2-c, III-1-a-2-d, III-1-a-2-e, II-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, III-1-b-2-f, III-2, III-3, III-4, III-x, III-y, or III-5), Formula D (e.g., Formula IV), Formula E (e.g., Formula V, V-1, V-2, V-3, V-4, V-5, V-6, V-7, V-4-a, V-4-b, V-4-c, V-5-a, or VI), Formula F (e.g., Formula VII, VII-1, VII-2, VII-3, VII-4, VII-1-a, VII-1-b, VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b), any compound selected from the compounds shown in Table A herein, any of compounds shown in the Examples section, isotopically labeled compound(s) thereof (such as a deuterated analog wherein one or

more of the hydrogen atoms is substituted with a deuterium atom with an abundance above its natural abundance), possible stereoisomers thereof (including diastereoisomers, enantiomers, and racemic mixtures), geometric isomers thereof, atropisomers thereof, tautomers thereof, conformational isomers thereof, and/or pharmaceutically acceptable salts or ester thereof (e.g., acid addition salt such as HCl salt or base addition salt such as Na salt). Hydrates and solvates of the compounds of the present disclosure are considered compositions of the present disclosure, wherein the compound(s) is in association with water or solvent, respectively. For the avoidance of doubt, the compounds shown in Examples section refer to the compounds described herein labeled as integers 1, 2, 3, . . . , see for example the title compounds of Examples. For ease of description, synthetic starting materials or intermediates may be labeled with an integer (compound number) followed by a "-" and additional numeric values, such as 1-1, 1-2, etc., see examples for details. The labeling of such synthetic starting materials or intermediates should not be confused with the compounds labeled with an integer only without the "-" and additional numeric value. In some embodiments, the compound of the present disclosure can be any of those defined in embodiments and claims herein. In some embodiments, the compound of the present disclosure can be any of those defined in enumerated Embodiments 1-38 herein. In some embodiments, the compound of the present disclosure can be any of those defined in enumerated Embodiments B1-87 herein. In some embodiments, the compound of the present disclosure can be any of those defined in the as-filed claims **1-81** herein.

[0821] Compounds of the present disclosure can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to 2H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O ^{32}P ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

[0822] As used herein, the phrase "administration" of a compound, "administering" a compound, or other variants thereof means providing the compound or a prodrug of the compound to the individual in need of treatment.

[0823] The term "aromatic" means a planar ring having 4n+2 electrons in a conjugated system. As used herein, "conjugated system" means a system of connected p-orbitals with delocalized electrons, and the system may include lone electron pairs.

[0824] As used herein, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic saturated hydrocarbon. In some embodiments, the alkyl which can include one to twelve carbon atoms (i.e., C_{1-12} alkyl) or the number of carbon atoms designated (i.e., a C_1 alkyl such as methyl, a C_2 alkyl such as ethyl, a C_3 alkyl such as propyl or isopropyl, etc.). In one embodiment, the alkyl group is a straight chain C_{1-10} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-10} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-6} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-6} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-4} alkyl group. In one embodiment, the alkyl group is a C_{1-4} alkyl group selected from methyl, ethyl, propyl (n-propyl), isopropyl, butyl (n-butyl), sec-butyl, tert-butyl, and iso-butyl. As used herein, the term "alkylene" as used by itself or as part of another group refers to a divalent radical derived from an alkyl group. For example, non-limiting straight chain alkylene groups include —CH_2—CH_2—CH_2—CH_2—, —CH_2—CH_2—CH_2—, —CH_2—CH_2—, and the like.

[0825] As used herein, the term "alkenyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more, such as one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is a C_{2-6} alkenyl group. In another embodiment, the alkenyl group is a C_{2-4} alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl, pentenyl, and hexenyl.

[0826] As used herein, the term "alkynyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more, such as one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-carbon triple bond. In one embodiment, the alkynyl group is a C_{2-6} alkynyl group. In another embodiment, the alkynyl group is a C_{2-4} alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0827] As used herein, the term "alkoxy" as used by itself or as part of another group refers to a radical of the formula OR^{a1}, wherein Rai is an alkyl. As used herein, the term "cycloalkoxy" as used by itself or as part of another group refers to a radical of the formula OR^{a1}, wherein R^{a1} is a cycloalkyl.

[0828] As used herein, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more fluorine, chlorine, bromine and/or iodine atoms. In preferred embodiments, the haloalkyl is an alkyl group substituted with one or more fluorine atoms, alternatively referred to herein as fluorine-substituted alkyl, such as with one, two, or three fluorine atoms. In one embodiment, the haloalkyl group is a C_{1-4} haloalkyl group. In one embodiment, the haloalkyl group is a fluorine-substituted C_{1-4} alkyl group.

[0829] As used herein, the term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched-chain alkyl group, e.g., having from 2 to 14 carbons, such as 2 to 10 carbons in the chain, one or more of the carbons has been replaced by a heteroatom selected from S, O, P and N, and wherein the nitrogen, phosphine, and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) S, O, P and N may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. When the heteroalkyl is said to be substituted, the substituent(s) can replace one or more hydrogen atoms attached to the carbon atom(s) and/or the heteroatom (s) of the heteroalkyl. In some embodiments, the heteroalkyl is a C_{1-4} heteroalkyl, which refers to the heteroalkyl defined herein having 1-4 carbon atoms. Examples of C_{1-4} heteroalkyl include, but are not limited to, C_4 heteroalkyl such as —CH_2—CH_2—N(CH_3)—CH_3, C_3 heteroalkyl such as —CH_2—CH_2—O—CH_3, —CH_2—CH_2—NH—CH_3, —CH_2—S—CH_2—CH_3, —CH_2—CH_2—S(O)—CH_3,

—CH_2—CH_2—$S(O)_2$—CH_3, C_2 heteroalkyl such as —CH_2—CH_2—OH, —CH_2—CH_2—NH_2, —CH_2—NH(CH_3), —O—CH_2—CH_3 and C_1 heteroalkyl such as, —CH_2—OH, —CH_2—NH_2, —O—CH_3. Preferably, the C_{1-4} heteroalkyl (or C_{1-4} heteroalkylene) herein contains 1 or 2 heteroatoms, such as one oxygen, one nitrogen, two oxygens, two nitrogens, or one oxygen and one nitrogen. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, —CH_2—CH_2—O—CH_2—CH_2— and —O—CH_2—CH_2—NH—CH_2—. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as —NR'R" or the like, it will be understood that the terms heteroalkyl and —NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as —NR'R" or the like.

[0830] "Carbocyclyl" or "carbocyclic" as used by itself or as part of another group refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. The carbocyclyl group can be either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. Non-limiting exemplary carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclopentenyl, and cyclohexenyl.

[0831] In some embodiments, "carbocyclyl" is fully saturated, which is also referred to as cycloalkyl. In some embodiments, the cycloalkyl can have from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In preferred embodiments, the cycloalkyl is a monocyclic ring.

[0832] "Heterocyclyl" or "heterocyclic" as used by itself or as part of another group refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3-10 membered heterocyclyl"). Heterocyclyl or heterocyclic ring that has a ring size different from the 3-10 membered heterocyclyl is specified with a different ring size designation when applicable. Those having ordinary skill in the art would understand that such different ring-sized heterocyclyl is also a non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged, or spiro ring system, such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings.

[0833] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiiranyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0834] "Aryl" as used by itself or as part of another group refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 pi electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{1-4} aryl"; e.g., anthracyl).

[0835] "Aralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more aryl groups, preferably, substituted with one aryl group. Examples of aralkyl include benzyl, phenethyl, etc. When an aralkyl is said to be optionally substituted, either the alkyl portion or the aryl portion of the aralkyl can be optionally substituted.

[0836] "Heteroaryl" as used by itself or as part of another group refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5-10 membered heteroaryl"). Heteroaryl that has a ring size different from the 5-10 membered heteroaryl is specified with a different ring size designation when applicable. Those having ordinary skill in the art would understand that such different ring-

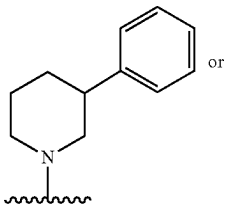
sized heteroaryl is also a 4n+2 aromatic ring system (e.g., having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, and the like) the point of attachment can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl).

[0837] Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzothiazolyl, benzisothiazolyl, benzothiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0838] "Heteroaralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more heteroaryl groups, preferably, substituted with one heteroaryl group. When a heteroaralkyl is said to be optionally substituted, either the alkyl portion or the heteroaryl portion of the heteroaralkyl can be optionally substituted.

[0839] As used herein, unless specified or otherwise contrary, a "ring structure", "cyclic structure", or simply "ring", with a designated number of ring members, such as a "3-10 membered ring structure", a "3-12 membered ring structure", or a "5- or 6-membered ring", should be understood as encompassing any ring structure (e.g., carbocyclic, heterocyclic, aryl, heteroaryl, etc.) having the designated number of ring members, which can be (1) monocyclic or polycyclic (as chemically feasible), such as a monocyclic ring or a bicyclic ring (including fused, spiro, and bridged bicyclic ring, and those ring systems where two monocyclic rings are connected through a single or double bond); (2) aromatic, partially unsaturated, or fully saturated; and in the case of a polycyclic structure, each ring can be independently aromatic, partially unsaturated, or fully saturated; and (3) contain no heteroatom or 1-4 heteroatoms; in the case of a polycyclic structure, each ring can independently have no ring heteroatom or 1-4 ring heteroatoms (e.g., O, N, S, etc.). When a ring is said to contain a ring sulfur or nitrogen atom, the sulfur or nitrogen atom can be optionally oxidized. One or more ring carbon atoms in a ring structure can be present as C(═O). A fully saturated ring refers to a ring in which none of the ring carbon and nitrogen (if present) atoms forms a double bond or triple bond with any other atom. The ring structure can be optionally substituted with one or more substituents described herein. The substituents of a ring structure herein can also have a cyclic structure, and in some cases, two substituents of a ring structure may be said to be joined to form a cyclic structure.

[0840] As commonly understood in the art, for clarity, when a structure can be characterized in multiple ways, as long as one such characterization falls within the scope of the definition of a variable herein, it can be said that the structure is a suitable definition for the variable. For example, when a monovalent variable is defined as an optionally substituted 6-membered ring, the variable encompasses, among other structures, (a) the structure of



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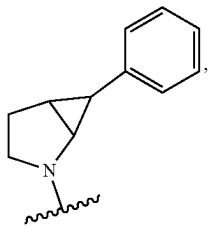

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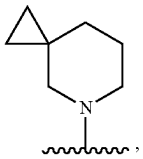
which can be viewed as a 6-membered monocyclic or bicyclic ring substituted with a phenyl group; and (b) the structure of



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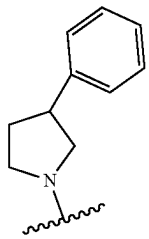
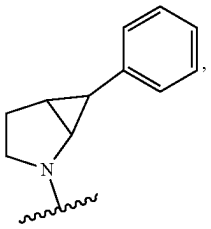
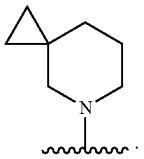
which can be viewed as a 6-membered ring, wherein two substituents are joined to form a cyclopropyl ring; but the variable would not encompass



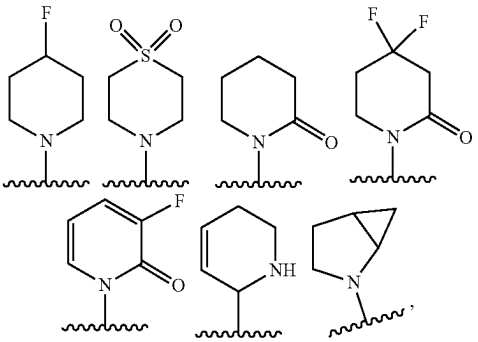
because the attaching ring is not a 6-membered ring under any characterization of the structure. To further explain, when the variable is instead defined as an optionally substituted monocyclic 6-membered ring, then the variable does not encompass



but encompasses the structure of



And if the variable is defined as a 6-membered ring optionally substituted with halogen, then the variable can encompass structures such as,



as each of which can be viewed as a 6-membered ring that is unsubstituted or substituted with 1 or two fluorine atoms.

[0841] As commonly understood in the art, alkylene, alkenylene, alkynylene, heteroalkylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene refer to the corresponding divalent radicals of alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, respectively.

[0842] An "optionally substituted" group, such as an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroalkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl group, or an optionally substituted ring structure, refers to the respective group that is unsubstituted or substituted. In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent can be the same or different at each position. Typically, when substituted, the optionally substituted groups herein can be substituted with 1-5 substituents. Substituents can be a carbon atom substituent, a nitrogen atom substituent, an oxygen atom substituent or a sulfur atom substituent, as applicable.

[0843] Unless expressly stated to the contrary, combinations of substituents and/or variables are allowable only if such combinations are chemically allowed and result in a stable compound. A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic administration to a subject).

[0844] In some embodiments, the "optionally substituted" alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclic, cycloalkyl, alkoxy, cycloalkoxy, or heterocyclic group herein can be unsubstituted or substituted with 1, 2, 3, or 4 substituents or even 5 substituents independently selected from F, Cl, —OH, protected hydroxyl, oxo (as applicable), NH_2, protected amino, $NH(C_{1-4}$ alkyl) or a protected derivative thereof, $N(C_{1-4}$ alkyl($(C_{1-4}$ alkyl), C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2, or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, or independently selected from Br, —NH_2, and —CN, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents or even 4 or 5 substituents independently selected from F, —OH, oxo (as applicable), C-4 alkyl, fluoro-substituted C_{1-4} alkyl (e.g., CF_3), C_{1-4} alkoxy and fluoro-substituted C_{1-4} alkoxy, or independently selected from Cl, Br, —NH_2, and —CN. In some embodiments, the "optionally substituted" aryl or heteroaryl group herein can be unsubstituted or substituted with 1, 2, 3, or 4 substituents or even 5 substituents independently selected from F, Cl, —OH, —CN, NH_2, protected amino, $NH(C_{1-4}$ alkyl) or a protected derivative thereof, $N(C_{1-4}$ alkyl($(C_{1-4}$ alkyl), —S(═O)(C_{1-4} alkyl), —SO_2(C_{1-4} alkyl), C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6}

cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2 or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents or even 4 or 5 substituents independently selected from F, —OH, oxo (as applicable), C-4 alkyl, fluoro-substituted C_{1-4} alkyl, C_{1-4} alkoxy and fluoro-substituted C_{1-4} alkoxy, or independently selected from Cl, Br, —NH_2, and —CN.

[0845] Exemplary carbon atom substituents include, but are not limited to, halogen, —CN, —NO_2, —N_3, —SO_2H, —SO_3H, —OH, —OR^{aa}, —$ON(R^{bb})_2$, —$N(R^{bb})_2$, —$N(R^{bb})_3{}^+X^-$, —$N(OR^{cc})R^{bb}$, —SH, —SR^{aa}, —SSR^{cc}, —$C(=O)R^{aa}$, —CO_2H, —CHO, —$C(OR^{cc})_2$, —CO_2R^{aa}, —$OC(=O)R^{aa}$, —OCO_2R^{aa}, —$C(=O)N(R^{bb})_2$, —$OC(=O)N(R^{bb})_2$, —$NR^{bb}C(=O)R^{aa}$, —$NR^{bb}CO_2R^{aa}$, —$NR^{bb}C(=O)N(R^{bb})_2$, —$C(=NR^{bb})R^{aa}$, —$C(=NR^{bb})OR^{aa}$, —$OC(=NR^{bb})R^{aa}$, —$OC(=NR^{bb})OR^{aa}$, —$C(=NR^{bb})N(R^{bb})_2$, —$OC(=NR^{bb})N(R^{bb})_2$, —$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, —$C(=O)NR^{bb}SO_2R^{aa}$, —$NR^{bb}SO_2R^{aa}$, $SO_2N(R^{bb})_2$, —SO_2R^{aa}, —SO_2OR^{aa}, —OSO_2R^{aa}, —$S(=O)R^{aa}$, —$OS(=O)R^{aa}$, —$Si(R^{aa})_3$, —$OSi(R^{aa})_3$, —$C(=S)N(R^{bb})_2$, —$C(=O)SR^{aa}$, —$C(=S)SR^{aa}$, —$SC(=S)SR^{aa}$, —$SC(=O)SR^{aa}$, —$OC(=O)SR^{aa}$, —$SC(=O)OR^{aa}$, —$SC(=O)R^{aa}$, —$P(=O)(R^{aa})_2$, —$P(=O)(OR^{cc})_2$, —$OP(=O)(R^{aa})_2$, —$OP(=O)(OR^{cc})_2$, —$P(=O)(N(R^{bb})_2)_2$, —$OP(=O)(N(R^{bb})_2)_2$, —$NR^{bb}P(=O)(R^{aa})_2$, —$NR^{bb}P(=O)(OR^{cc})_2$, $NR^{bb}P(=O)(N(R^{bb})_2)_2$, —$P(R^{cc})_2$, —$P(OR^{cc})_2$, —$P(R^{cc})_3{}^+X^-$, —$P(OR^{cc})_3{}^+X^-$, —$P(R^{cc})_4$, —$P(OR^{cc})_4$, —$OP(R^{cc})_2$, —$OP(R^{cc})_3X^-$, —$OP(OR^{cc})_2$, —$OP(OR^{cc})_3{}^+X^-$, —$OP(R^{cc})_4$, —$OP(OR^{cc})_4$, —$B(R^{aa})_2$, —$B(OR^{cc})_2$, —$BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =$NN(R^{bb})_2$, =$NNR^{bb}C(=O)R^{aa}$, =$NNR^{bb}C(=O)OR^{aa}$, =$NNR^{bb}S(=O)_2R^{aa}$, =NR^{bb}, or =NOR^{cc};

[0846] each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

[0847] each instance of R^{bb} is, independently, selected from hydrogen, —OH, —OR^{aa}, —$N(R^{cc})_2$, —CN, —$C(=O)R^{aa}$, —$C(=O)N(R^{cc})_2$, —CO_2R^{aa}, —SO_2R^{aa}, —$C(=NR^{cc})OR^{aa}$, —$C(=NR^{cc})N(R^{cc})_2$, —$SO_2N(R^{cc})_2$, —SO_2R^{cc}, —SO_2OR^{cc}, —SOR^{cc}, —$C(=S)N(R^{cc})_2$, —$C(=O)SR^{cc}$, —$C(=S)SR^{cc}$, —$P(=O)(R^{cc})_2$, —$P(=O)(OR^{cc})_2$, —$P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^+ is a counterion;

[0848] each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two RC groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

[0849] each instance of R^{dd} is, independently, selected from halogen, —CN, —NO_2, —N_3, —SO_2H, —SO_3H, —OH, —OR^{ee}, —$ON(R^{ff})_2$, —$N(R^{ff})_2$, —$N(R^{cc})_3{}^+X^-$, —$N(OR^{ee})R^{ff}$, —SH, —SR^{ee}, —SSR^{ee}, —$C(=O)R^{ee}$, —CO_2H, —CO_2R^{ee}, —$OC(=O)R^{ee}$, —OCO_2R^{ee}, —$C(=O)N(R^{ff})_2$, —$OC(=O)N(R^{ff})_2$, —$NR^{ff}C(=O)R^{ee}$, $NR^{ff}CO_2R^{ee}$, $NR^{ff}C(=O)N(R^{ff})_2$, —$C(=NR^{ff})OR^{ee}$, —$OC(=NR^{ff})R^{ee}$, —$OC(=NR^{ff})OR^{ee}$, —$C(=NR^{ff})N(R^{ff})_2$, —$OC(=NR^{ff})N(R^{ff})_2$, —$NR^{ff}C(=NR^{ff})N(R^{ff})_2$, —$NR^{ff}SO_2R^{ee}$, —$SO_2N(R^{ff})_2$, —$SO_2R^{cc}$, —$SO_2OR^{ee}$, —$OSO_2R^{ee}$, —$S(=O)R^{ee}$, —$Si(R^{ee})_3$, —$OSi(R^{ee})_3$, —$C(=S)N(R^{cc})_2$, —$C(=O)SR^{ee}$, —$C(=S)SR^{ee}$, —$SC(=S)SR^{ee}$, —$P(=O)(OR^{ee})_2$, —$P(=O)(R^{ee})_2$, —$OP(=O)(R^{ee})_2$, —$OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion;

[0850] each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

[0851] each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C-6 haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

[0852] each instance of R^{gg} is, independently, halogen, —CN, —NO_2, —N_3, —SO_2H, —SO_3H, —OH, —OC_{1-6} alkyl, —$ON(C_{1-6}$ alkyl$)_2$, —$N(C_{1-6}$ alkyl$)_2$, —$N(C_{1-6}$ alkyl$)_3{}^+X^-$, —$NH(C_{1-6}$ alkyl$)_2{}^+X^-$, —$NH_2(C_{1-6}$ alkyl$)^+X^-$, —$NH_3{}^+X^-$, —$N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), —$N(OH)(C_{1-6}$ alkyl), —NH(OH), —SH, —SC_{1-6} alkyl, —$SS(C_{1-6}$ alkyl), —$C(=O)(C_{1-6}$ alkyl), —CO_2H, —$CO_2(C_{1-6}$ alkyl), —$OC(=O)(C_{1-6}$ alkyl), —$OCO_2(C_{1-6}$ alkyl), —$C(=O)NH_2$, —$C(=O)N(C_{1-6}$ alkyl$)_2$, —$OC(=O)NH(C_{1-6}$ alkyl), —$NHC(=O)(C_{1-6}$ alkyl), —$N(C_{1-6}$ alkyl$)C(=O)(C_{1-6}$ alkyl), —$NHCO_2(C_{1-6}$ alkyl), —$NHC(=O)N(C_{1-6}$ alkyl$)_2$, —$NHC(=O)NH(C_{1-6}$ alkyl), —$NHC(=O)NH_2$, —$C(=NH)O(C_{1-6}$ alkyl), —$OC(=NH)(C_{1-6}$ alkyl), —$OC(=NH)$

OC_{1-6} alkyl, —C(═NH)N(C_{1-6} alkyl)$_2$, —C(═NH)NH(C_{1-6} alkyl), —C(═NH)NH_2, —OC(═NH)N(C_{1-6} alkyl)$_2$, —OC(NH)NH(C_{1-6} alkyl), —OC(NH)NH_2, —NHC(NH)N(C_{1-6} alkyl)$_2$, —NHC(═NH)NH_2, —NHSO_2(C_{1-6} alkyl), —SO_2N(C_{1-6} alkyl)$_2$, —SO_2NH(C_{1-6} alkyl), —SO_2NH_2, —SO_2C_{1-6} alkyl, —SO_2OC_{1-6} alkyl, —OSO_2C_{1-6} alkyl, —SOC_{1-6} alkyl, —Si(C_{1-6} alkyl)$_3$, —OSi(C_{1-6} alkyl)$_3$, —C(═S)N(C_{1-6} alkyl)$_2$, C(═S)NH(C_{1-6} alkyl), C(═S)NH_2, —C(═O)S(C_{1-6} alkyl), —C(═S)SC_{1-6} alkyl, —SC(═S)SC_{1-6} alkyl, —P(═O)(OC_{1-6} alkyl)$_2$, —P(═O)(C_{1-6} alkyl)$_2$, —OP(═O)(C_{1-6} alkyl)$_2$, —OP(═O)(OC_{1-6} alkyl)$_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{98} substituents can be joined to form ═O or ═S; wherein X is a counterion.

[0853] "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (i.e., including one formal negative charge). An anionic counterion may also be multivalent (i.e., including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (e.g., F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (e.g., methansulfonate, trifluoromethanesulfonate, p-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), carboxylate ions (e.g., acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and a carborane anion (e.g., $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (e.g., tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, Salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[0854] "Halo" or "halogen" refers to fluorine (fluoro, —F), chlorine (chloro, —Cl), bromine (bromo, —Br), or iodine (iodo, —I).

[0855] "Acyl" refers to a moiety selected from the group consisting of —C(═O)R^{aa}, —CHO, —CO_2R^{aa}, —C(═O)N(R^{bb})$_2$, —C(═NR^{bb})R^{aa}, —C(═NR^{bb})OR^{aa}, —C(═NR^{bb})N(R^{bb})$_2$, —C(═O)$NR^{bb}SO_2R^{aa}$, —C(═S)N(R^{bb})$_2$, —C(═O)SR^{aa}, or —C(═S)SR^{aa}, wherein R^{aa} and R^{bb} are as defined herein.

[0856] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, —OH, —OR^{aa}, —N(R^{cc})$_2$, —CN, —C(═O)R^{aa}, —C(═O)N(R^{cc})$_2$, —CO_2R^{aa}, —SO_2R^{aa}, —C(═NR^{bb})R^{aa}, —C(═NR^{cc})OR^{aa}, —C(═NR^{cc})N(R^{cc})$_2$, —SO_2N(R^{cc})$_2$, —SO_2R^{cc}, —SO_2OR^{cc}, —SOR^{aa}, —C(═S)N(R^{cc})$_2$, —C(═O)SR^{cc}, —C(═S)SR^{cc}, —P(═O)(OR^{cc})$_2$, —P(═O)(R^{aa})$_2$, —P(═O)(N(R^{cc})$_2$)$_2$, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as defined above.

[0857] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated by reference herein. Exemplary nitrogen protecting groups include, but not limited to, those forming carbamates, such as Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonyl (Moz or MeOZ) group, tert-Butyloxycarbonyl (BOC) group, Troc, 9-Fluorenylmethyloxycarbonyl (Fmoc) group, etc., those forming an amide, such as acetyl, benzoyl, etc., those forming a benzylic amine, such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, etc., those forming a sulfonamide, such as tosyl, Nosyl, etc., and others such as p-methoxyphenyl.

[0858] Exemplary oxygen atom substituents include, but are not limited to, —R^{aa}, —C(═O)SR^{aa}, —C(═O)R^{aa}, —CO_2R^{aa}, —C(═O)N(R^{bb})$_2$, —C(═NR^{bb})R^{aa}, —C(═NR^{bb})OR^{aa}, —C(═NR^{bb})N(R^{bb})$_2$, —S(═O)R^{aa}, —SO_2R^{aa}, —Si(R^{aa})$_3$, —P(R^{cc})$_2$, —P(R^{cc})$_3^+X^-$, —P(OR^{cc})$_2$, —P(OR^{cc})$_3X^-$, —P(═O)(R^{aa})$_2$, —P(═O)(OR^{cc})$_2$, and —P(═O)(N(R^{bb})$_2$)$_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, alkyl ethers or substituted alkyl ethers such as methyl, allyl, benzyl, substituted benzyls such as 4-methoxybenzyl, methoxymethyl (MOM), benzyloxymethyl (BOM), 2-methoxyethoxymethyl (MEM), etc., silyl ethers such as trymethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), t-butyldimethylsilyl (TBDMS), etc., acetals or ketals, such as tetrahydropyranyl (THP), esters such as formate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, etc., carbonates, sulfonates such as methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts), etc.

[0859] The term "leaving group" is given its ordinary meaning in the art of synthetic organic chemistry, for example, it can refer to an atom or a group capable of being displaced by a nucleophile. See, for example, Smith, *March Advanced Organic Chemistry* 6th ed. (501-502). Examples of suitable leaving groups include, but are not limited to, halogen (such as F, Cl, Br, or I (iodine)), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (e.g., acetoxy), arylcarbonyloxy, aryloxy, methoxy, N,O-dimethylhydroxylamino, pixyl, and haloformates.

[0860] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

[0861] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (i.e., the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0862] The term "subject" (alternatively referred to herein as "patient") as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

[0863] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound described herein to a subject in need of such treatment.

[0864] As used herein, the singular form "a", "an", and "the", includes plural references unless it is expressly stated or is unambiguously clear from the context that such is not intended.

[0865] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0866] Headings and subheadings are used for convenience and/or formal compliance only, do not limit the subject technology, and are not referred to in connection with the interpretation of the description of the subject technology. Features described under one heading or one subheading of the subject disclosure may be combined, in various embodiments, with features described under other headings or subheadings. Further it is not necessarily the case that all features under a single heading or a single subheading are used together in embodiments.

EXAMPLES

[0867] The various starting materials, intermediates, and compounds of the preferred embodiments can be isolated and purified where appropriate using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds can be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses. The examples are illustrative only and do not limit the claimed invention in any way.

[0868] Exemplary embodiments of steps for performing the synthesis of products described herein are described in greater detail infra. Some of the Examples discussed herein can be prepared by separating the corresponding racemic mixtures. As would be understood by a person of ordinary skill in the art, the compounds described in Examples section immediately prior to the chiral separation step, e.g., by supercritical fluid chromatography (SFC), exist in racemic and/or stereoisomeric mixture forms. It should be understood that the enantiomeric excesses ("ee") and/or diastereomeric excesses ("de") reported for these examples are only representative from the exemplified procedures herein and not limiting; those of ordinary skill in the art would understand that such enantiomers and/or diastereomers with a different ee and/or de, such as a higher ee and/or de, can be obtained in view of the present disclosure. Typically, a "de" value is reported herein when a pair of diastereomers, having only one of the chiral centers being different, are separated from a corresponding diastereomeric mixture. In such cases, the "de" value indicates the degree of enrichment of one of the diastereomers.

[0869] The abbreviations used in Examples section should be understood as having their ordinary meanings in the art unless specifically indicated otherwise or obviously contrary from context. The following shows certain abbreviations used in Examples section herein.

Abbreviations	Chemical Name
$(Boc)_2O$	di-tert-butyl dicarbonate
AcOH/HOAc	Acetic acid
AcONa/NaOAc	Sodium acetate
CDI	Di(1H-imidazol-1-yl)methanone
DAST	Diethylaminosulphur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEA	Diethylamine
DIPEA	N,N-Diisopropylethylamine
DMAc	N,N-dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
DMPU	N,N'-Dimethylpropyleneurea
dppf	1,1-Bis(diphenylphosphino)ferrocene
EDCI	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
EtOAc/EA	Ethyl acetate
EtOH/ETOH	ethanol
FA	Formic acid

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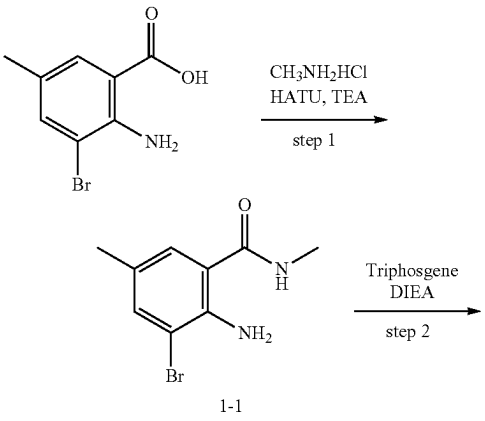
Abbreviations	Chemical Name
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
IPA	propan-2-ol
KHMDS	Potassium bis(trimethylsilyl)amide
KOAc	Potassium acetate
LDA	Lithium diisopropylamide
mCPBA	3-Chloroperbenzoic acid
Me4t-BuXPhos	2-Di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-i-propyl)-1,1'-biphenyl
MeCN/ACN	acetonitrile
MeOH/MEOH	methanol
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
NBS	N-Bromosuccinimide
n-BuLi	n-butyllithium
NCS	N-Chlorosuccinimide
NMP	N-methylpyrrolidin-2-one
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(OAc)_2$	Palladium (II) acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PPA	polyphosphoric acid
PPh_3	triphenylphosphine
SEM	2-(Trimethylsilyl)ethoxymethyl
SEMCl	2-(Trimethylsilyl)ethoxymethyl Chloride
SFC	Supercritical Fluid Chromatography
TBAF	Tetra-n-butylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPSCl	tert-Butylchlorodiphenylsilane
TBSOTf	tert-Butyldimethylsilyl trifluoromethanesulfonate
t-BuBrettPhos	2-(Di-t-butylphosphino)-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl
t-BuONO	tert-Butyl nitrite
TEA	Triethylamine
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPSCl	Triisopropylsilyl Chloride
TMSCN	Trimethylsilyl cyanide
TMSI	Trimethyliodosilane
Xantphos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

[0870] Compounds of the present disclosure can be synthesized by those having ordinary skill in the art in view of the present disclosure. Representative further compounds synthesized by following similar procedures/methods described herein in Examples section.

Example 1 Synthesis of Compounds 1 and 2



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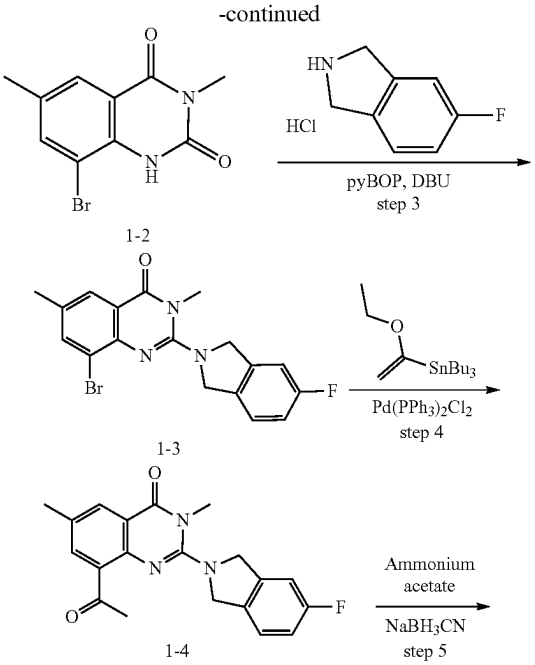

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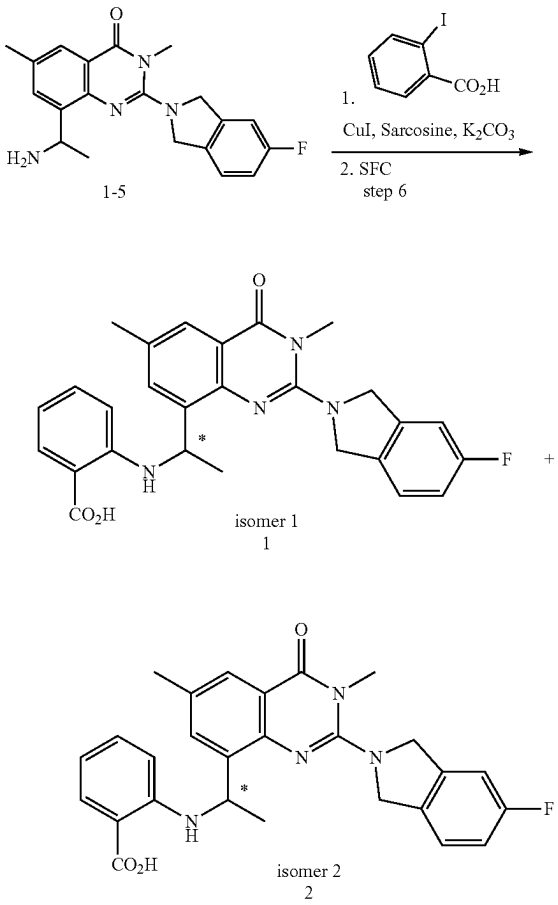


[0871] Step 1: To a solution of 2-amino-3-bromobenzoic acid (5.0 g, 23.15 mmol), methylamine hydrochloride (2.34 g, 34.72 mmol) and triethylamine (12.9 mL, 92.58 mmol) in N, N-dimethylformamide (100 mL) was added N, N, N', N'-tetramethyluronium hexafluorophosphate (10.6 g, 27.77 mmol) at room temperature, then the reaction mixture stirred at 50° C. for 4 hours. The reaction mixture was diluted with water, filtered and the filtrate cake was washed with water and dried to afford 1-1 (3.1 g).

[0872] Step 2: To a mixture of 1-1 (3.1 g, 12.75 mmol) and N, N-disopropylethylamine (3.2 mL, 19.13 mmol) in dichloromethane (100 mL) was added triphosgene (1.5 g, 5.10 mmol) at 0° C. The mixture was stirred at 40° C. for 2 hours before it was concentrated, diluted with water, filtered and the filtrate cake was washed with water and dried to afford 1-2 (3.3 g).

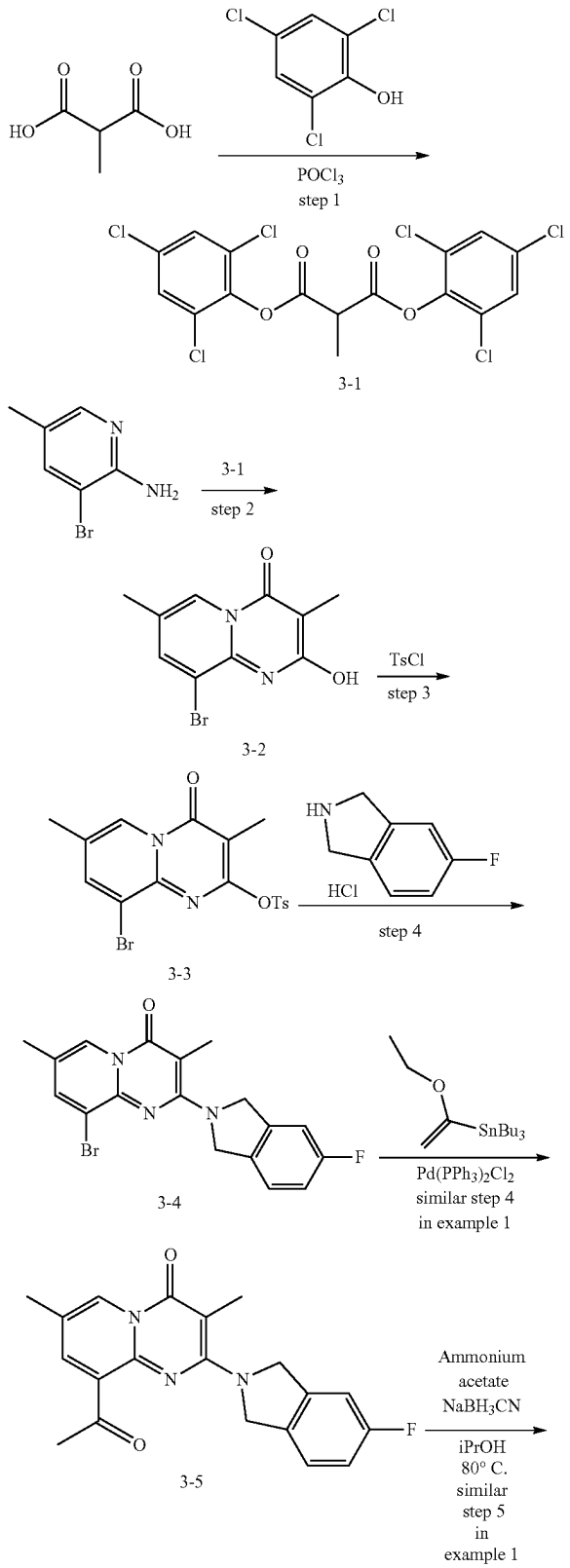
[0873] Step 3: To a solution of 1-2 (1.20 g, 4.46 mmol), 5-fluoro-2,3-dihydro-1H-isoindole hydrochloride (0.85 g, 4.91 mmol) and benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (3.0 g, 5.80 mmol) in N, N-dimethylformamide (20 mL) was added 1,8-diazabicyclo [5.4.0]undec-7-ene (2.0 g, 13.38 mmol) at 0° C., then the mixture was stirred at room temperature for 2 hours before it was diluted with water, filtered and the filtrate cake was washed with water. The collected solid was triturated with acetonitrile/water and filtered, filtered and dried to afford 1-3 (1.65 g).

[0874] Step 4: A mixture of 1-3 (1400 mg, 3.61 mmol), bis(triphenylphosphine) palladium (II) chloride (253 mg, 0.36 mmol) and tributyl(1-ethoxyvinyl) tin (1562 mg, 4.33 mmol) in dioxane (30 mL) was stirred at 100° C. for 16 hours under N_2 atmosphere. Then hydrochloric acid (1 M, 5 mL) was added to the reaction and the resulting mixture was stirred at 50° C. for 1 hour. The mixture was cooled down to room temperature and potassium fluoride solution was added and stirred at 25° C. for 0.5 hour. Then the resulting mixture was filtered and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/ethyl acetate=10/1) to give 1-4 (850 mg).

[0875] Step 5: A mixture of 1-4 (450 mg, 1.28 mmol), ammonium acetate (987 mg, 12.81 mmol) and sodium cyanoborohydride (161 mg, 2.56 mmol) in isopropyl alcohol (20 mL) was stirred at 85° C. for 2 hours under nitrogen atmosphere before it was diluted with ethyl acetate, washed with saturated sodium bicarbonate aqueous, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=10:1) to give 1-5 (350 mg). LCMS (ESI, m/z): $[M+H]^+$=353.2.

[0876] Step 6: A mixture of 1-5 (325 mg, 0.92 mmol), 2-iodobenzoic acid (686 mg, 2.77 mmol), cuprous iodide (35 mg, 0.18 mmol), potassium carbonate (510 mg, 3.69 mmol) and sarcosine (33 mg, 0.37 mmol) in DMSO (8 mL) was stirred at 70° C. for 3 hours under N_2 atmosphere before it was diluted with ethyl acetate and ammonium chloride solution, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with dichloromethane to dichloromethane/methanol=20:1), then separated by SFC (DAICELCHIRALCEL® OZ with Supercritical CO_2/MEOH (+0.1% 7.0 mol/l Ammonia in MeOH)) to give 1 (isomer 1, 75 mg) and 2 (isomer 2, 65 mg). 1 (isomer 1): LCMS (ESI, m/z): $[M+H]^+$=473.4; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.64 (brs, 1H), 8.55-8.29 (m, 1H), 7.82-7.74 (m, 1H), 7.74-7.64 (m, 1H), 7.47-7.36 (m, 2H), 7.32-7.21 (m, 1H), 7.20-7.10 (m, 2H), 6.54-6.40 (m, 2H), 5.54-5.32 (m, 1H), 5.18-4.91 (m, 4H), 3.60 (s, 3H), 2.30 (s, 3H), 1.57 (d, 3H, J=6.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ−115.76 (1F). Chiral SFC analysis: >99% ee. Retention time 2.148 min on Waters UPCC (CA-060) (DAICEL CHIRALPAK® OZ) 100*3.0 mm 3 μm (35° C.); mobile phase: MeOH (0.1% DEA) in Supercritical CO_2, 1800 psi, 1.5 mL/min. 2 (isomer 2): LCMS (ESI, m/z): $[M+H]^+$=473.4; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.65 (brs, 1H), 8.60-8.30 (m, 1H), 7.83-7.73 (m, 1H), 7.73-7.65 (m, 1H), 7.46-7.36 (m, 2H), 7.30-7.21 (m, 1H), 7.20-7.10 (m, 2H), 6.54-6.40 (m, 2H), 5.54-5.32 (m, 1H), 5.18-4.91 (m, 4H), 3.60 (s, 3H), 2.30 (s, 3H), 1.57 (d, 3H, J=6.4 Hz). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −115.76 (1F). Chiral SFC analysis: 98.9% ee. Retention time 2.793 min on Waters UPCC (CA-060) (DAICEL CHIRALPAK® OZ) 100*3.0 mm 3 μm (35° C.); mobile phase: MeOH (0.1% DEA) in Supercritical CO_2, 1800 psi, 1.5 mL/min.

Example 2 Synthesis of Compounds 3 and 4



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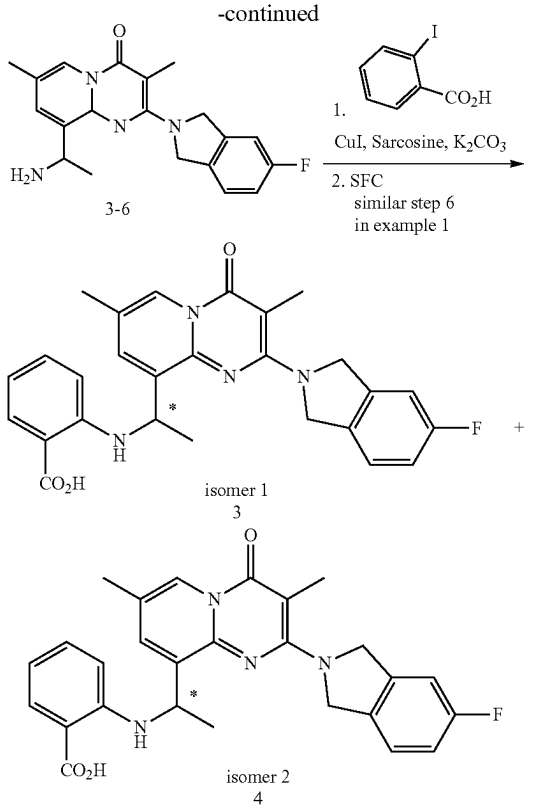


[0877] Step 1: To a mixture of 2-methylpropanedioic acid (10 g, 84.681 mmol) and 2,4,6-trichlorophenol (35.11 g, 177.830 mmol) was added phosphorus oxychloride (50 mL, 538.055 mmol). This mixture was heated at 90° C. until hydrochloric acid evolution stopped. The excess of phosphorus oxychloride was distilled under reduced pressure. The residue was poured into an ice-water and the resulting mixture was neutralized with saturated sodium carbonate to pH 7-8, extracted with chloroform, dried over anhydrous sodium sulphate, filtered, and concentrated. The residue was purified by silica gel chromatography (eluted with 0%~30% ethyl acetate in petroleum ether) to afford 3-1 (39 g).

[0878] Step 2: A mixture of 3-1 (17.85 g, 37.42 mmol) and 3-bromo-5-methylpyridin-2-amine (5 g, 26.73 mmol) in toluene (100 mL) was stirred at 110° C. for 3 hours under N_2 atmosphere. The reaction mixture was cooled to room temperature and diluted with ethyl acetate, filtered and washed with petroleum ether/ethyl acetate (5:1). The collected solid was dried to afford 3-2 (6.5 g).

[0879] Step 3: To a mixture of 3-2 (2 g, 7.43 mmol) and triethylamine (3.1 mL, 22.30 mmol) in dichloromethane (30 mL) was added 4-methylbenzenesulfonyl chloride (1.63 g, 8.55 mmol) at 0° C. The mixture was stirred at room temperature for 2 hours before it was concentrated and diluted with petroleum ether/ethyl acetate (5:1), filtered and washed with petroleum ether/ethyl acetate (5:1). The collected solid was dried to afford 3-3 (2.8 g).

[0880] Step 4: A mixture of 3-3 (2.1 g, 4.96 mmol), 5-fluoro-2,3-dihydro-1H-isoindole hydrochloride (0.95 g, 5.46 mmol) and N, N-diisopropylethylamine (3.28 mL, 19.84 mmol) in dioxane (50 mL) was stirred at 100° C. for 16 hours under nitrogen atmosphere. The reaction mixture

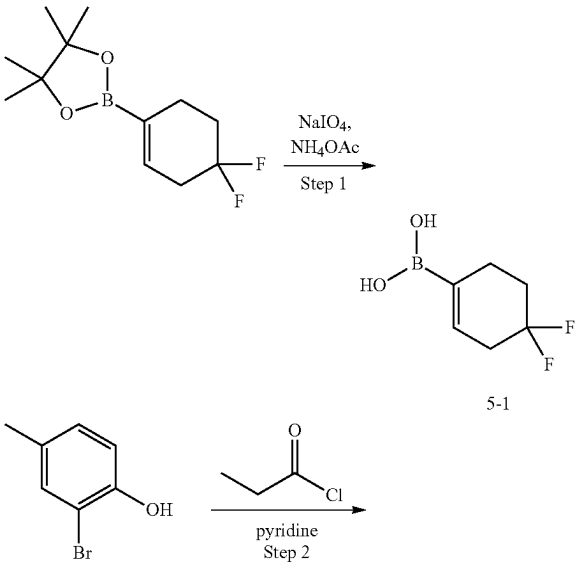
was diluted with dichloromethane and saturated sodium bicarbonate aqueous, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was triturated with petroleum ether/ethyl acetate (2:1), filtered and the filtrate cake was washed with petroleum ether/ethyl acetate (5:1) and dried to afford 3-4 (1.35 g).

[0881] Compound 3-5 was prepared from 3-4 and tributyl (1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[0882] Compound 3-6 was prepared from 3-5 and ammonium acetate and sodium cyanoborohydride following the procedure for the synthesis of compound 1-5 in example 1.

[0883] Compounds 3 (isomer 1) and 4 (isomer 2) were prepared from 3-6 following procedure for the synthesis of compounds 1 and 2 in example 1. 3 (isomer 1): LCMS (ESI, m/z): $[M+H]^+$=473.4; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.77 (brs, 1H), 8.58-8.54 (m, 1H), 8.52-8.35 (m, 1H), 7.86-7.77 (m, 1H), 7.59-7.52 (m, 1H), 7.45-7.39 (m, 1H), 7.29-7.19 (m, 2H), 7.18-7.08 (m, 1H), 6.58-6.50 (m, 1H), 6.45-6.35 (m, 1H), 5.39-5.30 (m, 1H), 5.23-5.09 (m, 4H), 2.41 (s, 3H), 2.26 (s, 3H), 1.63 (d, 3H, J=6.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −115.83 (1F). Chiral SFC analysis: >99% ee. Retention time 4.136 min on Waters UPCC (CA-352) (DAICEL CHIRALPAK® AD) 100*3.0 mm 3 μm (35° C.); mobile phase: MeOH (0.1% DEA) in Supercritical CO_2, 1800 psi, 1.5 mL/min. 4 (isomer 2): LCMS (ESI, m/z): $[M+H]^+$=473.3; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.75 (brs, 1H), 8.70-8.51 (m, 1H), 8.51-8.33 (m, 1H), 7.89-7.69 (m, 1H), 7.64-7.49 (m, 1H), 7.49-7.34 (m, 1H), 7.30-7.01 (m, 3H), 6.66-6.27 (m, 2H), 5.41-5.26 (m, 1H), 5.23-4.99 (m, 4H), 2.41 (s, 3H), 2.26 (s, 3H), 1.63 (d, 3H, J=4.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −115.83 (1F). Chiral SFC analysis: 97.6% ee. Retention time 4.788 min on Waters UPCC (CA-352) (DAICEL CHIRALPAK® AD) 100*3.0 mm 3 μm (35° C.); mobile phase: MeOH (0.1% DEA) in Supercritical CO_2, 1800 psi, 1.5 mL/min.

Example 3 Synthesis of Compound 5



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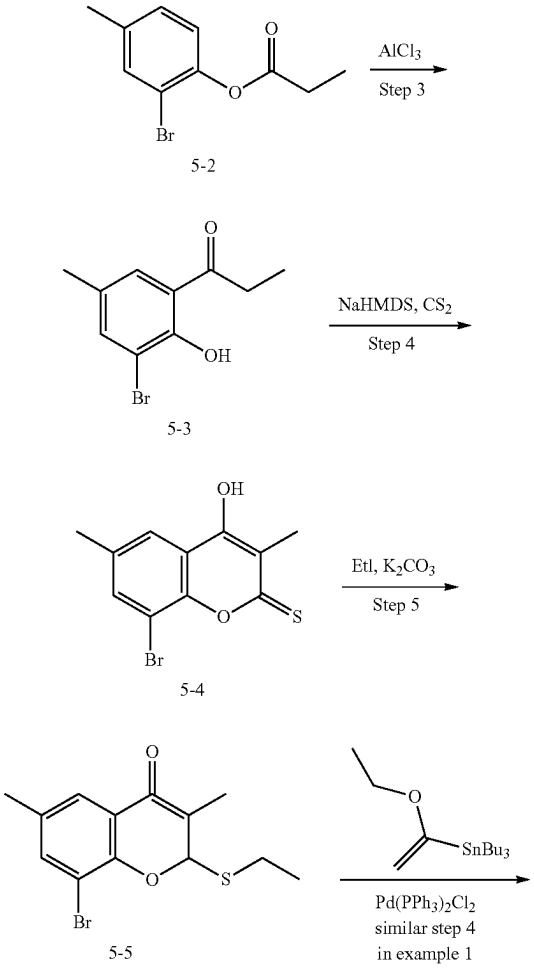

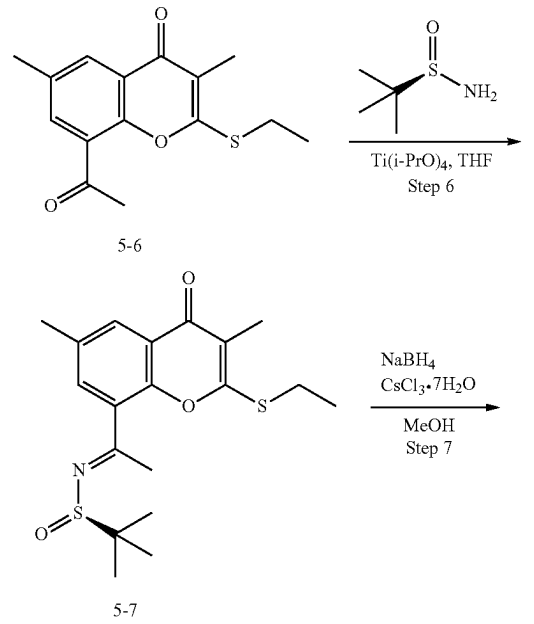

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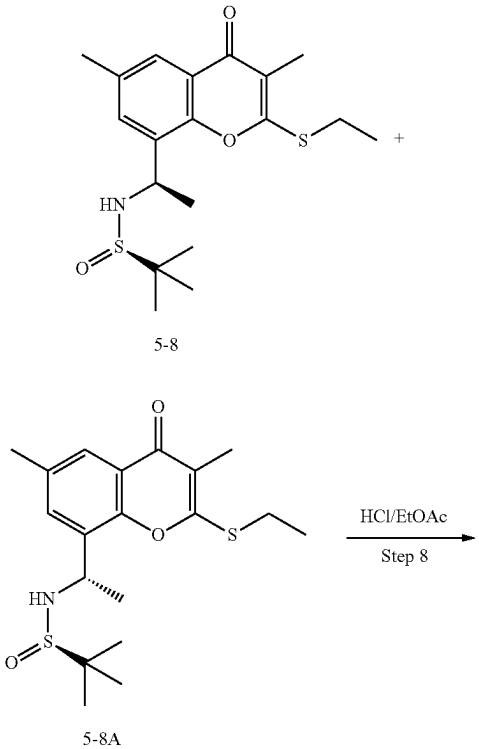

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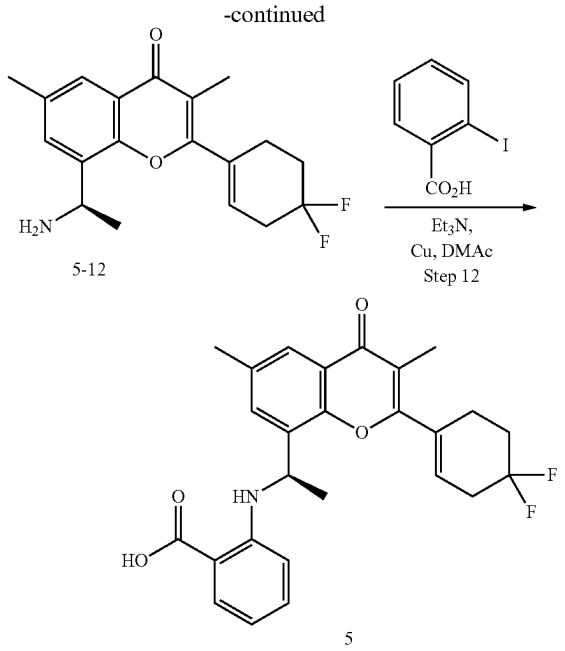


[0884] Step 1: To a mixture of 2-(4,4-difluorocyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mg, 0.819 mmol) in acetone (2 mL) and water (2 mL) was added ammonium acetate (189.5 mg, 2.458 mmol), followed by sodium metaperiodate (525.8 mg, 2.458 mmol). The reaction mixture was stirred at 20° C. for 18 hours. The reaction mixture was filtered, the filtrate was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford 5-1 (107 mg), which was used directly in next step without further purified.

[0885] Step 2: To a mixture of 2-bromo-4-methylphenol (40 g, 213.858 mmol) and pyridine (25.8 mL, 320.787 mmol) in dichloromethane (400 mL) was added propanoyl chloride (20.362 mL, 235.244 mmol) at 0° C., and then stirred at 20° C. for 16 hours. The mixture was diluted with water and adjusted pH to 5 with hydrochloric acid (2 M) and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford 5-2 (70 g, crude).

[0886] Step 3: A mixture of 5-2 (55 g, 226.244 mmol) and aluminium chloride (105.6 g, 791.855 mmol) was stirred at 140° C. for 1 hr. The mixture was cooled to room temperature and quenched with water dropwise and stirred for 30 minutes. Then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was triturated with petroleum ether for 1 h and the solid was collected by filtration and washed with petroleum ether and dried to afford 5-3 (36.86 g).

[0887] Step 4: To a stirred mixture of 5-3 (36.86 g, 151.625 mmol) in tetrahydrofuran (500 mL) was added sodium bis(trimethylsilyl)amide (265.343 mL, 530.687 mmol) at −50° C. dropwise under nitrogen atmosphere, the inner temperature was kept below −45° C. After addition, the temperature was warmed to −5~0° C. and stirred for 1 h.

Then the reaction mixture was cooled to −20° C. and carbon disulfide (14.6 mL, 242.600 mmol) was added dropwise, stirred at 20° C. for 40 hrs. The mixture was cooled to −50° C. and quenched with 15% sulfuric acid dropwise, diluted with ethyl acetate, stirred for 0.5 h and filtered. The organic phase was separated out, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was triturated with ethyl acetate for 2 hrs and the solid was collected by filtration and washed with ethyl acetate, dried to afford 5-4 (36.64).

[0888] Step 5: To a stirred mixture of 5-4 (36.64 g, 128.489 mmol) in acetone (500 mL) was added potassium carbonate (21.3 g, 154.187 mmol), purged with nitrogen three times. Then ethyl iodide (80.16 g, 513.957 mmol) was added dropwise. After addition, the mixture was stirred at 60° C. for 8 hrs. The mixture was cooled to room temperature and filtered. The cake was washed with acetone and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (eluted with ethyl acetate in petroleum ether from 0 ~20%) to afford 5-5 (33.2 g).

[0889] Compound 5-6 was prepared from 5-5 and tributyl (1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[0890] Step 6: To a mixture of 5-6 (9.2 g, 33.290 mmol) and (R)-2-methylpropane-2-sulfinamide (8.07 g, 66.580 mmol) in tetrahydrofuran (92 mL) was added titanium(IV) isopropoxide (10.7 g, 37.632 mmol), then stirred at 75° C. for 15 hrs under nitrogen. The mixture was cooled to room temperature and quenched with brine, stirred for 0.5 h and filtered. The cake was washed with ethyl acetate, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (eluted with ethyl acetate in petroleum ether from 0% ~40%) to afford 5-7 (6.4 g).

[0891] Step 7: To a mixture of 5-7 (6.2 g, 16.335 mmol) and cerium (III) chloride heptahydrate (3.0 g, 8.168 mmol) in methanol (62 mL) was added sodium borohydride (1.2 g, 32.670 mmol) in portions at −65° C. ~−70° C. under nitrogen, then stirred at 20° C. for 22 hrs. The reaction mixture was quenched with saturated ammonium chloride solution and filtered. The filtrate cake was washed with dichloromethane. The aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was purified by C-18 column chromatography (0.05% TFA in water/acetonitrile: 5% ~50%) to afford 5-8 (isomer 1, 3.68 g) and 5-8A (isomer 2, 0.33 g).

[0892] Step 8: To a solution of 5-8 (3.68 g, 9.645 mmol) in ethyl acetate (100 mL) was added hydrochloric acid in ethyl acetate (9.6 mL, 38.578 mmol) at 0° C., and then stirred at 20° C. for 6 hrs. Water was added to the reaction mixture, then the collected aqueous phase was adjusted pH=9~10 with 25% ammonium hydroxide, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford 5-9 (2.5 g).

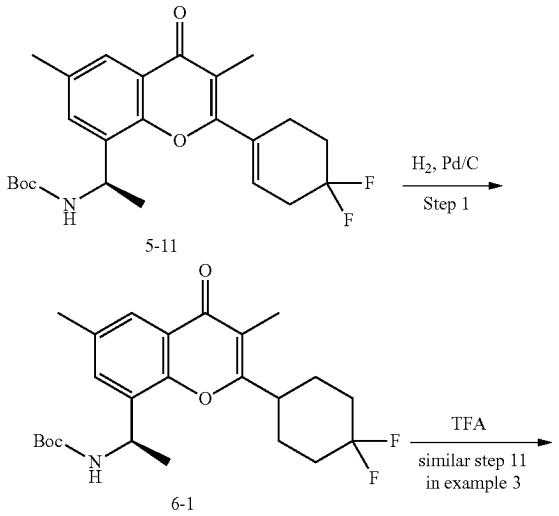
[0893] Step 9: To a solution of 5-9 (100 mg, 0.361 mmol) in dichloromethane (3 mL) was added triethylamine (0.075 mL, 0.541 mmol), followed by di-tert-butyl dicarbonate (0.083 mL, 0.361 mmol), then stirred at 20° C. for 2 hours. The solvent was removed in vacuo. The residue was purified by silica gel chromatography (eluted by ethyl acetate in petroleum ester from 0%~20%) to afford 5-10 (110 mg).

[0894] Step 10: To a mixture of 5-10 (90 mg, 0.238 mmol) and 5-1 (57.91 mg, 0.358 mmol) in anhydrous dioxane (4 mL) was added cesium carbonate (155.4 mg, 0.477 mmol), followed by tetrakis(triphenylphosphine)palladium (27.5 mg, 0.024 mmol) and copper (I) thiophene-2-carboxylate (90.9 mg, 0.477 mmol), purged with nitrogen for 2 minutes. The reaction mixture was irradiated by microwave at 90° C. for 2 hours. The reaction mixture was cooled and the solvent was removed in vacuo. The residue was purified by silica gel chromatography (eluted by ethyl acetate in petroleum ester from 0%~25%) to afford 5-11 (27 mg).

[0895] Step 11: A solution of 5-11 (70 mg, 0.161 mmol) and trifluoroacetic acid (0.4 mL, 0.161 mmol) in dichloromethane (2 mL) was stirred at room temperature for 1 hour. The resulting mixture was concentrated and dried under vacuum to afford 5-12 (crude), which was used directly in next step.

[0896] Step 12: To a mixture of 5-12 (40 mg, 0.108 mmol) and 2-iodobenzoic acid (53.65 mg, 0.216 mmol) in N, N-dimethylacetamide (3 mL) was added copper (4.1 mg, 0.065 mmol), followed by triethylamine (0.060 mL, 0.433 mmol), purged with nitrogen three times. Then the mixture was stirred at 100° C. for 10 hours. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were concentrated and purified by Prep-HPLC (acetonitrile/0.05% formic acid in water: 0% ~60%) to afford 5 (7.9 mg). LCMS (ESI, m/z): $[M+H]^+$ =454.2; ^{1}H NMR (400 MHz, Methanol-d_4, ppm): δ 7.94-7.85 (m, 1H), 7.83-7.78 (m, 1H), 7.60-7.53 (m, 1H), 7.21-7.10 (m, 1H), 6.58-6.50 (m, 1H), 6.41 (d, J=8.4 Hz, 1H), 6.19-6.10 (m, 1H), 5.19-5.09 (m, 1H), 2.88-2.65 (m, 4H), 2.38 (s, 3H), 2.30-2.17 (m, 2H), 2.11 (s, 3H), 1.64 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, Methanol-d_4, ppm): δ −98.15 (2F).

Example 4 Synthesis of Compound 6



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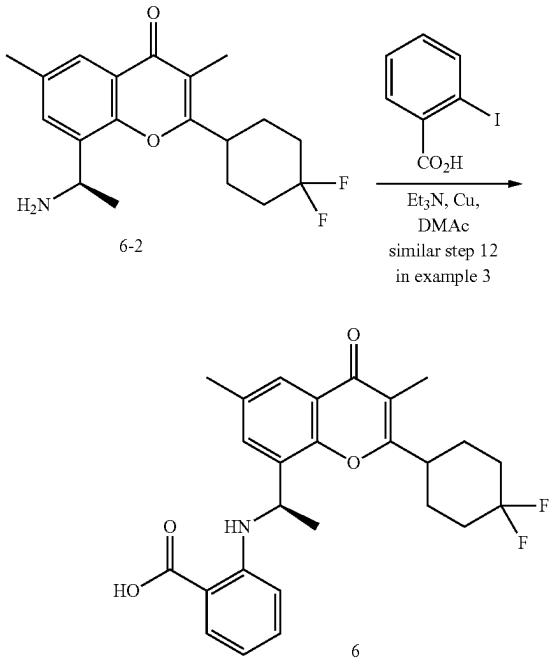
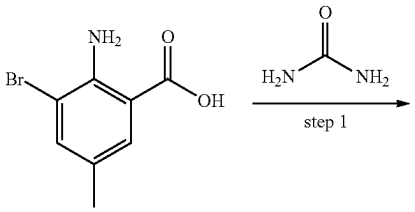


[0897] Step 1: A mixture of 5-11 (67 mg, 0.155 mmol) and Pd/C (10% wet, 7 mg, 0.066 mmol) in MeOH (2 mL) was stirred at room temperature for 2 hours under hydrogen atmosphere. The resulting mixture was filtered and washed with ethyl acetate. The filtrate was concentrated and dried to afford 6-1 (60 mg), which was used directly in next step.

[0898] Compound 6-2 was prepared from 6-1 following the procedure for the synthesis of compound 5-12 in example 3.

[0899] Compound 6 was prepared from 6-2 and 2-iodobenzoic acid following the procedure for the synthesis of compound 5 in example 3. LCMS (ESI, m/z): $[M+H]^+$=456.2; ^{1}H NMR (400 MHz, Methanol-d_4, ppm): δ 7.95-7.88 (m, 1H), 7.81-7.76 (m, 1H), 7.55-7.50 (m, 1H), 7.20-7.11 (m, 1H), 6.59-6.51 (m, 1H), 6.38-6.31 (m, 1H), 5.22-5.13 (m, 1H), 3.29-3.19 (m, 1H), 2.35 (s, 3H), 2.26-2.16 (m, 2H), 2.13 (s, 3H), 2.11-1.90 (m, 6H), 1.65 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, Methanol-d_4, ppm): δ−92.84 (1F), −104.26 (1F).

Example 5 Synthesis of Compound 7



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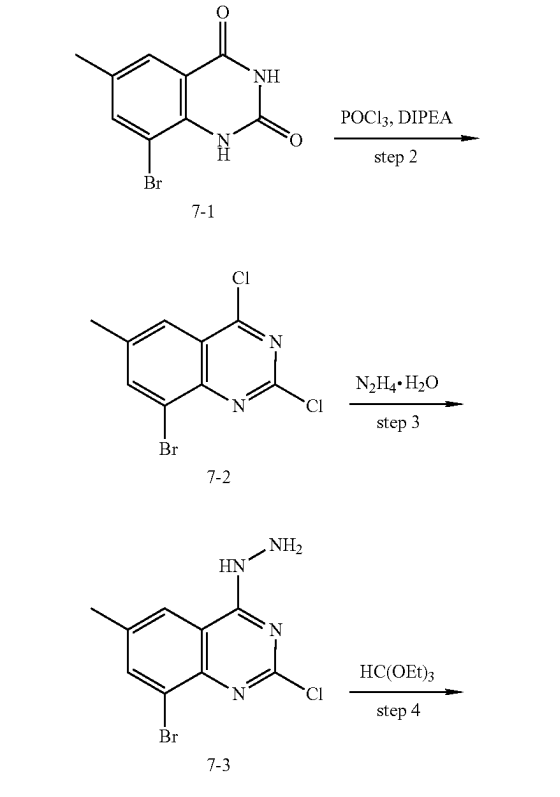

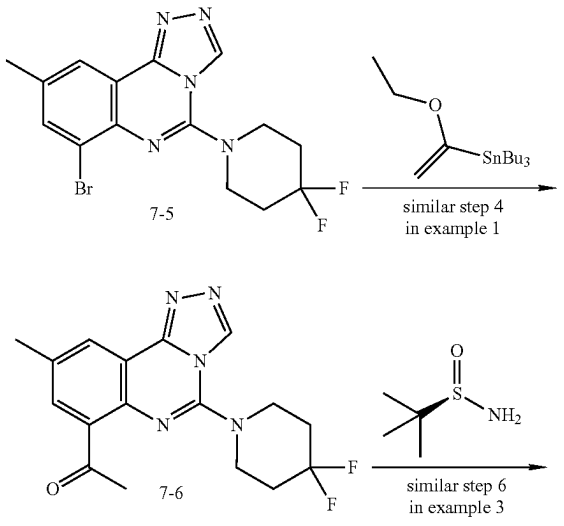

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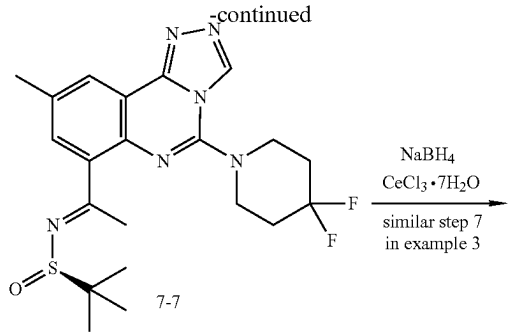

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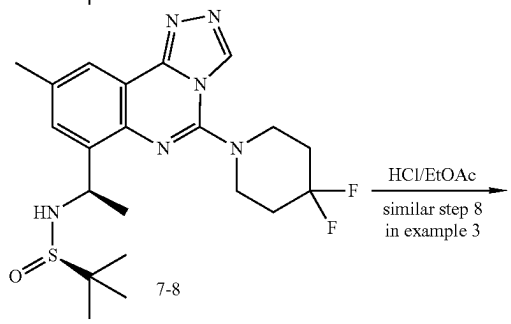

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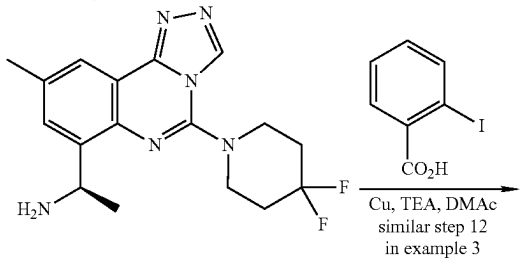

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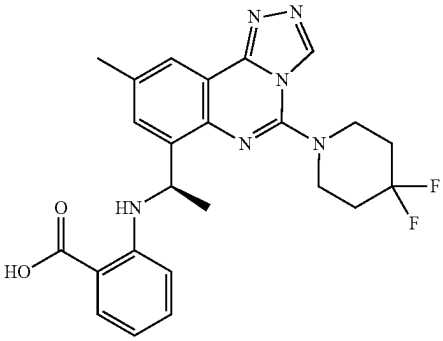


7

[0900] Step 1: A mixture of 2-amino-3-bromo-5-methylbenzoic acid (19 g, 82.587 mmol) and urea (74.40 g, 1238.805 mmol) was stirred at 180° C. for 2 hours. The mixture was cooled down to room temperature and water was added and stirred for 10 minutes. The reaction mixture was filtered and NaH aqueous solution was added and stirred for 1 hour. Then the reaction mixture was acidified by acetic acid. The precipitate was collected by filtration and dried to give 7-1 (13.5 g).

[0901] Step 2: To a suspension of 7-1 (5 g, 19.602 mmol) in toluene (50 mL) were added N, N-diisopropylethylamine (9.7 mL, 58.81 mmol) and $POCl_3$ (9.1 mL, 98.01 mmol) under N_2. Then the mixture was stirred at 110° C. for 16 hours. The reaction was quenched by addition of water and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford 7-2 (4.46 g).

[0902] Step 3: To a mixture of 7-2 (3.6 g, 12.330 mmol) in EtOH (100 mL) was added hydrazinium hydroxide (1.2 mL, 24.661 mmol). Then the mixture was stirred at room temperature for 1 h. The mixture was quenched by addition of water and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford 7-3 (3.5 g).

[0903] Step 4: A mixture of 7-3 (3.5 g, 12.172 mmol) in trimethoxymethane (25.83 g, 243.436 mmol) was stirred at 110° C. for 1 h. The mixture was concentrated to afford the product 7-4 (crude), which was used in next step without purification.

[0904] Step 5: To a mixture of 7-4 (3 g, 10.083 mmol) in ACN (80 mL) was added 4,4-difluoropiperidine (1.47 g, 12.099 mmol) and N, N-diisopropylethylamine (8.3 mL, 50.413 mmol). Then the mixture was stirred at 50° C. for 1 h. The reaction was quenched by addition of water and extracted with DCM. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, concentrated. The residue was purified by column chromatography on silica gel eluted with (10% MeOH/DCM) to give 7-5 (3.5 g).

[0905] Compound 7-6 was prepared from 7-5 and tributyl (1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

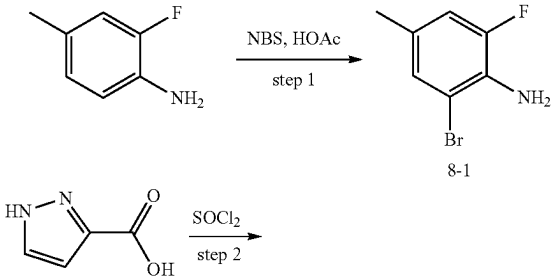
[0906] Compound 7-7 was prepared from 7-6 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

[0907] Compound 7-8 was prepared from 7-7 following the procedure for the synthesis of compound 5-8 in example 3.

[0908] Compound 7-9 was prepared from 7-8 following the procedure for the synthesis of compound 5-9 in example 3.

[0909] Compound 7 was prepared from 7-9 following the procedure for the synthesis of compound 5 in example 3. LCMS (ESI, m/z): $^{+}$=467.2; as a 2 TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.70 (s, 1H), 9.51 (s, 1H), 8.46 (s, 1H), 8.08 (s, 1H), 7.79 (d, J=8.0 Hz, 1H), 7.51 (s, 1H), 7.15 (t, J=8.0 Hz, 1H), 6.59-6.41 (m, 2H), 5.62-5.43 (m, 1H), 3.79-3.62 (m, 4H), 2.43 (s, 3H), 2.32-2.15 (m, 4H), 1.61 (d, J=6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −95.02 (2F).

Example 6 Synthesis of Compounds 8 and 9



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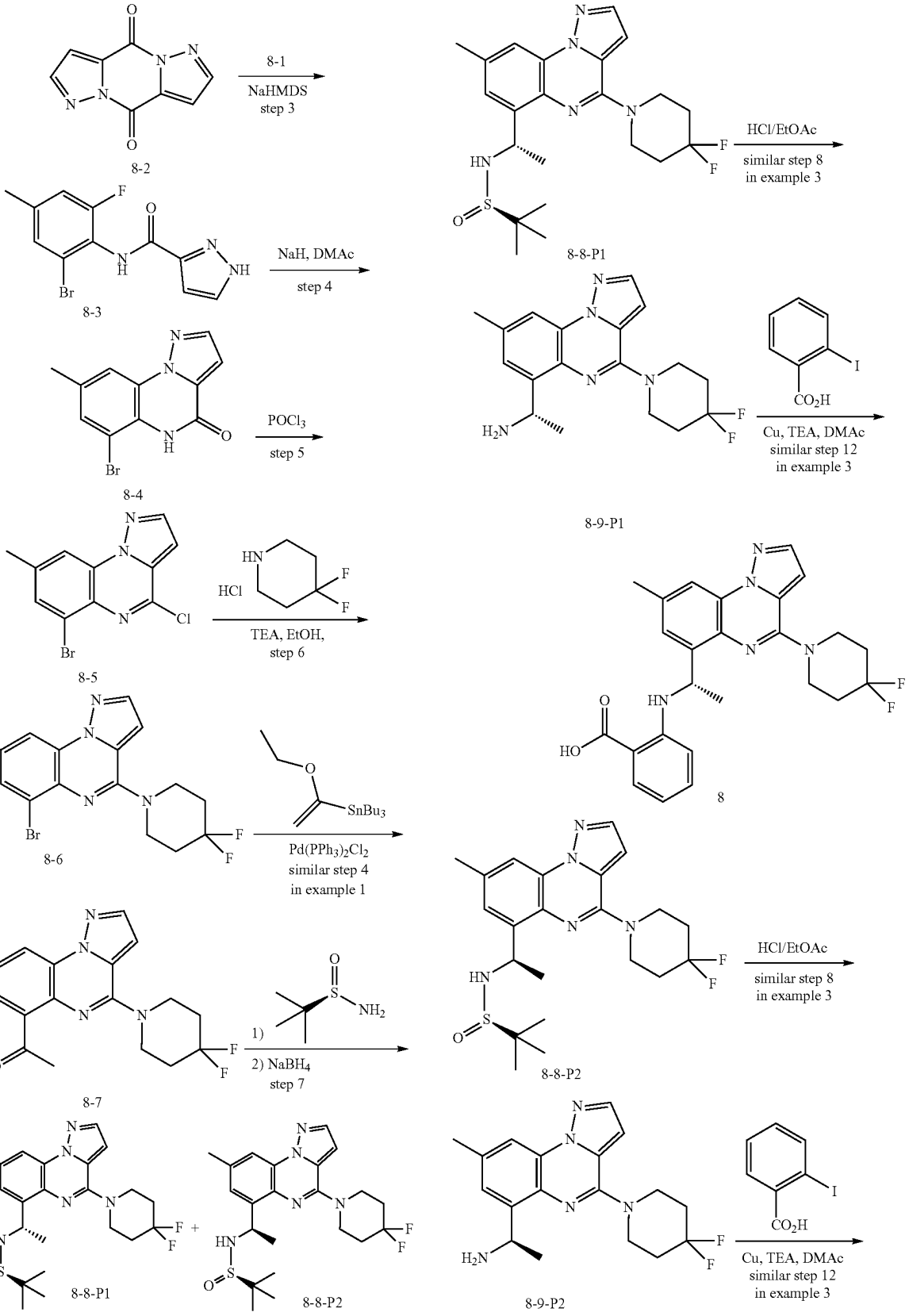
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NaHMDS
step 3
8-2
NaH, DMAc
step 4
8-3
POCl3
step 5
8-4
HCl
TEA, EtOH,
step 6
8-5
8-6
Pd(PPh3)2Cl2
similar step 4
in example 1
SnBu3
1)
2) NaBH4
step 7
8-7
8-8-P1
8-8-P2
HCl/EtOAc
similar step 8
in example 3
8-8-P1
8-9-P1
Cu, TEA, DMAc
similar step 12
in example 3
8
8-9-P2

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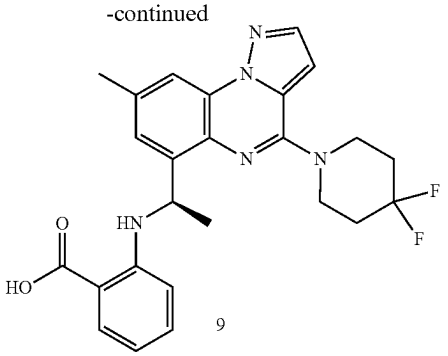


9

[0910] Step 1: To a solution of 2-fluoro-4-methylaniline (50 g, 399.52 mmol) in HOAc (420 mL) was added NBS (80.1 g, 450.05 mmol) in portions at an ice-water bath under N_2, then the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was washed with water, then 10% aq. Na_2CO_3 solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford 8-1 (76 g). LCMS (ESI, m/z): $[M+H]^+$=204.0.

[0911] Step 2: The mixture of 1H-pyrazole-3-carboxylic acid (50 g, 446.07 mmol) in $SOCl_2$ (150 mL) was heated to reflux under agitation for 18 hours. After cooled to room temperature, the suspension was filtered and the filtered cake was washed with toluene, dried to afford 8-2 (75 g).

[0912] Step 3: To a solution of 8-1 (16 g, 78.42 mmol) in THF (85 mL) at −10° C. was added dropwise 2 M NaHMDS solution in THF (98 mL, 196.00 mmol). After stirring for 1 hour, a suspension of 8-2 (7.37 g, 39.17 mmol) in THF (60 mL) was added dropwise to the solution above at −10° C. The resulting mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was quenched with sat. aq. NH_4C_1 solution and extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give 8-3 (17.95 g), which was used directly in next step. LCMS (ESI, m/z): $[M+H]^+$=298.0.

[0913] Step 4: A mixture of 8-3 (13 g, 43.61 mmol) and NaH (60% wt., 2.65 g, 66.25 mmol) in N, N-dimethylacetamide (330 mL) was heated at reflux for 48 hours. The mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl solution and extracted with DCM/MeOH. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated give the crude 8-4, which was used directly in next step. LCMS (ESI, m/z): $[M+H]^+$=278.0.

[0914] Step 5: A mixture of 8-4 (17.08 g, 61.42 mmol) and N, N-dimethylaniline (14.89 g, 67.91 mmol) in $POCl_3$ (250 mL) was stirred at 130° C. for 4 hrs. The reaction mixture was concentrated and the residue was neutralized with saturated aqueous Na_2CO_3 solution, extracted with dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give 8-5 (17.5 g). LCMS (ESI, m/z): $[M+H]^+$=296.0.

[0915] Step 6: A mixture of 8-5 (3 g, 10.12 mmol), 4,4-difluoropiperidine hydrochloride (1.4 g, 8.88 mmol) and TEA (3.1 g, 30.64 mmol) in EtOH (10 mL) was irradiated by microwave at 140° C. for 0.5 h. The reaction mixture was concentrated and the residue was diluted with DCM, washed with sat. aq. Na_2CO_3 solution, dried over anhydrous Na_2SO_4, filtered and concentrated to give 8-6 (2.9 g, crude), which used directly in next step. LCMS (EST, m/z): $[M+H]^+$=381.0.

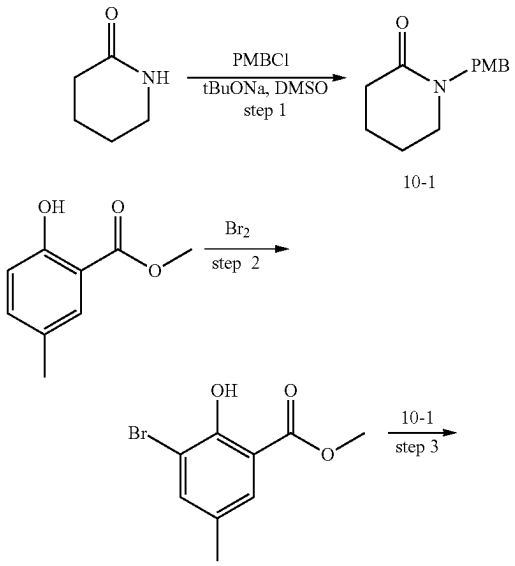
[0916] Compound 8-7 was prepared from 8-6 and tributyl (1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[0917] Step 7: A solution of 8-7 (1.75 g, 5.08 mmol), (R)-2-methylpropane-2-sulfinamide (2.13 g, 17.57 mmol) and $Ti(OEt)_4$ (10 g, 43.84 mmol) in 1,4-dioxane (150 mL) was stirred at 110° C. for 16 hrs. After cooled to 0° C., NaBH4 (0.50 g, 13.22 mmol) was added and the mixture was stirred at 0 to 10° C. for 16 hrs. The reaction mixture was quenched with MeOH and water (v/v, 1/1), filtered through celite and the cake was washed with EtOAc. The filtrate was concentrated to dryness and the residue was purified by C18 reverse phase column (Acetonitrile; 0.05% TFA in water: 0 to 68%, keep at 68%) to afford 8-8-P1 (220 mg) and 8-8-P2 (576 mg). LCMS (ESL, m/z): $[M+H]^+$=405.2.

[0918] Compounds 8-9-P1 and 8-9-P2 was prepared from 8-8-P1 and 8-9-P2 respectively following the procedure for the synthesis of compound 5-9 in example 3.

[0919] Compounds 8 and 9 was prepared from 8-9-P1 and 8-9-P2 respectively following the procedure for the synthesis of compound 5-9 in example 3. 8: LCMS (ESI, m/z): $[M+H]^+$=466.4; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.67 (brs, 1H), 8.46 (brs, 1H), 8.20 (s, 1H), 8.01 (s, 1H), 7.79 (d, J=7.6 Hz, 1H), 7.31-7.20 (m, 2H), 7.19-7.08 (m, 1H), 6.53-6.41 (m, 2H), 5.65-5.51 (m, 1H), 4.05-3.86 (m, 4H), 2.41 (s, 3H), 2.30-2.11 (m, 4H), 1.62 (d, J=6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −94.46 (2F). 9: LCMS (ESI, m/z): $[M+H]^+$=466.4; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.78 (br, 1H), 8.46 (brs, 1H), 8.20 (s, 1H), 8.01 (s, 1H), 7.82-7.74 (m, 1H), 7.30-7.20 (m, 2H), 7.19-7.09 (m, 1H), 6.53-6.41 (m, 2H), 5.64-5.53 (m, 1H), 4.04-3.88 (m, 4H), 2.41 (s, 3H), 2.28-2.12 (m, 4H), 1.62 (d, J=6.6 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-de, ppm): δ −94.46 (2F).

Example 7 Synthesis of Compound 10



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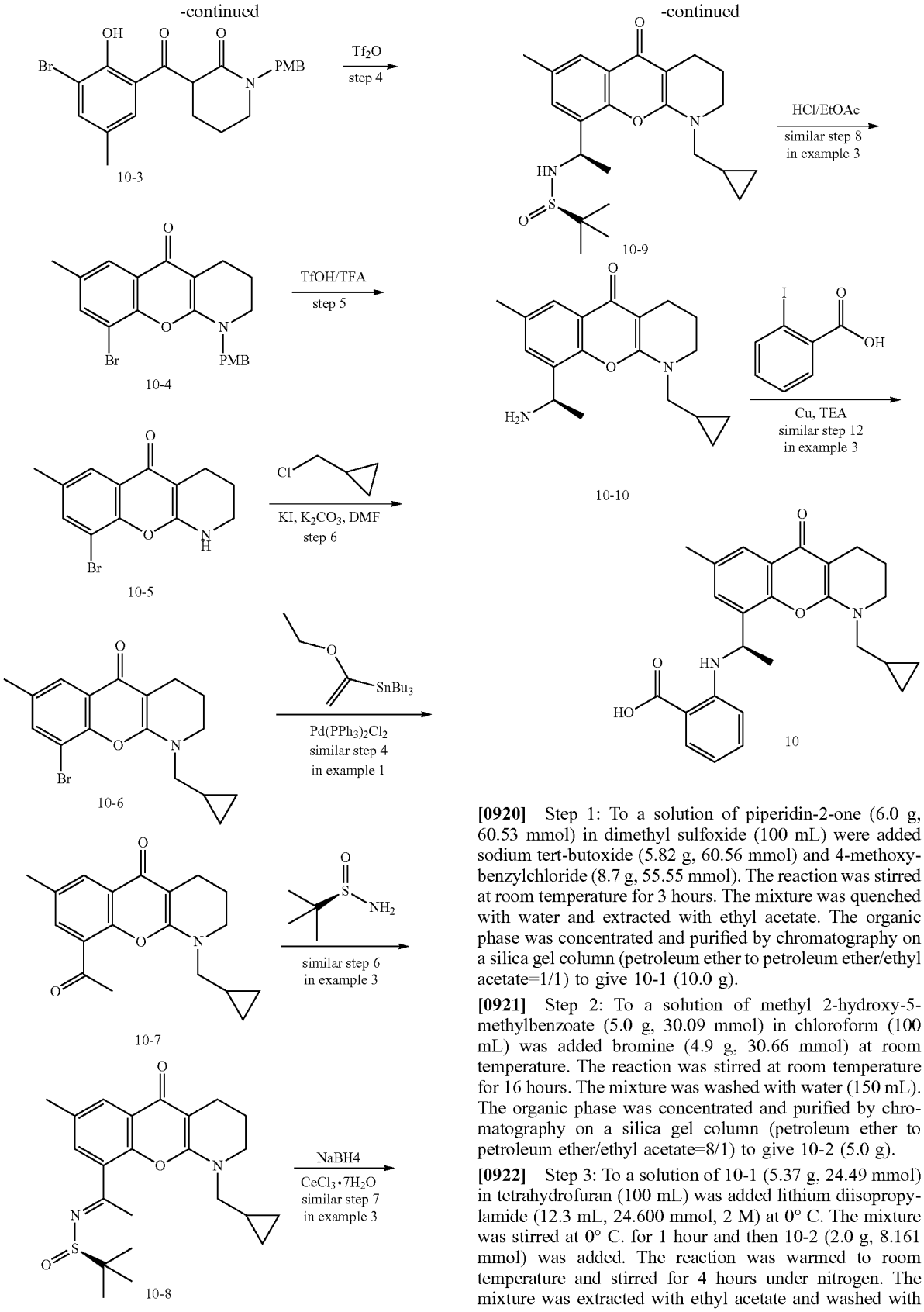


[0920] Step 1: To a solution of piperidin-2-one (6.0 g, 60.53 mmol) in dimethyl sulfoxide (100 mL) were added sodium tert-butoxide (5.82 g, 60.56 mmol) and 4-methoxybenzylchloride (8.7 g, 55.55 mmol). The reaction was stirred at room temperature for 3 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic phase was concentrated and purified by chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate=1/1) to give 10-1 (10.0 g).

[0921] Step 2: To a solution of methyl 2-hydroxy-5-methylbenzoate (5.0 g, 30.09 mmol) in chloroform (100 mL) was added bromine (4.9 g, 30.66 mmol) at room temperature. The reaction was stirred at room temperature for 16 hours. The mixture was washed with water (150 mL). The organic phase was concentrated and purified by chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate=8/1) to give 10-2 (5.0 g).

[0922] Step 3: To a solution of 10-1 (5.37 g, 24.49 mmol) in tetrahydrofuran (100 mL) was added lithium diisopropylamide (12.3 mL, 24.600 mmol, 2 M) at 0° C. The mixture was stirred at 0° C. for 1 hour and then 10-2 (2.0 g, 8.161 mmol) was added. The reaction was warmed to room temperature and stirred for 4 hours under nitrogen. The mixture was extracted with ethyl acetate and washed with water. The organic phase was concentrated and purified by

chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate=1/1) to give 10-3 (2.0 g).

[0923] Step 4: To a solution of 10-3 (1.2 g, 2.776 mmol) in dichloromethane (30 mL) was added triflic anhydride (2.35 g, 8.329 mmol) at 0° C. The reaction was stirred at room temperature for 16 hours under nitrogen. The mixture was concentrated and purified by chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate=1/10) to give 10-4 (700 mg).

[0924] Step 5: A solution of 10-4 (700 mg, 1.690 mmol) in trifluoroacetic acid (6 mL) was added triflic acid (6 mL) was stirred at 50° C. for 16 hours under nitrogen. The mixture was poured into ice-water and neutralized with saturated sodium bicarbonate to pH=8. The mixture was extracted with dichloromethane and the organic phase was concentrated and purified by chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate =1/10) to give 10-5 (400 mg).

[0925] Step 6: To a solution of 10-5 (400 mg, 1.360 mmol) in dimethylformamide (20 mL) were added potassium carbonate (376 mg, 2.721 mmol), (chloromethyl)cyclopropane (493 mg, 5.445 mmol) and potassium iodide (450 mg, 2.711 mmol). The reaction was stirred at 60° C. for 16 hours under nitrogen. The mixture was extracted with ethyl acetate and washed with water. The organic phase was concentrated and concentrated and purified by chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate=1/10) to give 10-6 (300 mg).

[0926] Compound 10-7 was prepared from 10-6 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

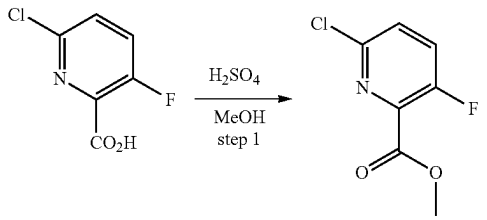
[0927] Compound 10-8 was prepared from 10-7 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

[0928] Compound 10-9 was prepared from 10-8 following the procedure for the synthesis of compound 5-8 in example 3.

[0929] Compound 10-10 was prepared from 10-9 following the procedure for the synthesis of compound 5-9 in example 3.

[0930] Compound 10 was prepared from 10-10 following the procedure for the synthesis of compound 5 in example 3. LCMS (ESI, m/z): $[M+H]^+$=433.4; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.67 (s, 1H), 7.83-7.81 (m, 1H), 7.61 (d, J=1.2 Hz, 1H), 7.32 (d, J=2.0 Hz, 1H), 7.18-7.15 (m, 1H), 6.54-6.50 (m, 1H), 6.35 (d, J=8.4 Hz, 1H), 5.05-5.04 (m, 1H), 3.54-3.52 (m, 2H), 3.47-3.45 (m, 2H), 2.53-2.50 (m, 2H), 2.29 (s, 3H), 1.87-1.85 (m, 2H), 1.56 (d, J=6.8 Hz, 3H), 1.16-1.12 (m, 1H), 0.53-0.48 (m, 2H), 0.31-0.27 (m, 2H).

Example 8 Synthesis of Compound 11



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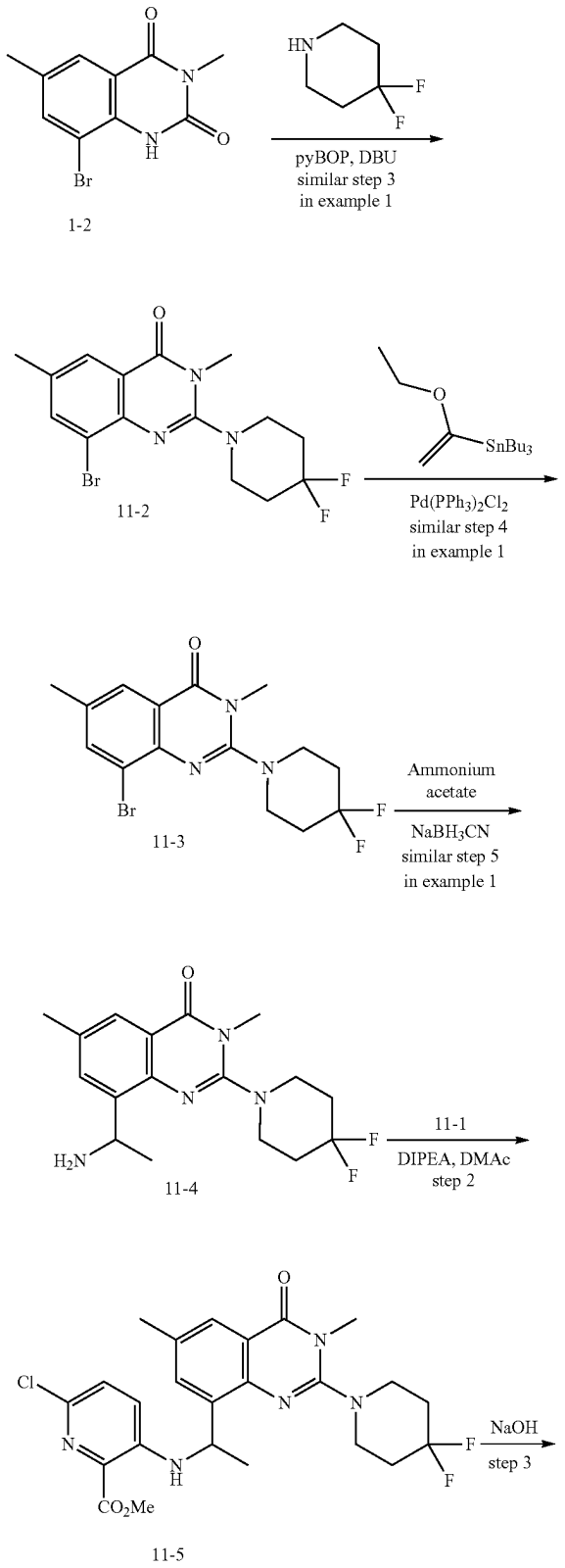

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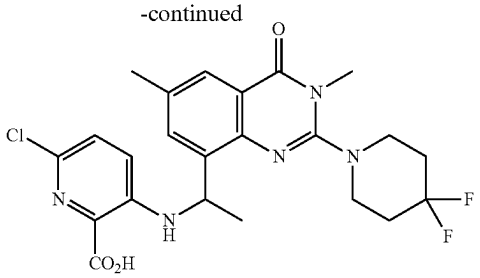

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[0931] Step 1: To a stirred solution of 6-chloro-3-fluoro-pyridine-2-carboxylic acid (1000 mg, 5.696 mmol) in methanol (10 mL) was added sulfuric acid (1 mL, 18.000 mmol), then stirred at 70° C. under nitrogen for 16 hrs. After cooling, the reaction mixture was added to saturated sodium bicarbonate dropwise, stirred for 10 minutes and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford 11-1 (1000 mg).

[0932] Compound 11-2 was prepared from 1-2 and 4,4-difluoropiperidine following the procedure for the synthesis of compound 1-3 in example 1.

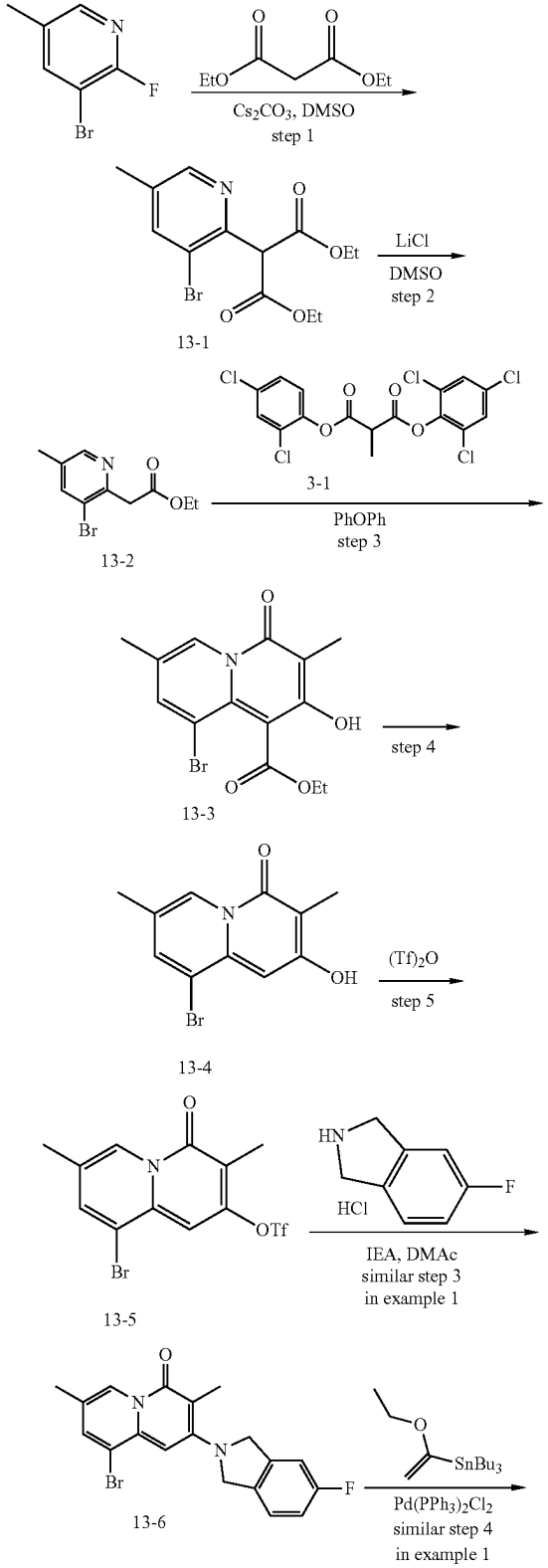
[0933] Compound 11-3 was prepared from 11-2 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[0934] Compound 11-4 was prepared from 11-3 following the procedure for the synthesis of compound 1-5 in example 1.

[0935] Step 2: A mixture of 11-4 (330 mg, 0.98 mmol), 11-1 (223 mg, 1.18 mmol) and N, N-diisopropylethylamine (0.33 mL, 1.96 mmol) in N, N-dimethylacetamide (5 mL) was stirred at 100° C. for 16 hours before it was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 11-5 (280 mg).

[0936] Step 3: To a mixture of 11-5 (60 mg, 0.12 mmol) in methanol (2 mL) and tetrahydrofuran (1 mL) was added sodium hydroxide (0.18 mL, 0.36 mmol, 2N in water) at room temperature. The mixture was stirred at 50° C. for 1 hour. The reaction mixture was acidified pH to 4 with saturated ammonium chloride solution at room temperature. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC (acetonitrile/0.05% FA in water: 10%~95%) to give racemic 11 (35 mg). LCMS (ESI, m/z): $[M+H]^+$=492.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.95 (brs, 1H), 8.52-8.36 (m, 1H), 7.78-7.70 (m, 1H), 7.54-7.46 (m, 1H), 7.36-7.29 (m, 1H), 7.09-7.00 (m, 1H), 5.40-5.30 (m, 1H), 3.51 (s, 3H), 3.44-3.34 (m, 4H), 2.34 (s, 3H), 2.28-2.11 (m, 4H), 1.60 (d, 3H, J=6.4 Hz); ^{1}F NMR (376 MHz, DMSO-d_6, ppm): δ −95.21 (2F).

Example 9 Synthesis of Compound 13



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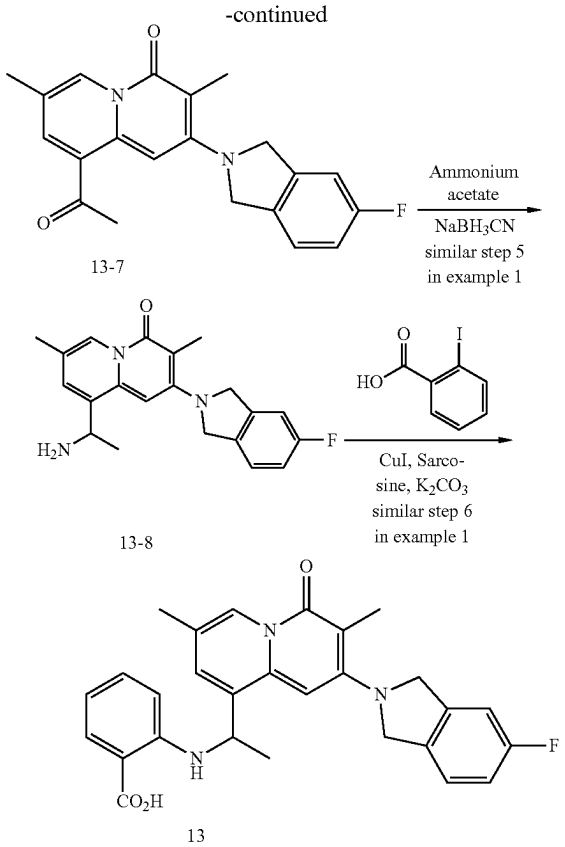


[0937] Step 1: A mixture of 3-bromo-2-fluoro-5-methylpyridine (50 g, 263.144 mmol), 1,3-diethyl propanedioate (84.30 g, 526.288 mmol) and cesium carbonate (17.5 g, 526.288 mmol) in dimethyl sulfoxide (300 mL) was stirred at 100° C. for 4 hours. The reaction mixture was diluted with ethyl acetate and ice-water, and washed with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0%~40% ethyl acetate in petroleum ether) to give 13-1 (70 g).

[0938] Step 2: To a solution of 13-1 (70 g, 212.006 mmol) in dimethyl sulfoxide (200 mL) were added lithium chloride (18.0 g, 424.011 mmol) and water (3.820 mL, 212.006 mmol). The solution was stirred at 100° C. for 36 hours. The reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was purified by column chromatography (eluted with 0%~40% ethyl acetate in petroleum ether) to give 13-2 (44 g).

[0939] Step 3: A mixture of 13-2 (5 g, 19.371 mmol) and 3-1 was stirred at 170° C. for 1 hour. The resulting mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were concentrated purified by silica gel chromatography (eluted with 0%~30% ethyl acetate in petroleum ether) to afford 13-3 (5.2 g).

[0940] Step 3: 4: A mixture of 13-3 (5 g, 14.699 mmol) in 33% hydrogen bromide in acetic acid (20 mL) was stirred at 100° C. for 16 hrs. The reaction mixture was cooled to room temperature and poured into ice-water and filtered. The filtrate cake was washed with water and dried under vacuum to afford 13-4 (3 g).

[0941] Step 5: A mixture of 13-4 (4.3 g, 16.038 mmol) and pyridine (1.936 mL, 24.057 mmol) in dichloromethane (20 mL) was added trifluoromethanesulfonic anhydride (5.43 g, 19.246 mmol) at 0° C., then stirred at room temperature for 3 hours. The resulting mixture was diluted with dichloromethane and washed with water. The organic layer was concentrated and dried under vacuum to afford 13-5 (5.4 g), which was used directly in next step.

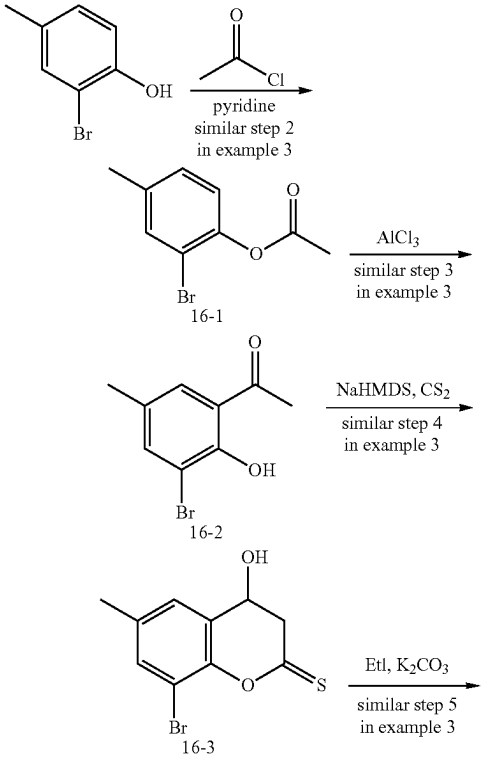
[0942] Compound 13-6 was prepared from 13-5 and 5-fluoroisoindoline hydrochloride following the procedure for the synthesis of compound 1-3 in example 1.

[0943] Compound 13-7 was prepared from 13-6 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[0944] Compound 13-8 was prepared from 13-7 following the procedure for the synthesis of compound 1-5 in example 1.

[0945] Racemic compound 13 was prepared from 13-8 and 2-iodobenzoic acid following the procedure for the synthesis of compound 1 in example 1. LCMS (ESI, m/z): $[M+H]^+$=472.4; 1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.82 (s, 1H), 8.61 (s, 1H), 8.43-8.39 (m, 1H), 7.86-7.79 (m, 1H), 7.43-7.35 (m, 1H), 7.31-7.18 (m, 2H), 7.17-7.10 (m, 2H), 6.63-6.54 (m, 1H), 6.46-6.39 (m, 2H), 5.14-5.06 (m, 1H), 5.03-4.79 (m, 4H), 2.42 (s, 3H), 2.19 (s, 3H), 1.61 (d, J=6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −115.78 (1F).

Example 10 Synthesis of Compound 1



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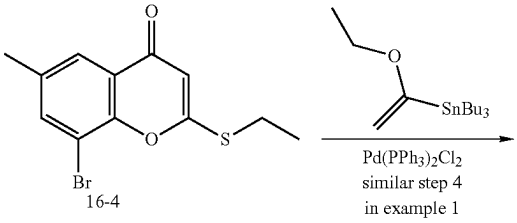

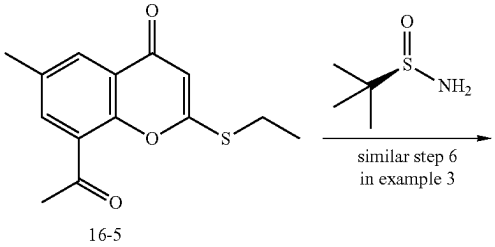

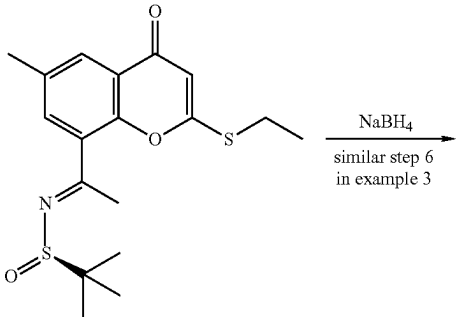

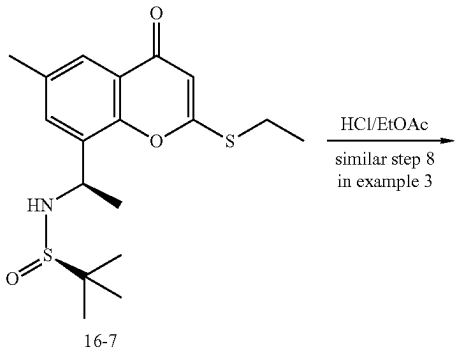

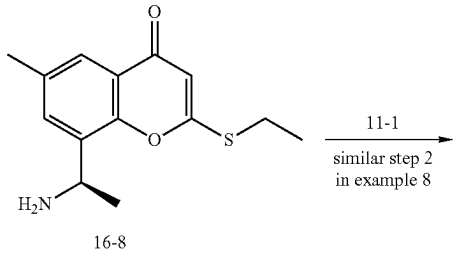

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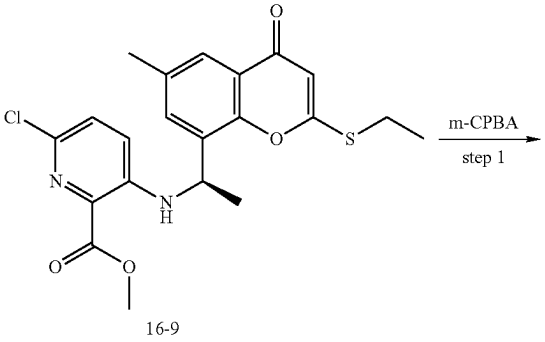

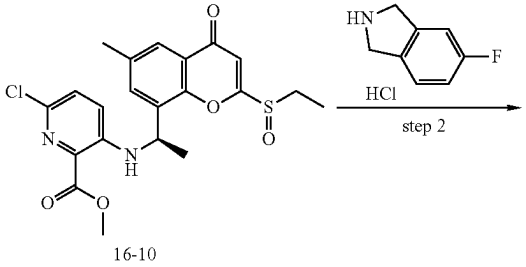

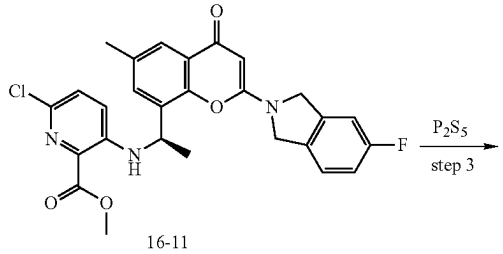

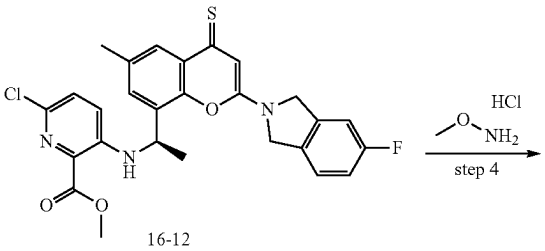

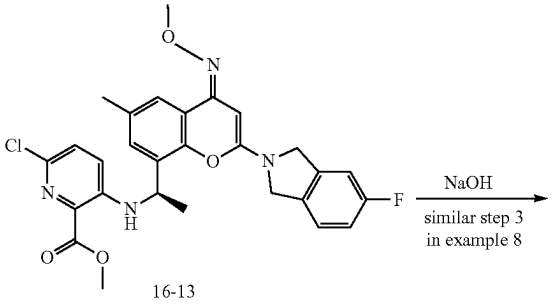

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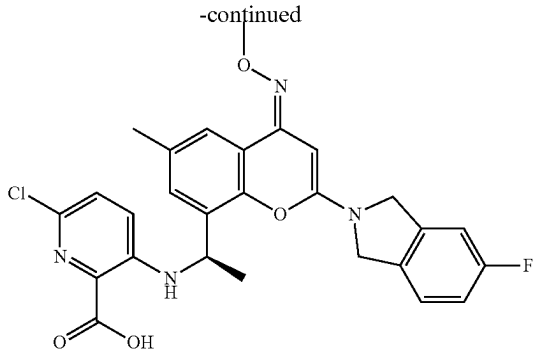


16

[0946] Compound 16-1 was prepared from 2-bromo-4-methylphenol and acetyl chloride following the procedure for the synthesis of compound 5-2 in example 3.

[0947] Compound 16-2 was prepared from 16-1 following the procedure for the synthesis of compound 5-3 in example 3.

[0948] Compound 16-3 was prepared from 16-2 following the procedure for the synthesis of compound 5-4 in example 3.

[0949] Compound 16-4 was prepared from 16-3 following the procedure for the synthesis of compound 5-5 in example 3.

[0950] Compound 16-5 was prepared from 16-4 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-5 in example 1.

[0951] Compound 16-6 was prepared from 16-5 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

[0952] Compound 16-7 was prepared from 16-6 following the procedure for the synthesis of compound 5-8 in example 3.

[0953] Compound 16-8 was prepared from 16-7 following the procedure for the synthesis of compound 5-9 in example 3.

[0954] Compound 16-9 was prepared from 16-8 and 11-1 following the procedure for the synthesis of compound 11-5 in example 8.

[0955] Step 1: To a solution of 16-9 (300 mg, 0.69 mmol) in dichloromethane (8 mL) was added m-chloroperbenzoic acid (182.9 mg, 0.90 mmol) at 0° C., then stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate aqueous and brine. The combined organic layer was dried over sodium sulfate, filtered and concentrated to give 16-10 (310 mg).

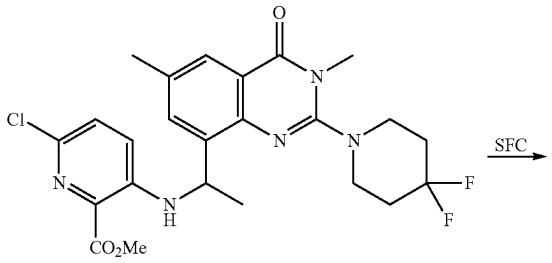
[0956] Step 2: A mixture of 16-10 (150 mg, 0.33 mmol), 5-fluoro-2,3-dihydro-1H-isoindole chlorane (116 mg, 0.67 mmol) and N, N-diisopropylethylamine (0.22 mL, 1.34 mmol) in dimethyl sulfoxide (5 mL) was stirred at 80° C. for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1/4) to give 16-11 (150 mg).

[0957] Step 3: A mixture of 16-11 (150 mg, 0.295 mmol) and phosphorus sulfide (18.6 mg, 0.295 mmol) in toluene (3 mL) was stirred at 90° C. for 3 hours. The reaction mixture was cooled down room temperature and filtered, concentrated to 16-12 (110 mg, crude), which was used directly in next step.

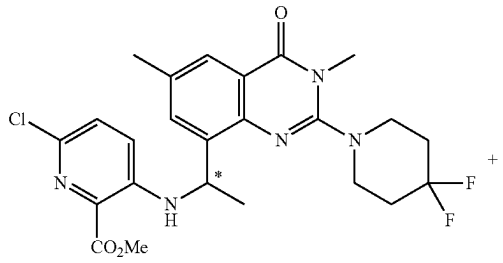
[0958] Step 4: A mixture of 16-12 (110 mg, 0.210 mmol), sodium acetate (51.7 mg, 0.630 mmol) and O-methylhydroxylamine hydrochloride (35.1 mg, 0.420 mmol) in ethanol (3 mL) was stirred at 35° C. for 48 hours. The reaction was concentrated and purified by Prep-HPLC (0.05% FA in water/acetonitrile) to afford 16-13 (13 mg).

[0959] Step 5: Compound 16 was prepared from 16-13 following the procedure for the synthesis of compound 11 in example 8. LCMS (ESI, m/z): $[M+H]^+$=523.3; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.71-7.58 (m, 2H), 7.53-7.42 (m, 1H), 7.38-7.04 (m, 4H), 5.34-5.23 (m, 1H), 5.22-4.96 (m, 5H), 3.98 (s, 3H), 2.43 (s, 3H), 1.91-1.73 (m, 3H). ^{19}F NMR (376 MHz, MeOH-d_4, ppm): δ −116.16 (1F).

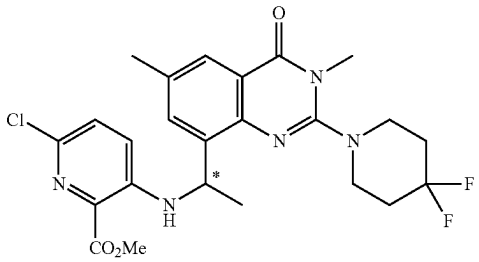
Example 11 Synthesis of Compounds 18 and 19



11-5

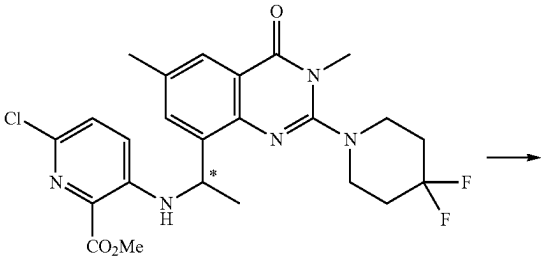


isomer 1
18-1

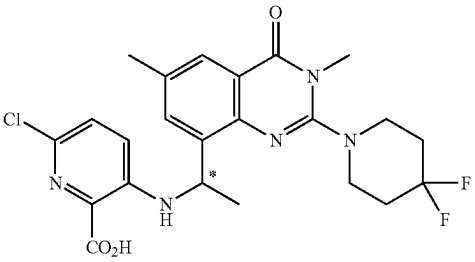


isomer 2
18-2

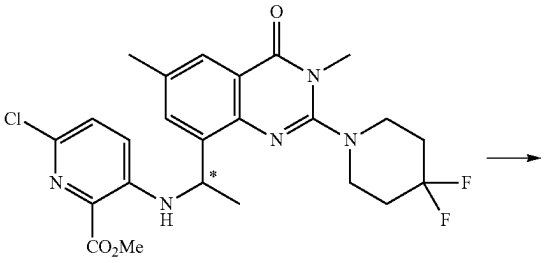
-continued



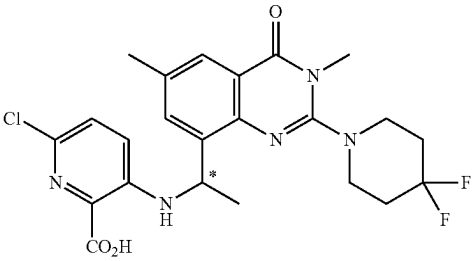
isomer 1
18-1



18



isomer 2
18-2

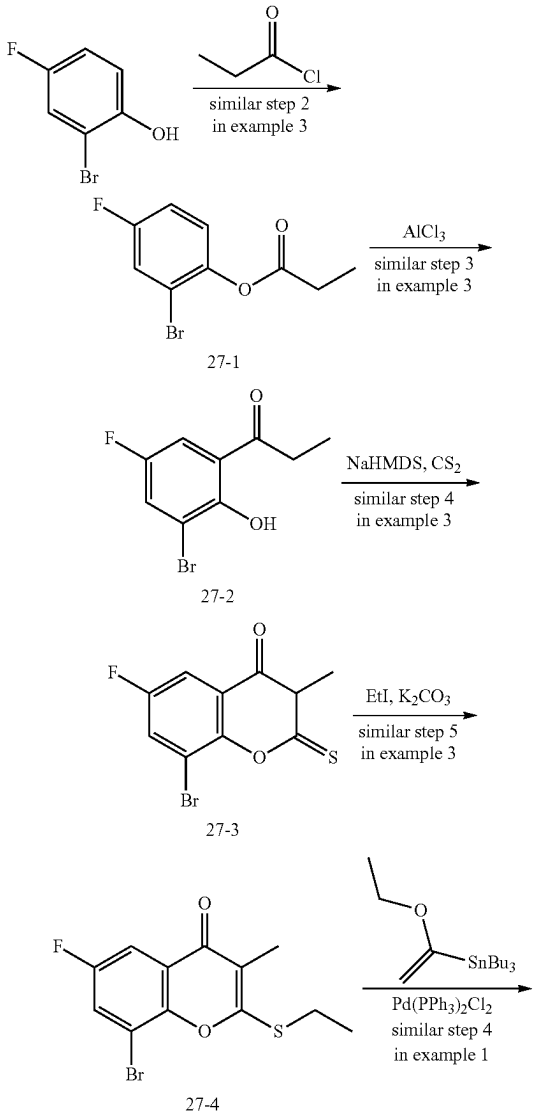


19

[0960] Compound 11-5 (180 mg) was separated via SFC (ChiralPak AS, 250×30 mm I.D., 10 μm with Supercritical CO_2/Ethanol) to give 18-1 (isomer 1, 81 mg) and 18-2 (isomer 2, 50 mg). 18-1 (isomer 1): Chiral SFC analysis: 99.2% ee. Retention time 2.624 min on ChiralPak AS, 150×4.6 mm I.D., 3 μm; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), 1500 psi, 2.5 mL/min. 18-2 (isomer 2): Chiral SFC analysis: 99.8% ee. Retention time 2.912 min on ChiralPak AS, 150×4.6 mm I.D., 3 μm; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), 1500 psi, 2.5 mL/min.

[0961] Compounds 18 and 19 was prepared from 18-1 and 18-2 respectively following the procedure for the synthesis of compound 11 in example 8. Compound 18: LCMS (ESI, m/z): $[M+H]^+$=492.4; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.95 (brs, 1H), 8.52-8.36 (m, 1H), 7.80-7.64 (m, 1H), 7.60-7.42 (m, 1H), 7.37-7.26 (m, 1H), 7.10-7.00 (m, 1H), 5.46-5.24 (m, 1H), 3.51 (s, 3H), 3.45-3.35 (m, 4H), 2.34 (s, 3H), 2.27-2.12 (m, 4H), 1.60 (d, 3H, J=6.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −95.21 (2F). Compound 19: LCMS (ESI, m/z): $[M+H]^+$=492.2; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.94 (brs, 1H), 8.52-8.38 (m, 1H), 7.81-7.67 (m, 1H), 7.57-7.45 (m, 1H), 7.38-7.25 (m, 1H), 7.14-7.00 (m, 1H), 5.44-5.25 (m, 1H), 3.51 (s, 3H), 3.44-3.34 (m, 4H), 2.34 (s, 3H), 2.27-2.12 (m, 4H), 1.60 (d, 3H, J=6.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −95.24 (2F).

Example 11A Synthesis of Compound 27



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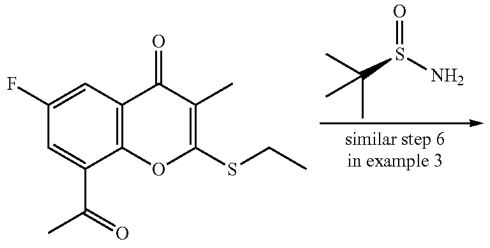
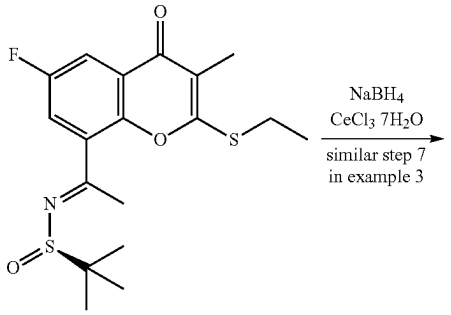


27-5



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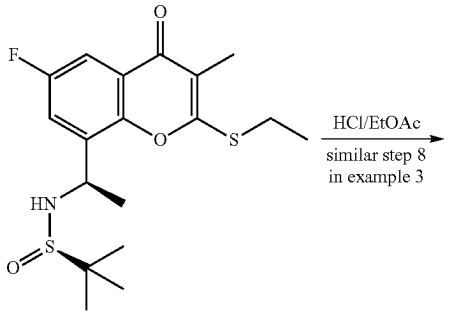

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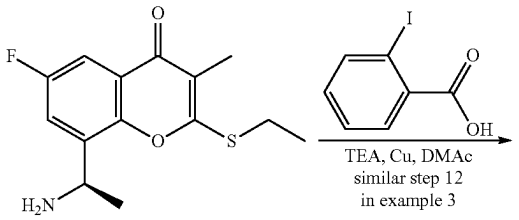

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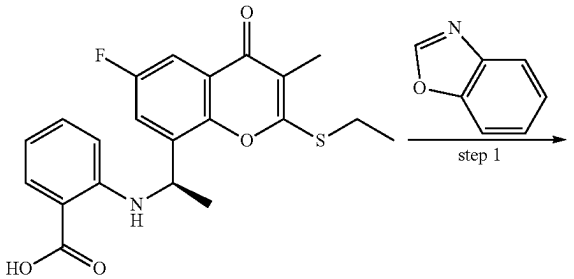

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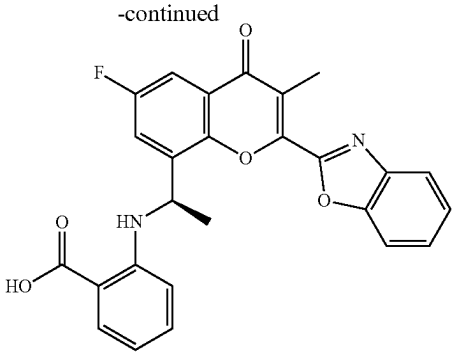


27

[0962] Compound 27-1 was prepared from 2-bromo-4-fluorophenol and propionyl chloride following the procedure for the synthesis of compound 5-2 in example 3.

[0963] Compound 27-2 was prepared from 27-1 following the procedure for the synthesis of compound 5-3 in example 3.

[0964] Compound 27-3 was prepared from 27-2 following the procedure for the synthesis of compound 5-4 in example 3.

[0965] Compound 27-4 was prepared from 27-3 following the procedure for the synthesis of compound 5-5 in example 3.

[0966] Compound 27-5 was prepared from 27-4 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[0967] Compound 27-6 was prepared from 27-5 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

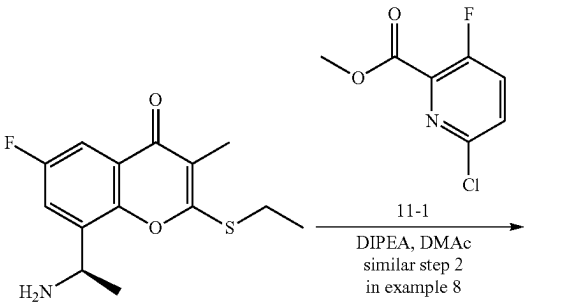
[0968] Compound 27-7 was prepared from 27-6 following the procedure for the synthesis of compound 5-8 in example 3.

[0969] Compound 27-8 was prepared from 27-7 following the procedure for the synthesis of compound 5-9 in example 3.

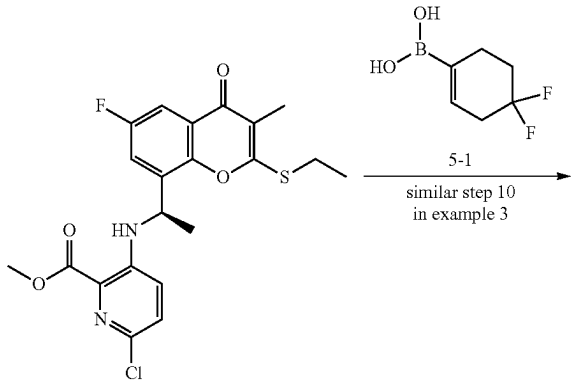
[0970] Compound 27-9 was prepared from 27-8 and 2-iodobenzoic acid following the procedure for the synthesis of compound 5 in example 3.

[0971] Step 1: A mixture of 27-9 (50 mg, 0.125 mmol), benzo[d][1,3]oxazole (14.89 mg, 0.125 mmol), [1,3-bis(2,6-diisopropylphenyl)-2H-imidazol-2-yl]-chloro-palladium (7.1 mg, 0.013 mmol), dicyclohexyl[2-(dicyclohexylphosphanyl)ethyl]phosphane (10.6 mg, 0.025 mmol) and potassium tert-butoxide (42.1 mg, 0.375 mmol) in N, N-dimethylacetamide (1 mL) was stirred at 140° C. for 16 hours under nitrogen atmosphere. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were concentrated and purified by Prep-HPLC (0.05% FA in water/acetonitrile) to afford 27 (3 mg). LCMS (ESI, m/z): $[M+H]^+$=459.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.05-8.75 (m, 1H), 8.06-7.92 (m, 2H), 7.87-7.78 (m, 1H), 7.72-7.65 (m, 1H), 7.64-7.50 (m, 3H), 7.20-7.10 (m, 1H), 6.59-6.43 (m, 2H), 5.41-5.23 (m, 1H), 2.58 (s, 3H), 1.75 (d, J=6.6 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −114.51 (1F).

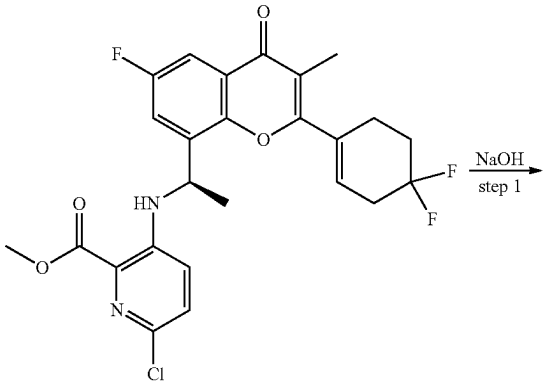
Example 12 Synthesis of Compounds 29 and 30



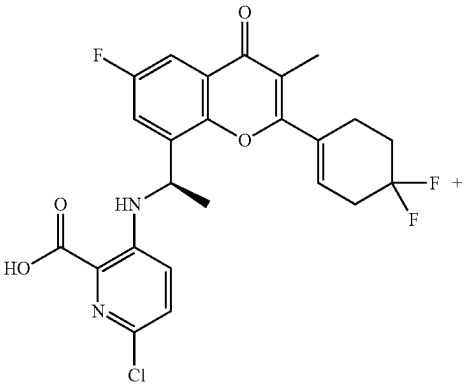
27-8



29-1



29-2



29

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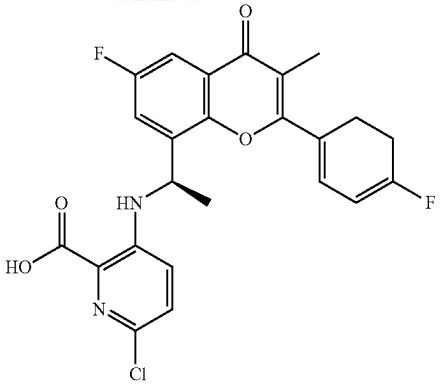


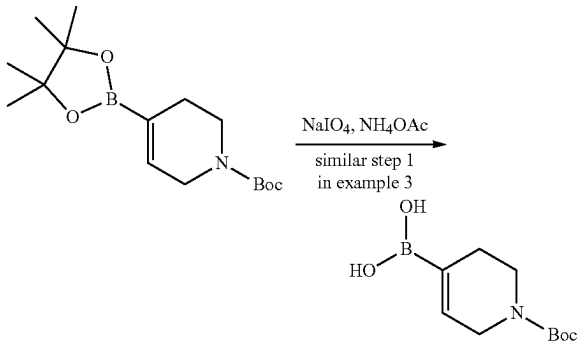
30

[0972] Compound 29-1 was prepared from 27-8 and 11-1 following the procedure for the synthesis of compound 11-2 in example 8.

[0973] Compound 29-2 was prepared from 29-1 and 5-1 following the procedure for the synthesis of compound 5-11 in example 3.

[0974] Step 1: To a solution of methyl 29-2 (30 mg, 0.059 mmol) in THF/H_2O (6 mL) were added NaOH (7.1 mg, 0.177 mmol), and the reaction was stirred at room temperature for 30 min. The reaction was adjusted to pH~3 with HCl (2 M), extracted with EtOAc. The collected organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified using prep-HPLC (acetonitrile/0.05% formic acid in water: 25%~95%) to afford the title compound 29 (2.7 mg) and 30 (3.4 mg). Compound 29: LCMS (ESI, m/z): $[M+H]^+$=493.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.74 (s, 1H), 7.61-7.54 (m, 2H), 7.25 (d, J=8.8 Hz, 1H), 6.97 (d, J=9.2 Hz, 1H), 6.18 (s, 1H), 5.14-5.11 (m, 1H), 2.90-2.83 (m, 2H), 2.69 (s, 2H), 2.27-2.19 (m, 2H), 2.04 (s, 3H), 1.62 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −94.47 (2F), −115.36 (1F). Compound 30: LCMS (ESI, m/z): $[M+H]^+$=473.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.55 (s, 1H), 7.60-7.52 (m, 2H), 7.29-7.26 (m, 1H), 7.01-6.99 (m, 1H), 6.56-6.53 (m, 1H), 5.87-5.82 (m, 1H), 5.16-5.13 (m, 1H), 2.92-2.88 (m, 2H), 2.64-2.61 (m, 2H), 2.11 (s, 3H), 1.63 (d, J=6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −94.59 (1F), −115.50 (1F).

Example 13 Synthesis of Compound 43



43-1

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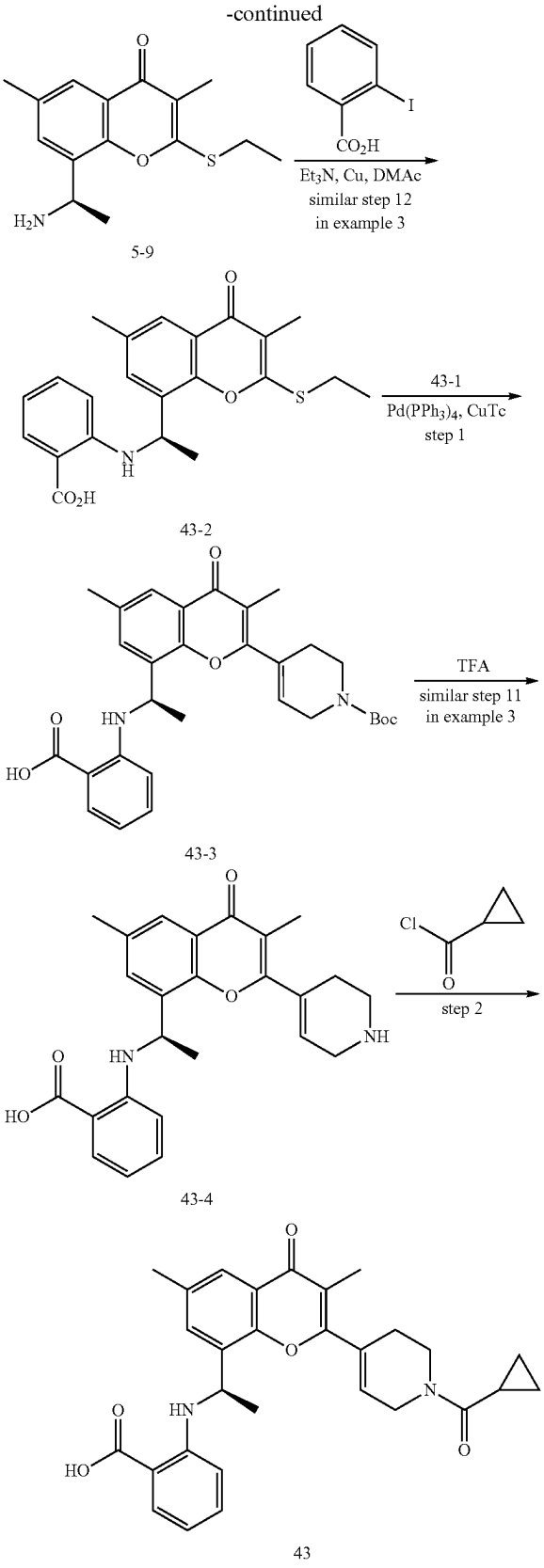


[0975] Compound 43-1 was prepared from tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate following the procedure for the synthesis of compound 5-1 in example 3.

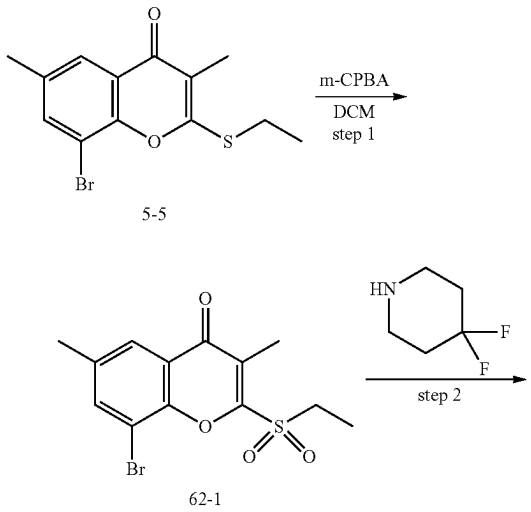
[0976] Compound 43-2 was prepared from 5-9 and 2-iodobenzoic acid following the procedure for the synthesis of compound 5 in example 3.

[0977] Step 1: A mixture of 43-2 (100 mg, 0.252 mmol), 43-1 (171.38 mg, 0.755 mmol), tetrakis(triphenylphosphine) palladium (58.1 mg, 0.050 mmol) and copper (I) thiophene-2-carboxylate (95.9 mg, 0.503 mmol) in methanol (5 mL) was stirred at room temperature for 3 hours under nitrogen atmosphere. The resulting mixture was concentrated and purified by silica gel chromatography (eluted with ethyl acetate in petroleum ether from 10%-30%) to afford 43-3 (60 mg).

[0978] Compound 43-4 was prepared from 43-3 following the procedure for the synthesis of compound 5-12 in example 3.

[0979] Step 2: A solution of 43-4 (48.54 mg, 0.116 mmol) and triethylamine (0.081 mL, 0.580 mmol) in tetrahydrofuran (5 mL) was added cyclopropanecarbonyl chloride (18.19 mg, 0.174 mmol) at −45° C., then stirred at −45° C. for 30 minutes. The resulting mixture was diluted with water and extracted with ethyl acetate. The organic layer was concentrated and purified by Prep-HPLC (0.05% FA in water/acetonitrile) to afford 43 (5.5 mg). LCMS (ESI, m/z): $[M+H]^+$=487.2; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 8.47-8.42 (m, 1H), 7.84-7.77 (m, 1H), 7.74-7.69 (m, 1H), 7.54-7.49 (m, 1H), 7.25-7.16 (m, 1H), 6.57-6.49 (m, 1H), 6.46-6.39 (m, 1H), 6.39-6.34 (m, 1H), 5.14-5.10 (m, 1H), 4.51-4.47 (m, 1H), 4.23-4.18 (m, 1H), 3.95-3.88 (m, 1H), 3.81-3.60 (m, 2H), 2.66-2.62 (m, 1H), 2.34 (s, 3H), 2.08 (s, 3H), 2.03-1.92 (m, 1H), 1.58 (d, J=6.6 Hz, 3H), 0.81-0.71 (m, 4H).

Example 14 Synthesis of Compound 62



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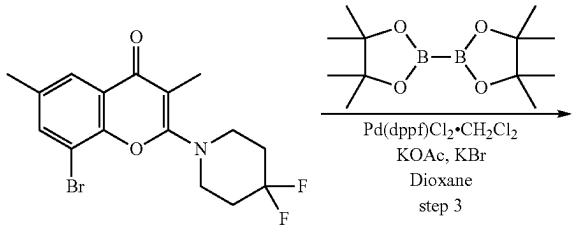

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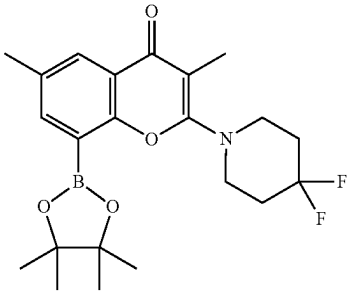

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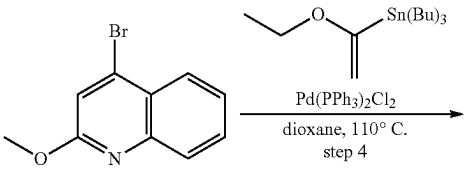

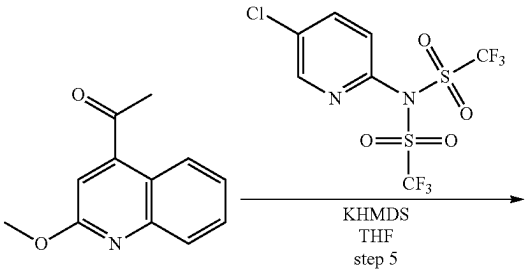

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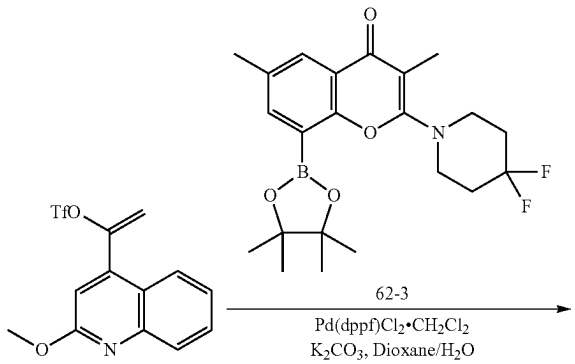

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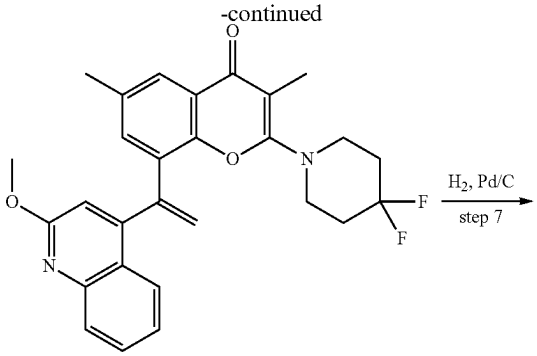

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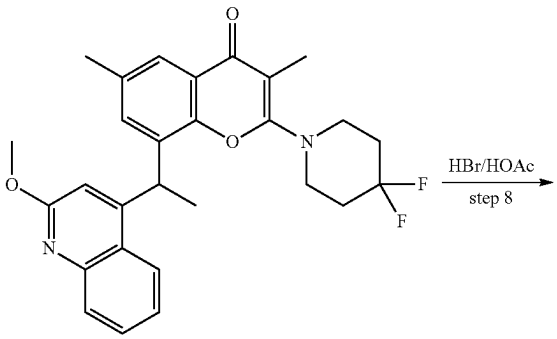

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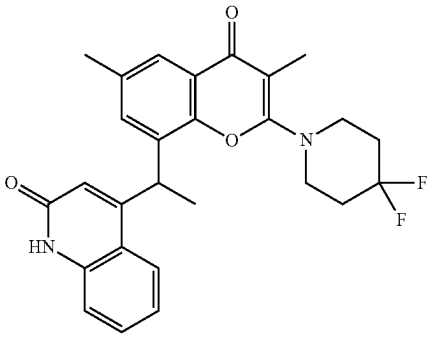


62

[0980] Step 1: To a solution of 5-5 (100 mg, 0.319 mmol) in DCM (1.5 mL) was added 3-chloroperbenzoic acid (200.8 mg, 0.989 mmol), the reaction mixture was stirred at 20° C. for 2 hrs. The reaction mixture was quenched with saturated $Na_2S_2O_3$ and extracted with DCM. The combined organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to give 62-1 (110 mg).

[0981] Step 2: A mixture of 62-1 (0.9 g, 2.607 mmol) and 4,4-difluoropiperidine (2.3 mL, 20.857 mmol) was stirred at 50° C. for 1 hr. The reaction mixture was quenched with H_2O and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (eluted with EtOAc in Petroleum ether from 0%~40%) to give 62-2 (700 mg).

[0982] Step 3: To a mixture of 62-2 (200 mg, 0.537 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (136.45 mg, 0.537 mmol) in dioxane (1.5 mL) were added KOAc (105.5 mg,

1.075 mmol), KBr (127.9 mg, 1.075 mmol) and Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (43.9 mg, 0.054 mmol), the reaction mixture was stirred at 110° C. for 16 hrs under N_2. The reaction mixture was concentrated and the residue was purified by silica gel column (eluted by EtOAc in petroleum ether from 0%~75%) to give 62-3 (200 mg).

[0983] Step 4: To a solution of 4-bromo-2-methoxyquinoline (500 mg, 2.100 mmol) and tributyl(1-ethoxyvinyl) tin (0.780 mL, 2.310 mmol) in DMF (5 mL) was added bis (triphenylphosphine)palladium(II) dichloride (81.7 mg, 0.105 mmol), the reaction was stirred at 120° C. for 1 hr under N_2. Saturated KF solution was added into the above reaction mixture and stirred at 25° C. for 1 hr. The mixture was filtered through a Celite pad and the filter cake was washed with EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in THF, and HCl (1 M) was added. The resulting solution was stirred at 25° C. for 0.5 hr. The reaction mixture was quenched with saturated $NaHCO_3$, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated to give 62-4 (270 mg), which was used directly in next step.

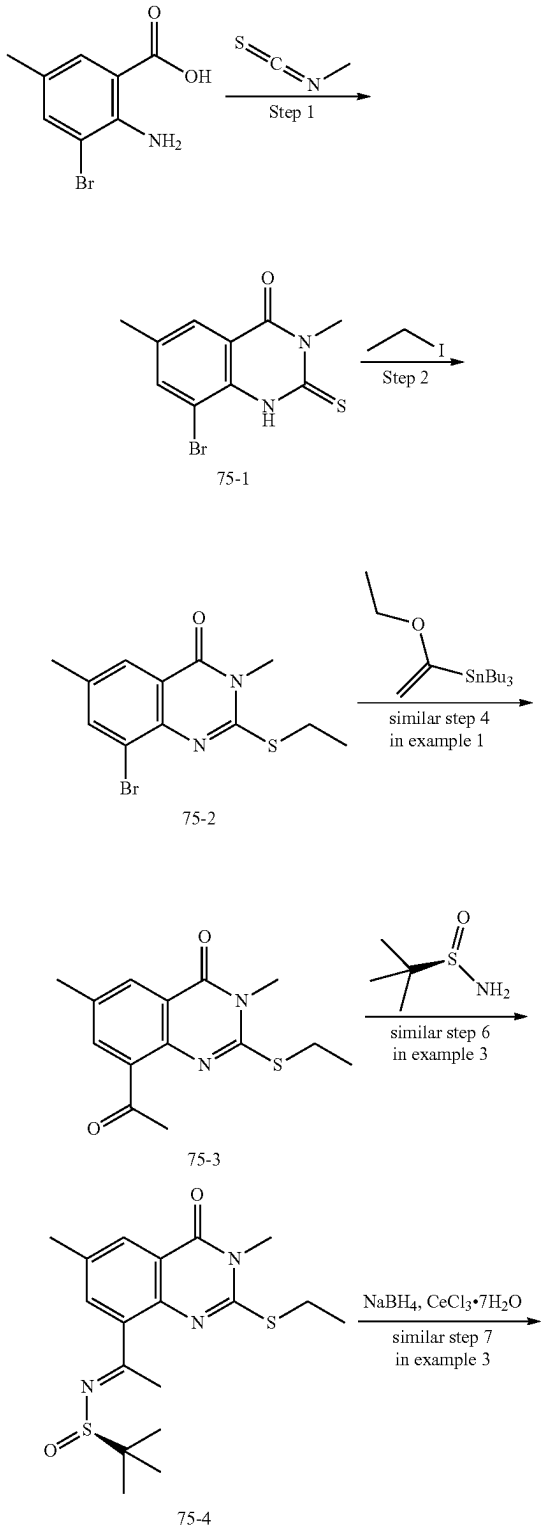
[0984] Step 5: To a solution of 62-4 (80 mg, 0.398 mmol) in THF (1.5 mL) was added potassium bis(trimethylsilyl) azanide (0.517 mL, 0.517 mmol) at −65° C., the reaction mixture was stirred at −65° C. for 0.5 hr. Then a solution of N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl) methanesulfonamide (234.2 mg, 0.596 mmol) in THF (0.5 mL) was added into the above mixture and stirred at −65° C. for 0.5 hr. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (eluted with DCM in petroleum ether from 0%~75%) to give 62-5 (40 mg).

[0985] Step 6: To a mixture of 62-5 (80 mg, 0.240 mmol) and 62-3 (100.64 mg, 0.240 mmol) in dioxane (2 mL) and H_2O (0.5 mL) were added Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (19.6 mg, 0.024 mmol) and K_2CO_3 (66.3 mg, 0.480 mmol), the reaction mixture was stirred at 110° C. for 16 hrs under N_2. The reaction mixture was concentrated and the residue was purified by silica gel column (eluted by EtOAc in petroleum ether from 0%~15%) to give 62-6 (80 mg).

[0986] Step 7: A mixture of 62-6 (80 mg, 0.168 mmol) and Pd/C (4.5 mg, 10% wt) in MeOH (1 mL) and THF (0.2 mL) was stirred at 20° C. under H_2 (15 Psi) for 2 hrs. The reaction mixture was filtered through a Celite pad, and the filter cake was washed with MeOH. The combined filtrate was concentrated to give 62-7 (75 mg), which was used directly in next step.

[0987] Step 8: A solution of 62-7 (40 mg, 0.084 mmol) in hydrobromic acid in acetic acid (0.5 mL, 2.595 mmol) was stirred at 100° C. for 0.5 hr. The solvent was removed and the residue was purified by prep-HPLC (water; Acetonitrile) to give compound 62 (13 mg). LCMS (ESI, m/z): $[M+H]^+$ =465.2; ^1H NMR (400 MHz, DMSO-d_6): δ 11.73 (s, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.70-7.47 (m, 2H), 7.36 (d, J=7.6 Hz, 1H), 7.21 (t, J=7.2 Hz, 1H), 6.02 (s, 1H), 5.19-5.14 (m, 1H), 3.28-3.14 (m, 4H), 2.40 (s, 3H), 1.91-1.80 (m, 7H), 1.66 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6): δ −95.73 (2F).

Example 15 Synthesis of Compound 75



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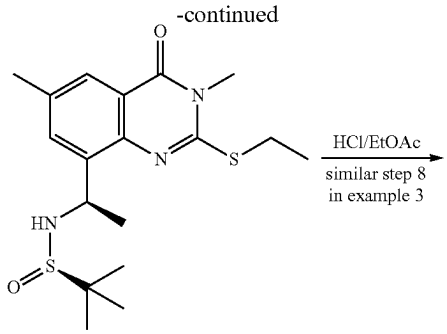
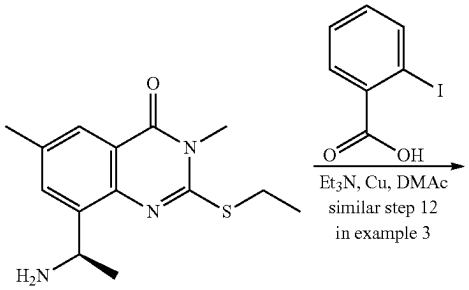


75-5



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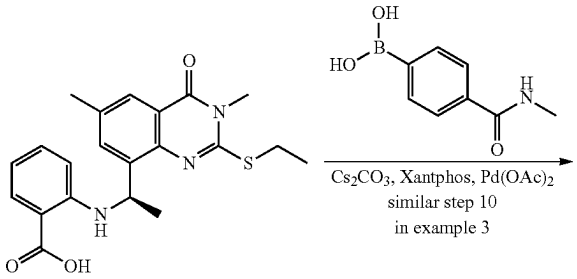

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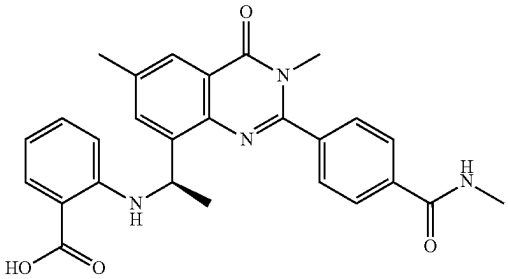


75

[0988] Step 1: To a solution of 2-amino-3-bromobenzoic acid (200 g, 0.87 mol) and isothiocyanatomethane (127 g, 1.74 mol) in EtOH (2000 mL) was added TEA (132 g, 0.13 mol). The reaction mixture was stirred at 80° C. under nitrogen for 4 hrs. Then the mixture was cooled to 0° C. The suspension mixture was filtered and the filtrate cake was washed with petroleum ether, dried in vacuum to afford 75-1 (241 g). LCMS (ESI, m/z): $[M+H]^+$=285.0.

[0989] Step 2: To a solution of 75-1 (140 g, 0.491 mol) and potassium carbonate (136 g, 0.98 mol) in THF (1400 mL) was added iodoethane (39.4 g, 0.25 mol). The reaction mixture was stirred at 65° C. for 6 hours. Then the reaction mixture was cooled to 0° C. and quenched with H_2O. The suspension was evaporated to remove THF and filtered. The filtrate cake was washed with water and dried in vacuum to afford 75-2 (130 g). LCMS (ESI, m/z): $[M+H]^+$=312.9.

[0990] Compound 75-3 was prepared from 75-2 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

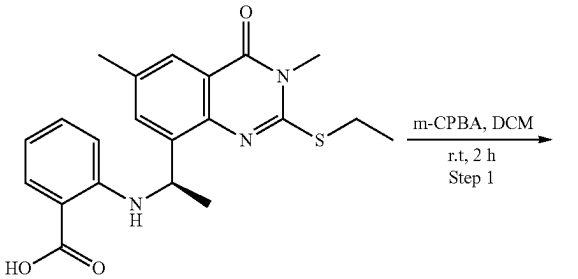
[0991] Compound 75-5 was prepared from 75-3 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

[0992] Compound 75-6 was prepared from 75-5 following the procedure for the synthesis of compound 5-8 in example 3.

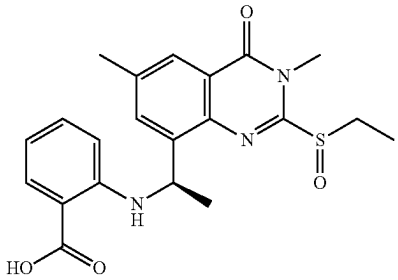
[0993] Compound 75-7 was prepared from 75-6 following the procedure for the synthesis of compound 5 in example 3.

[0994] Compound 75 was prepared from 75-7 following the procedure for the synthesis of compound 5-11 in example 3. LCMS (ESI, m/z): $[M+H]^+$=471.1; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 8.61-8.58 (m, 1H), 7.99 (d, J=8.4 Hz, 2H), 7.88-7.85 (m, 3H), 7.78 (d, J=6.8 Hz, 1H), 7.58 (d, J=1.6 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 6.48 (t, J=7.2 Hz, 1H), 6.39 (d, J=4.0 Hz, 1H), 5.49-5.43 (m, 1H), 3.41 (s, 3H), 2.83 (d, J=4.4 Hz, 3H), 2.39 (s, 3H), 1.53 (d, J=6.4 Hz, 3H).

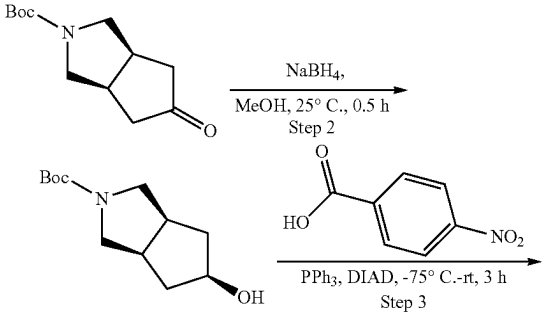
Example 16 Synthesis of Compound 82



75-7



82-1



82-2

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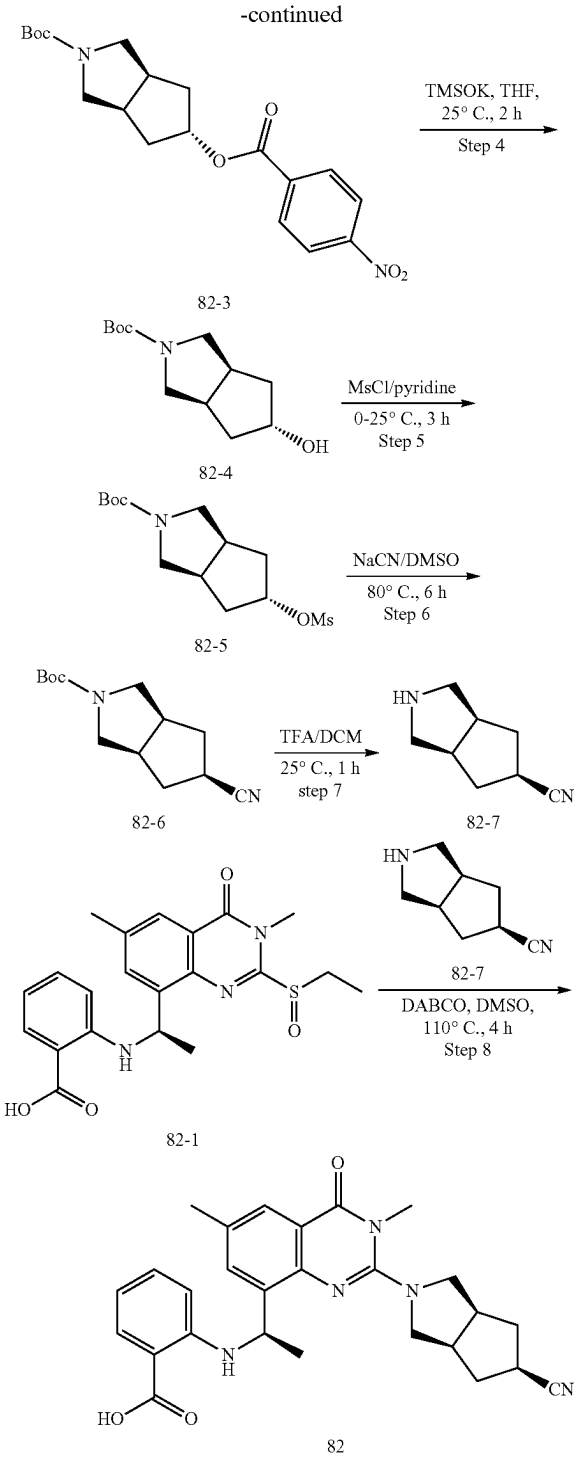


[0995] Step 1: To a stirred solution of 75-7 (800 mg, 2.02 mmol) in dichloromethane (16 mL) was added 3-chloroperbenzoic acid (451 mg, 2.22 mmol, 1.1 eq), the mixture was stirred at 25° C. for 1 h. Then another 0.3 eq of 3-chloroperbenzoic acid (123 mg, 0.61 mmol) was added and stirred at 25° C. for 1 h. The reaction mixture was diluted with dichloromethane, quenched with saturated sodium thiosulfate solution. The organic layer was separated out, washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuum to afford 82-1 (860 mg, crude), which was directly used in the next step without further purification.

[0996] Step 2: To a solution of tert-butyl (3aR,6aS)-5-oxohexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (2.00 g, 8.80 mmol) in MeOH (40 mL) was added NaBH4 (0.33 g, 8.80 mmol) at 0° C. The mixture was stirred at 25° C. for 0.5 h. The reaction mixture was dried in vacuum. The residue was treated with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 82-2 (3.90 g).

[0997] Step 3: To a mixture of 82-2 (3.90 g, 17.10 mmol), 4-nitrobenzoic acid (3.43 g, 20.52 mmol) and PPh_3 (5.38 g, 20.52 mmol) in THF (50 mL) was added dropwise a solution of DIAD (4.15 g, 20.52 mmol) in THF (30 mL) at −78° C. under nitrogen atmosphere. The mixture was warmed slowly to 25° C. and stirred for 3 hrs. The reaction mixture was concentrated in vacuum. The residue was purified by silica gel column (eluted with petroleum ether/EA=20/1~3/1) to give 82-3 (3.3 g).

[0998] Step 4: To a solution of 82-3 (3.3 g, 8.7 mmol) in THF (40 mL) was added TMSOK (5.58 g, 43.5 mmol). The mixture was stirred at 25° C. for 2 hrs. The reaction mixture was concentrated in vacuum. The residue was treated with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 82-4 (1.9 g).

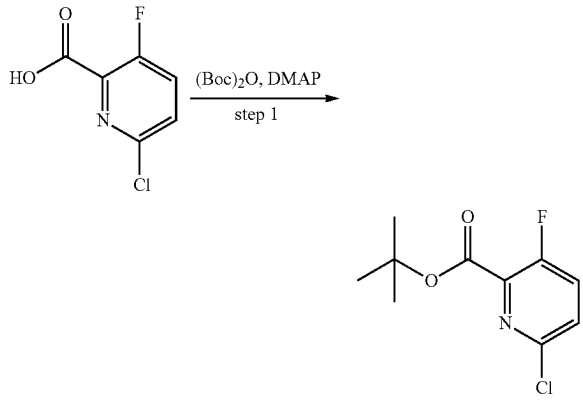
[0999] Step 5: To a solution of 82-4 (1.05 g, 4.60 mmol) in pyridine (10 mL) was added dropwise MsCl (1.57 g, 13.80 mmol) at 0° C. The mixture was stirred at 25° C. for 2 hrs. The mixture was treated with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 82-5 (2.60 g).

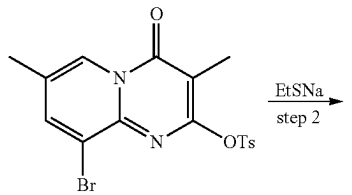
[1000] Step 6: A mixture of 82-5 (2.20 g, 7.20 mmol) and NaCN (1.76 g, 36.00 mmol) in DMSO (25 mL) was stirred at 80° C. for 6 hrs under nitrogen atmosphere. The mixture was treated with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column (eluted with petroleum ether/EA=10/1~2/1) to give 82-6 (0.71 g).

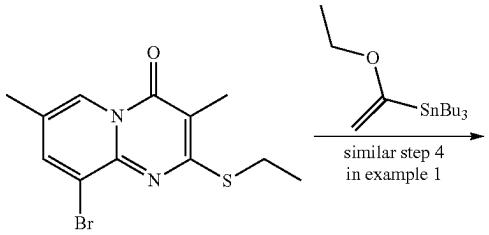
[1001] Step 7: To a stirred solution of 82-6 (200 mg, 0.84 mmol) in DCM (2 mL) was added TFA (0.5 mL). The mixture was stirred at 25° C. for 1 h. The mixture was concentrated in vacuum to give 82-7 (89 mg).

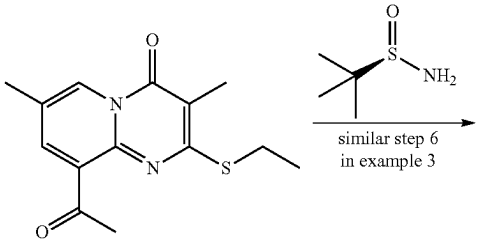
[1002] Step 8: A mixture of 82-1 (100 mg, 0.24 mmol), 82-7 (181.51 mg, 0.73 mmol) and DABCO (216.98 mg, 1.93 mmol) in DMSO (5 mL) was stirred at 110° C. for 16 hrs under nitrogen atmosphere. The reaction mixture was diluted with water, adjusted to pH=2 with 2 N hydrochloric acid and extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by Prep-HPLC (Columns: Sunfire 5 μm 19-150 mm; Mobile phase: ACN/H_2O (0.1% FA); Gradient: 40-80%, 8 min; flow rate: 60 mL/min) to afford 82 (26.20 mg). LCMS (ESI, m/z): $^+$=472.1; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.43 (s, 1H), 7.77 (d, J=6.4 Hz, 1H), 7.69 (s, 1H), 7.43 (d, J=1.6 Hz, 1H), 7.18 (t, J=7.2 Hz, 1H), 6.51-6.42 (m, 2H), 5.38 (s, 1H), 3.55-3.39 (m, 7H), 2.99-2.94 (m, 1H), 2.77 (s, 2H), 2.43-2.35 (m, 2H), 2.30 (s, 3H), 1.78-1.67 (m, 2H), 1.55 (d, J=6.8 Hz, 3H).

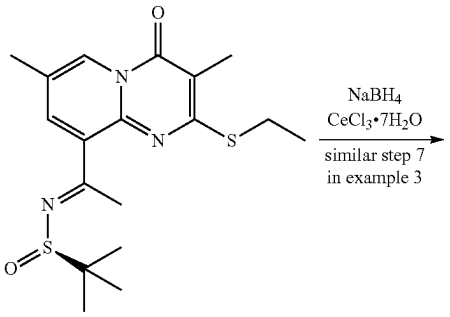
Example 17 Synthesis of Compound 86











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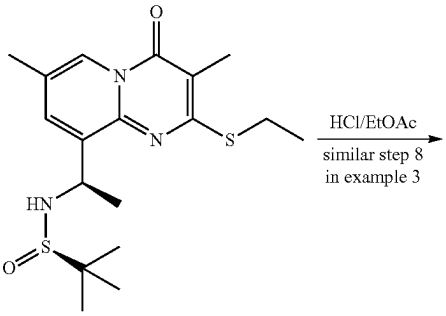
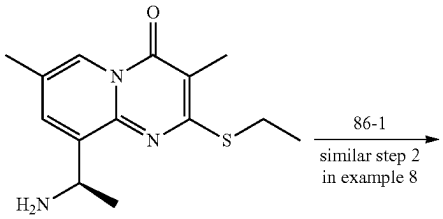
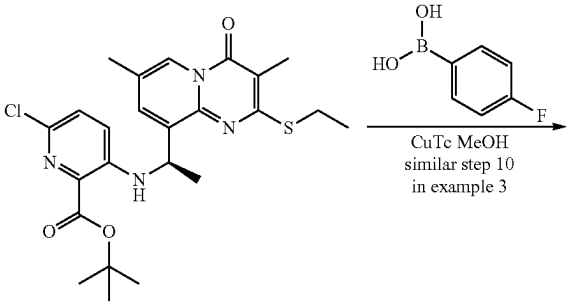
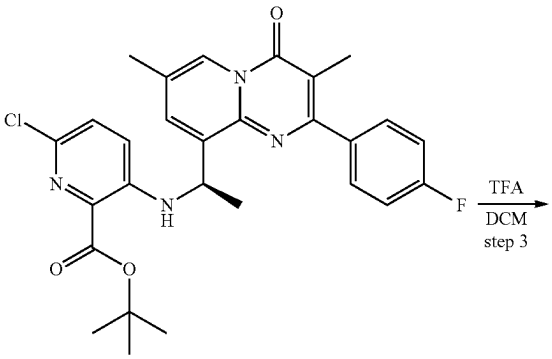
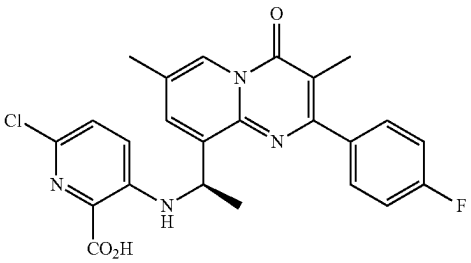










[1003] Step 1: A mixture of 6-chloro-3-fluoropyridine-2-carboxylic acid (5 g, 28.5 mmol), di-tert-butyl dicarbonate (13.1 mL, 57.0 mmol) and 4-dimethylaminopyridine (0.7 g, 5.7 mmol) in tetrahydrofuran (80 mL) was stirred at 40° C. overnight. The mixture was diluted with water, and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=10/1) to give 86-1 (6.5 g).

[1004] Step 2: A mixture of 3-3 (2.8 g, 6.62 mmol) and sodium ethanethiolate (1.39 g, 16.54 mmol) in acetonitrile (50 mL) was stirred at 50° C. for 2 hours under nitrogen atmosphere. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 86-2 (1.3 g).

[1005] Compound 86-3 was prepared from 86-2 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[1006] Compound 86-4 was prepared from 86-3 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

[1007] Compound 86-5 was prepared from 86-4 following the procedure for the synthesis of compound 5-8 in example 3.

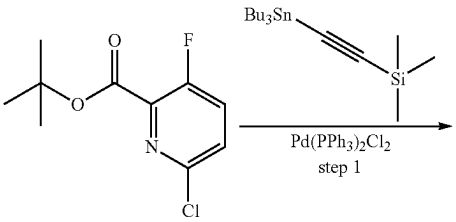
[1008] Compound 86-6 was prepared from 86-5 following the procedure for the synthesis of compound 5-9 in example 3.

[1009] Compound 86-7 was prepared from 86-6 and 86-1 following the procedure for the synthesis of compound 11-5 in example 8.

[1010] Compound 86-8 was prepared from 86-7 and (4-fluorophenyl)boronic acid following the procedure for the synthesis of compound 5-11 in example 3.

[1011] Step 3: To a mixture of 86-8 (35 mg, 0.067 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL) at 0° C. The mixture was stirred at rt for 16 hours, concentrated and purified by prep-HPLC (acetonitrile/0.05% FA in water: 15%~95%) to give 86 (12.8 mg). LCMS (ESI, m/z): $^{+}$=467.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.05 (brs, 1H), 8.71 (s, 1H), 8.47-8.32 (m, 1H), 7.84-7.75 (m, 2H), 7.72-7.68 (m, 1H), 7.41-7.32 (m, 2H), 7.31-7.24 (m, 1H), 7.00-6.89 (m, 1H), 5.43-5.32 (m, 1H), 2.34 (s, 3H), 2.23 (s, 3H), 1.63 (d, J=6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ−112.46 (1F).

Example 18 Synthesis of Compounds 113 and 114



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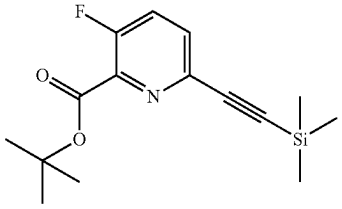

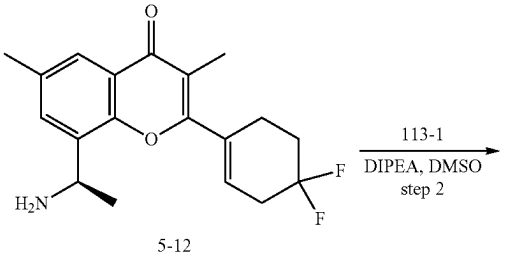

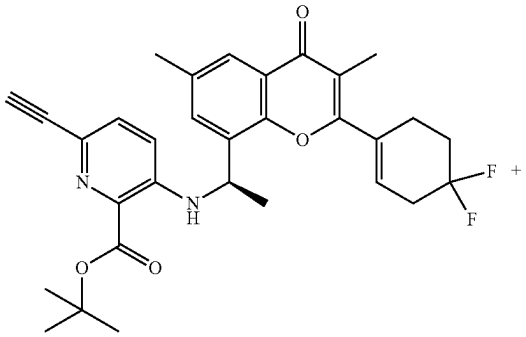

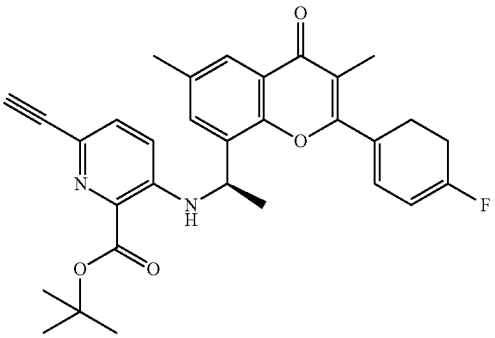

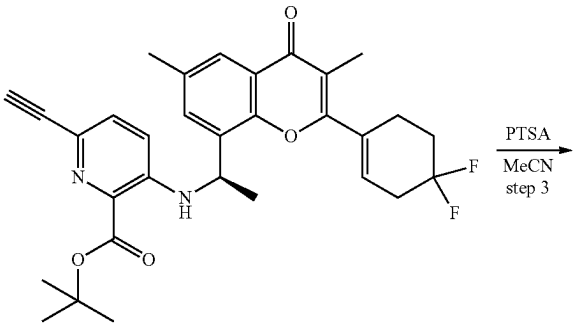

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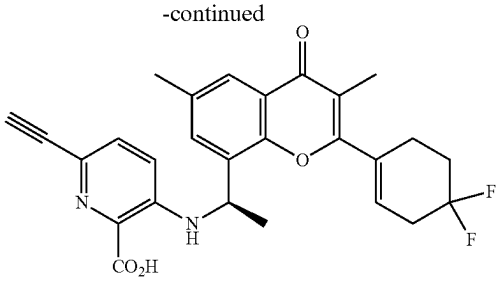

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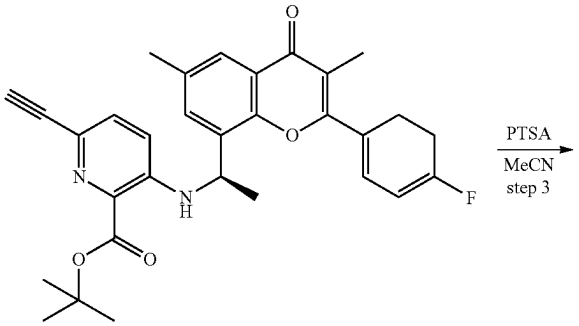
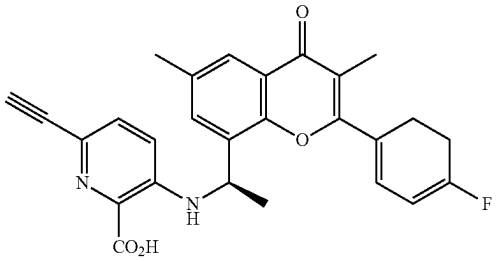


113-2A



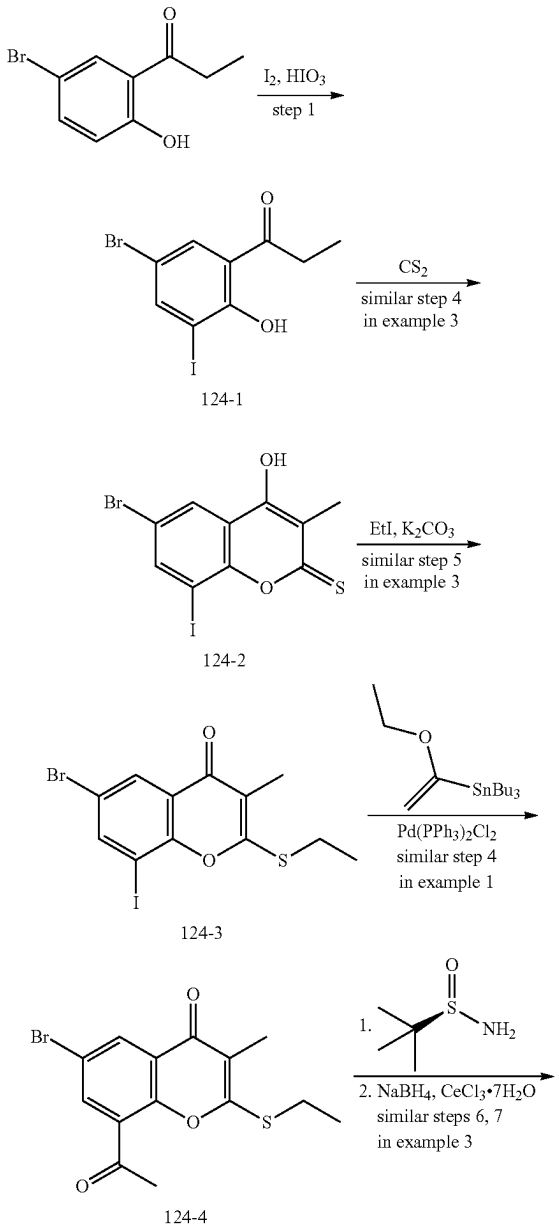
114

[1012] Step 1: To a solution of 86-1 (462 mg, 2.0 mmol) in toluene (5 mL) was added bis(triphenylphosphine)palladium(II) chloride (155.2 mg, 0.20 mmol), trimethyl silane (1.5 g, 3.99 mol). The resulting mixture was irradiated at 120° C. with microwave for 1 h under N_2. The mixture was quenched with water, extracted with DCM, the organic layer was concentrated to give a residue which was purified by Combi flash (ethyl acetate in petroleum ether=15%) to give 113-1 (593 mg).

[1013] Step 2: To a solution of 5-12 (300 mg, 0.90 mmol) in DMSO (1 mL) were added 113-1 (343.24 mg, 1.17 mmol) and ethyldiisopropylamine (0.45 mL), and the reaction was irradiated at 105° C. with microwave for 0.5 hours. The mixture was diluted with ethyl acetate, washed with water, organic layer was purified by combi flash (ethyl acetate in petroleum ether=30%) to give 113-2 (40 mg) and 113-2A (80 mg).

[1014] Step 3: To a solution of 113-2 (40 mg, 0.075 mmol) in acetonitrile (1 mL) was added p-toluenesulfonic acid (64.4 mg, 0.37 mmol), the mixture was stirred at 50° C. for 4 hours. The mixture was purified by pre-HPLC (acetonitrile/0.05% FA in water: 5%~95%) to give 113 (7 mg). LCMS (ESI, m/z): $^{+}$=479.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 14.2-11.37 (m, 1H), 8.75-8.47 (m, 1H), 7.77-7.67 (m, 1H), 7.58-7.51 (m, 1H), 7.44-7.34 (m, 1H), 6.99-6.84 (m, 1H), 6.14 (s, 1H), 5.20-5.05 (m, 1H), 4.07 (s, 1H), 2.92-2.78 (m, 2H), 2.71-2.63 (m, 2H), 2.35 (s, 3H), 2.28-2.14 (m, 2H), 2.03 (s, 3H), 1.67-1.56 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −99.50 (2F). Compound 114 was prepared from 113-2A following the procedure for the synthesis of compound 113. LCMS (ESI, n/z): $^{+}$=459.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.85-11.85 (m, 1H), 8.62-8.42 (m, 1H), 7.72 (s, 1H), 7.56-7.47 (m, 1H), 7.44-7.37 (m, 1H), 6.99-6.87 (m, 1H), 6.56-6.45 (m, 1H), 5.88-5.76 (m, 1H), 5.21-5.07 (m, 1H), 4.08 (s, 1H), 2.94-2.84 (m, 2H), 2.71-2.56 (m, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.67-1.56 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −95.05 (1F).

Example 19 Synthesis of Compound 124



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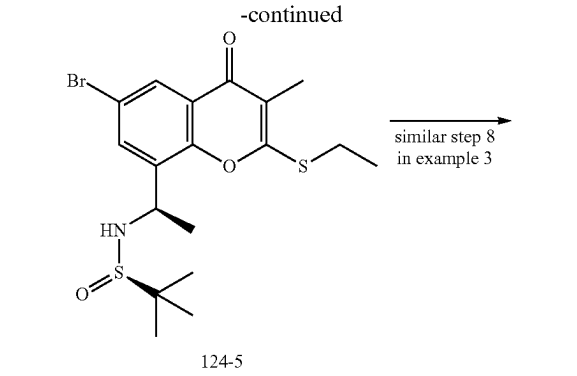
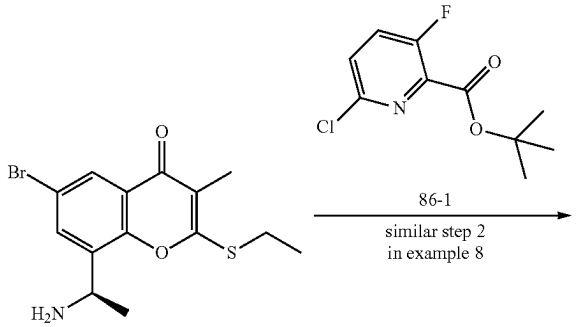
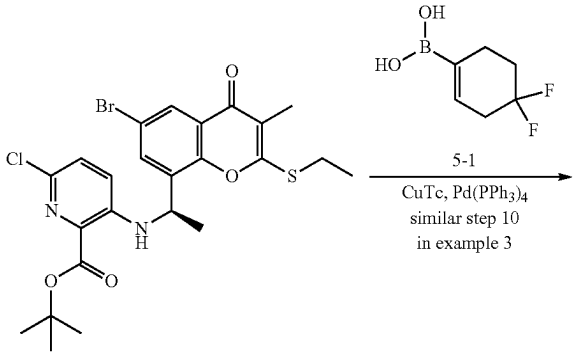


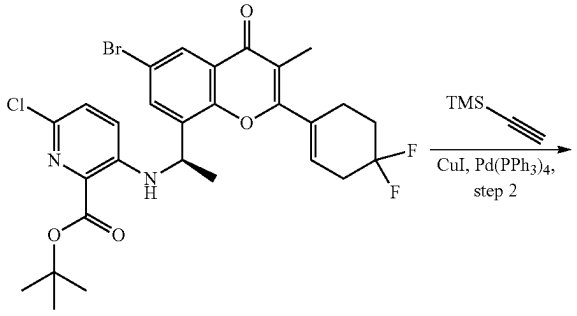
124-5



124-6



124-7



124-8

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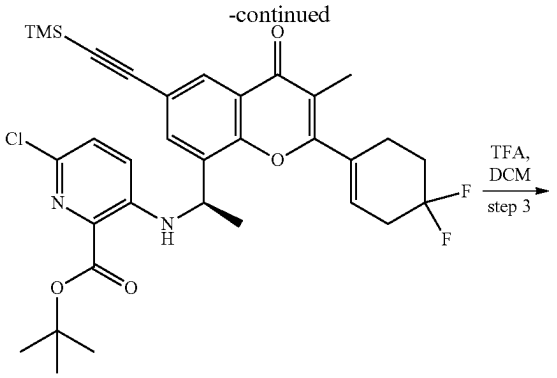
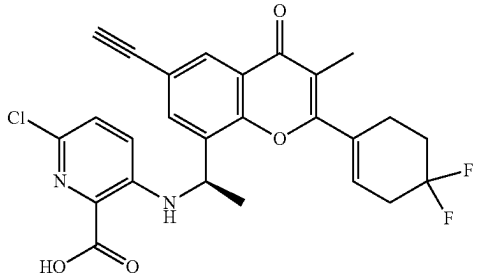


124-9



124

[1015] Step 1: To a mixture of 1-(5-bromo-2-hydroxyphenyl)propan-1-one (20 g, 87.31 mmol) and iodine (8.85 g, 34.84 mmol) in EtOH (60 mL) was added dropwise a solution of HIO_3 (3.1 g, 19.39 mmol) in water (6 mL) with stirring over 5 min and then the reaction mixture was stirred for 18 hrs at 35 to 40° C. The reaction was diluted with water and the precipitation was filtered. The solid residue was washed with saturated sodium thiosulfate solution and then with cold water. The product was recrystallized from ethanol to give 124-1 (31.7 g). LCMS (ESI, m/z): $^{+}$=357.0.

[1016] Compound 124-2 was prepared from 124-1 and carbon disulfide following the procedure for the synthesis of compound 5-4 in example 3.

[1017] Compound 124-3 was prepared from 124-2 and iodoethane following the procedure for the synthesis of compound 5-5 in example 3.

[1018] Compound 124-4 was prepared from 124-3 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[1019] Compound 124-5 was prepared from 124-4 following the procedure for the synthesis of compounds 5-7 and 5-8 in example 3.

[1020] Compound 124-6 was prepared from 124-5 following the procedure for the synthesis of compound 5-9 in example 8.

[1021] Compound 124-7 was prepared from 124-6 and 86-1 following the procedure for the synthesis of compound 11-5 in example 8.

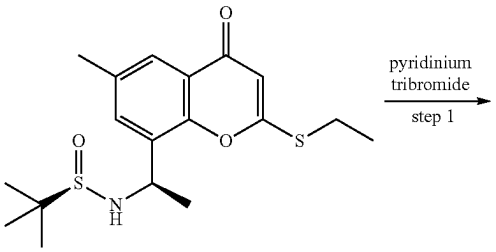
[1022] Compound 124-8 was prepared from 124-7 and 5-1 following the procedure for the synthesis of compound 5-11 in example 3.

[1023] Step 2: The mixture of 124-8 (84 mg, 0.14 mmol), ethynyltrimethylsilane (25 mg, 0.26 mmol), Pd $(PPh_3)_4$ (26 mg, 0.022 mmol), PPh_3 (6.5 mg, 0.025 mmol) and CuI (6 mg, 0.032 mmol) in TEA (4 mL) was stirred at 70° C. for 4

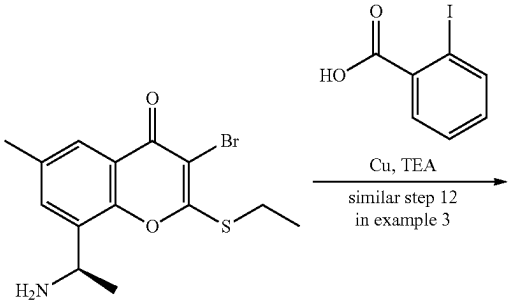
hrs under N_2. The reaction mixture was concentrated and the residue was purified by flash silica gel column (eluted with 0 to 35% EtOAc in petroleum) to give 124-9 (50 mg). LCMS (ESI, nm/z): +=649.4.

[1024] Step 3: To a solution of 124-9 (40 mg, 0.064 mmol) in DCM (4 mL) was added TFA (1 mL) and the mixture was stirred at room temperature for 3.5 hrs. The reaction mixture was concentrated and the residue was purified by C18 reverse phase column (Acetonitrile; 0.05% TFA in water: 0 to 50%, keep at 50%) to afford 124 (11.98 mg) as 2 TFA salts. LCMS (ESI, m/z): $^{+}$=497.2; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 8.09 (s, 1H), 7.74 (s, 1H), 7.28 (d, J=8.8 Hz, 1H), 7.07 (d, J=8.8 Hz, 1H), 6.14 (s, 1H), 5.19-5.09 (m, 1H), 3.59 (s, 1H), 2.89-2.69 (m, 4H), 2.34-2.17 (m, 2H), 2.09 (s, 3H), 1.71 (d, J=6.8 Hz, 3H); ^{19}F NMR (376 MHz, MeOH-d_4, ppm): δ −98.02 (2F).

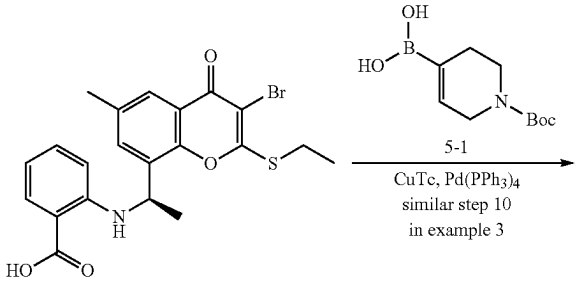
Example 20 Synthesis of Compound 125



16-7



125-1



125-2

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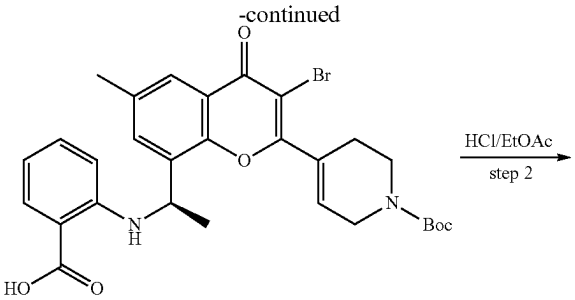

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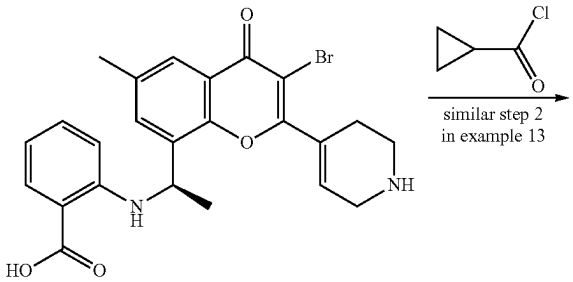
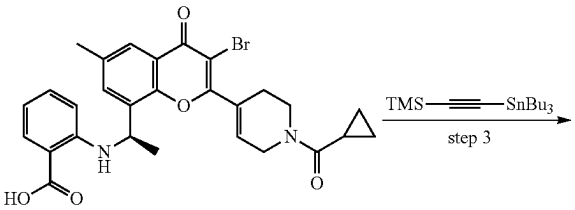
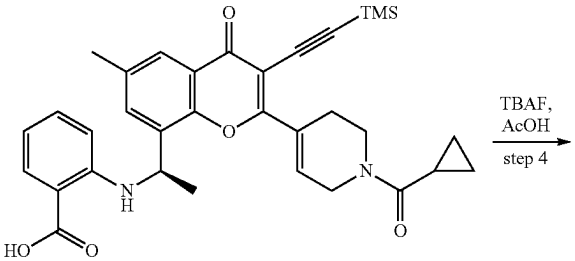


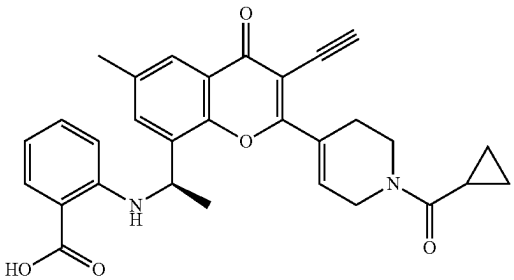
125-4



125-5



125-6



125

[1025] Step 1: To a solution of 16-7 (1000.0 mg, 2.61 mmol) in dichloromethane (10 mL) was added potassium carbonate (940.1 mg, 6.80 mmol) and pyridinium tribromide (870.2 mg, 2.72 mmol). The reaction was stirred at room temperature for 2 hrs. The reaction was diluted with water and extracted with ethyl acetate. The organic layers were concentrated and purified using C18 flash (eluted with

acetonitrile in 0.05% trifluoroacetic acid in water from 5% to 95%) to give 125-1 (388 mg).

[1026] Compound 125-2 was prepared from 125-1 and 2-iodobenzoic acid following the procedure for the synthesis of compound 5 in example 3.

[1027] Compound 125-3 was prepared from 125-2 and 5-1 following the procedure for the synthesis of compound 5 in example 3.

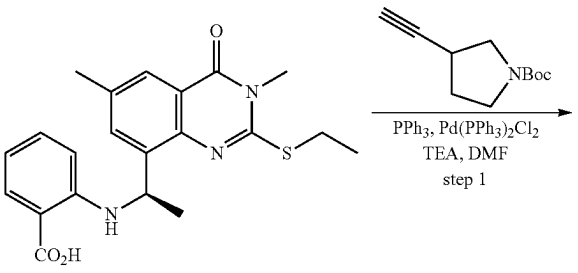
[1028] Step 2: To a solution of 125-3 (255 mg, 0.44 mmol) in ethyl acetate (5.0 mL) was added 4 M HCl in ethyl acetate (5 mL) at 0° C. The reaction was stirred at room temperature for 2 hrs. The solution was concentrated to give 125-4 (211 mg, crude), which was used directly in next step.

[1029] Compound 125-5 was prepared from 125-4 and cyclopropanecarbonyl chloride following the procedure for the synthesis of compound 43 in example 13.

[1030] Step 3: To a solution of 125-5 (168 mg, 0.31 mmol) in toluene (5 mL) were added tributyl(trimethylsilylethynyl) tin (330.4 mg, 0.85 mmol) and bis(triphenylphosphine) palladium(II) chloride (47.4 mg, 0.061 mmol). Then the reaction was stirred at 110° C. for 16 hrs under N_2. The solution was concentrated and the residue was purified using silica gel column chromatography (eluted with methanol in dichloromethane from 0% to 10%), then further purified by C18 flash (eluted with acetonitrile in water (0.05% trifluoroacetic acid) from 5% to 95%) to give 125-6 (33 mg).

[1031] Step 4: To a solution of 125-6 (32 mg, 0.056 mmol) in tetrahydrofuran (2 mL) was added 4 drops of acetic acid. Then tetrabutylammonium fluoride solution (2 mL, 1 M in THF) was added into the mixture. The reaction was stirred at room temperature for 20 mins. The reaction was purified by C18 flash (eluted with acetonitrile in water (0.05% trifluoroacetic acid) from 5% to 95%), then further purified by prep-HPLC to give the desired product 125 (3.2 mg). LCMS (ESI, m/z): $^{+}$=497.4; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.87-8.82 (m, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.72 (s, 1H), 7.53 (s, 1H), 7.30-7.20 (m, 1H), 7.15-7.11 (m, 1H), 6.53-6.49 (m, 1H), 6.39-6.36 (m, 1H), 5.19-5.10 (m, 1H), 4.56-4.54 (m, 2H), 4.26-4.24 (m, 1H), 3.95-3.90 (m, 1H), 3.71-3.69 (m, 1H), 2.81-2.79 (m, 1H), 2.69-2.67 (m, 1H), 2.42 (s, 3H), 2.09-1.97 (m, 1H), 1.64-1.57 (m, 3H), 0.81-0.72 (m, 4H).

Example 21 Synthesis of Compound 140



43-2

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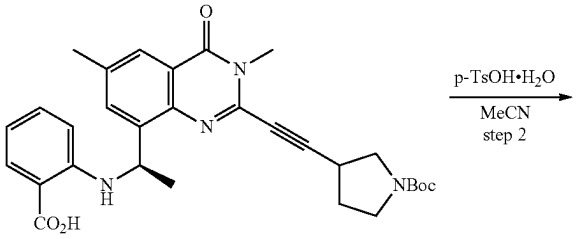
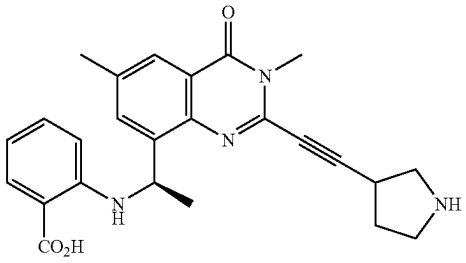


140-1

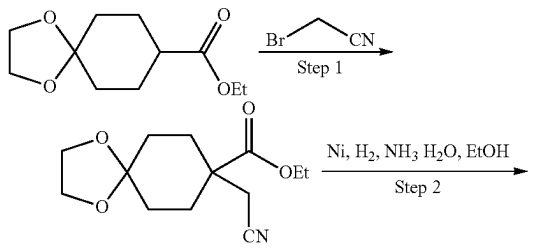


140

[1032] Step 1: A mixture of 43-2 (110 mg, 0.28 mmol), 2-methylpropan-2-yl 3-ethynyltetrahydropyrrole-1-carboxylate (162 mg, 0.83 mmol), triphenylphosphine (15 mg, 0.055 mmol), bis(triphenylphosphine) palladium(II) chloride (43.1 mg, 0.055 mmol) and triethylamine (1.54 mL, 11.08 mmol) in N, N-dimethylformamide (1.5 mL) was stirred at room temperature for 20 min under nitrogen atmosphere. To the mixture was added cuprous iodide (11 mg, 0.055 mmol), then stirred at 80° C. for 16 hours under N_2 atmosphere. The reaction mixture was acidified to pH~5 with ammonium chloride solution at 0° C., extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 140-1 (80 mg).

[1033] Step 2: To a mixture of 140-1 (80 mg, 0.15 mmol) in acetonitrile (2 mL) was added p-toluenesulfonic acid monohydrate (143 mg, 0.75 mmol) at room temperature. The mixture was stirred at 50° C. for 1 hour, and concentrated. The residue was purified by prep-HPLC (acetonitrile/0.05% FA in water: 15%~95%) to give 140 (25 mg). LCMS (ESI, m/z): $^{+}$=431.2; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.87-7.82 (m, 1H), 7.81-7.74 (m, 1H), 7.67-7.60 (m, 1H), 7.06-6.93 (m, 1H), 6.55-6.38 (m, 2H), 5.27-5.12 (m, 1H), 3.77-3.56 (m, 6H), 3.52-3.38 (m, 2H), 2.44-2.33 (m, 5H), 1.72-1.59 (m, 3H).

Example 22 Synthesis of Compounds 157 and 158



157-1

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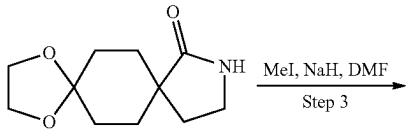
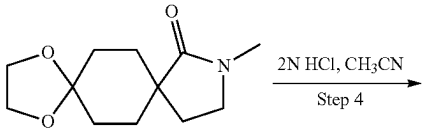


157-2



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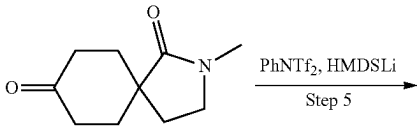

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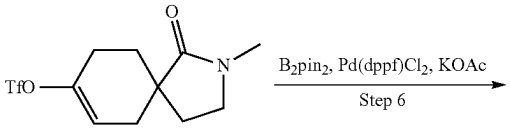

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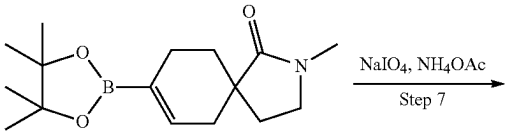

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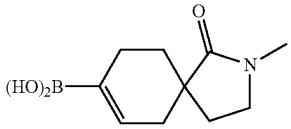

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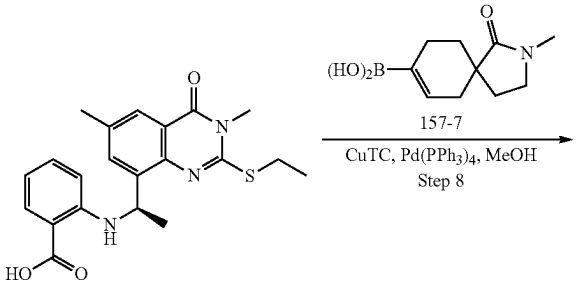
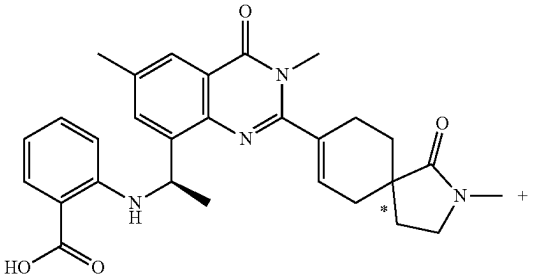


75-7



isomer 1
157

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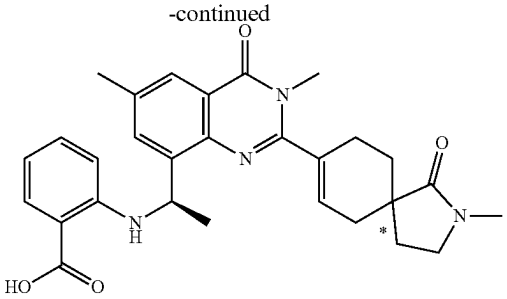


isomer 2
158

[1034] Step 1: To a solution of ethyl 1,4-dioxaspiro[4.5] decane-8-carboxylate (15 g, 0.07 mol) in THF (120 mL) was added LDA (70 mL, 0.14 mol, 2 M in THF) dropwise and stirred for 1 h at −78° C. under nitrogen. Then 2-bromoacetonitrile (12.59 g, 0.11 mol) and DMPU (8.97 g, 0.07 mol) in THF (30 mL) was added dropwise for 0.5 hrs. The reaction mixture was stirred at 25° C. for 15 hrs. The reaction was quenched with H_2O, and extracted with EtOAc. The organic layers were combined and washed with water, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column (eluted with petroleum ether/EA=6/1~2/1) to afford 157-1 (8.00 g).

[1035] Step 2: To a solution of 157-1 (8.00 g, 0.03 mol) in EtOH (150 mL), was added $NH_3 \cdot H_2O$ (16.61 g, 0.47 mol) and then raney nickle powder (18.55 g, 0.32 mol). The reaction mixture was stirred for 16 hrs at 90° C. in a sealed tube under H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuo to afford 157-2 (6.20 g).

[1036] Step 3: To a solution of 157-2 (4.60 g, 21.77 mmol) in DMF (46 mL) was added NaH (1.74 g, 43.55 mol) at 0° C. The reaction mixture was stirred for 0.5 h at 0° C. under nitrogen and then treated with MeI (6.18 g, 43.55 mol) at 0° C. and stirred for 16 h at 25° C. The reaction was quenched with water and extracted by EA, the organic layer was combined and washed with water and brine, dried over Na_2SO_4 and concentrated to afford 157-3 (4.40 g).

[1037] Step 4: To a solution of 157-3 (4.30 g, 19.09 mmol) in MeCN (33 mL) was added 2N HCl (33 mL) dropwise. The reaction mixture was stirred for 2 hrs at 25° C. under nitrogen. The reaction mixture was diluted with water. Then the mixture was neutralized with saturated sodium carbonate solution to pH=9. The organic phase was separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuum. The resulted residue was purified by silica gel column (eluted with petroleum ether/EA=10/1~3/1) to afford 157-4 (3.10 g).

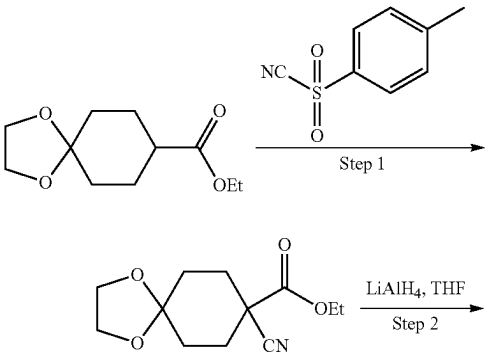
[1038] Step 5: A mixture of 157-4 (3.10 g, 17.11 mmol) and $PhNTf_2$ (9.16 g, 25.66 mmol) in THF (40 mL) was cooled to −78° C. under nitrogen atmosphere. LiHMDS (25.7 mL, 25.66 mmol, 1 N in THF) was then added dropwise at −78° C. Then the resulting mixture was stirred for 2 hrs at 25° C. The reaction was quenched with water and extracted by EA, the organic layers were combined and washed with brine, dried over Na_2SO_4 and concentrated to afford 157-5 (2.00 g crude), which was used directly in next step.

[1039] Step 6: To a solution of 157-5 (2.00 g, 6.38 mmol) in 1,4-dioxane (20 mL) was added $B2pin_2$ (1.62 g, 6.38 mmol), KOAc (1.88 g, 19.15 mmol) and $Pd(dppf)Cl_2$ (467.1 mg, 0.64 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 90° C. for 4 hrs. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuum. The residue was purified by silica gel column (eluted with petroleum ether/EA=10/1~3/1) to afford 157-6 (200.00 mg).

[1040] Step 7: A mixture of 157-6 (600.0 mg, 2.06 mmol), $NH_{40}Ac$ (476.5 mg, 6.18 mmol) and $NaIO_4$ (1.32 g, 6.18 mmol) in ACN: H_2O=1:1 (10 mL) was stirred for 8 hrs at 25° C. under nitrogen atmosphere. The resulting mixture was filtered and concentrated. The residue was purified by prep-HPLC (columns: sunfire 5 μm 19-150 mm, Mobile Phase: ACN-H_2O (0.1% FA), Gradient: 50-90-8GT-300VL) to afford 157-7 (180.00 mg).

[1041] Step 8: To a solution of 157-7 (94.64 mg, 0.45 mmol) in MeOH (20 mL) was added 75-7 (60 mg, 0.15 mmol), CuTC (57.55 mg, 0.30 mmol) and $Pd(PPh_3)_4$ (34.87 mg, 0.030 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 25° C. for 6 hrs. The mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (columns: sunfire 5 μm 19-150 mm, Mobile Phase: ACN-H_2O (0.1% FA), Gradient: 50-90-8GT-300VL) to afford 157 (isomer 1, 10.10 mg) and 158 (isomer 2, 13.30 mg). Compound 157: LCMS (ESI, m/z): $^+$=501.3; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.87-7.85 (m, 2H), 7.59 (s, 1H), 7.08 (t, J=7.6 Hz, 1H), 6.51-6.39 (m, 2H), 6.14 (s, 1H), 5.57 (d, J=6.4 Hz, 1H), 3.62 (s, 3H), 3.47 (t, J=6.8 Hz, 2H), 2.89 (s, 3H), 2.66-2.47 (m, 3H), 2.39 (s, 3H), 2.15-1.99 (m, 4H), 1.75-1.72 (m, 1H), 1.58 (d, J=6.4 Hz, 3H).

[1042] Compound 158: LCMS (ESI, m/z): $^+$=501.3; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.88-7.86 (m, 2H), 7.59 (s, 1H), 7.08 (t, J=7.2 Hz, 1H), 6.53-6.40 (m, 2H), 6.13 (s, 1H), 5.54 (q, J=6.4 Hz, 1H), 3.62 (s, 3H), 3.47 (t, J=6.8 Hz, 2H), 2.89 (s, 3H), 2.62 (s, 2H), 2.54-2.49 (m, 1H), 2.39 (s, 3H), 2.20-1.99 (m, 4H), 1.74-1.72 (m, 1H), 1.59 (d, J=6.4 Hz, 3H).



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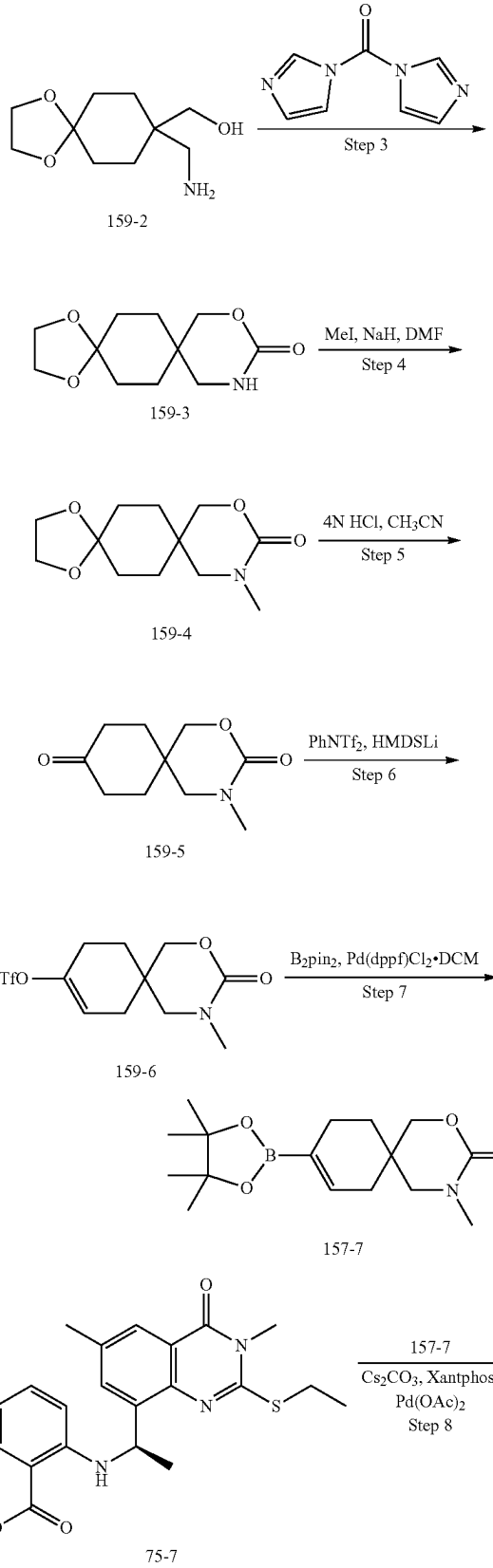

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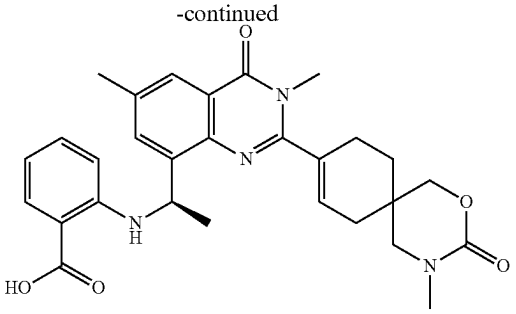


159

[1043] Step 1: To a solution of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (13.0 g, 0.06 mol) in THF (130 mL) at −70° C. under nitrogen atmosphere was added LDA (36.3 mL, 0.09 mol). The mixture was stirred at −70° C. for 1 h. Then 4-methylbenzenesulfonyl cyanide (21.77 g, 0.06 mol) in THF (30 mL) was added and stirred at −70° C. and stirred for 1 h. The reaction mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was purified by silica gel column (eluted with petroleum ether/EA=10/1~2/1) to give 159-1 (10.0 g).

[1044] Step 2: To a mixture of 159-1 (10 g, 41.78 mmol) in THF (100 mL) was added $LiAlH_4$ (1.90 g, 50.14 mmol) at 0° C. under nitrogen atmosphere. The resulting solution was stirred at 25° C. for 2 hrs under nitrogen atmosphere. The reaction was quenched $Na_2SO_4 \cdot 10H_2O$, filtered, and concentrated to give 159-2 (6.00 g).

[1045] Step 3: To a mixture of 159-2 (5.8 g, 28.8 mmol) and N, N-diisopropylethylamine (3.71 g, 28.8 mmol) in DCM (100 mL) was added 1-[(imidazole-1-yl)carbonyl] imidazole (4.67 g, 28.8 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 25° C. for 16 hrs. The mixture was quenched with water and extracted with DCM. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column (eluted with petroleum ether/EA=5/1~2/1) to give 159-3 (2.7 g).

[1046] Step 4: To a solution of 159-3 (2.7 g, 11.88 mmol) in DMF (40 mL) was added NaH (570 mg, 14.25 mmol) at 0° C. under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h under nitrogen atmosphere. To the above mixture was added MeI (2.19 g, 15.44 mmol) dropwise at 0° C. under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 hrs. The reaction was quenched with water, extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column (eluted with DCM/MeOH=50/1~20/1) to give 159-4 (2.20 g).

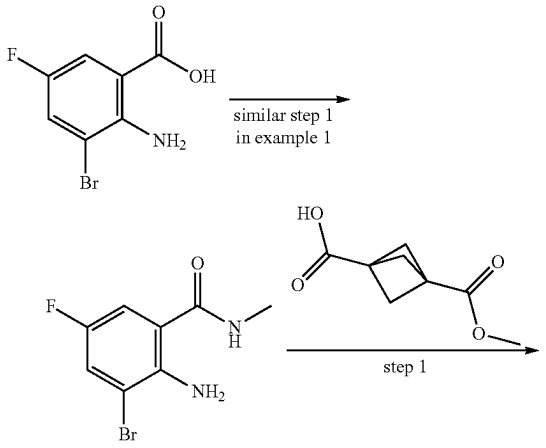
[1047] Step 5: A mixture of 159-4 (2.20 g, 9.11 mmol) in ACN (5 mL) and 4 N HCl (5 mL) was stirred at 25° C. for 2 hrs. The reaction was quenched with water, extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford 159-5 (1.40 g).

[1048] Step 6: A mixture of 159-5 (0.98 g, 4.96 mmol) in THF (20 mL) was treated with $PhNTf_2$ (2.13 g, 5.96 mmol) and stirred at −78° C. under nitrogen atmosphere. Then LiHMDS (5.96 mL, 5.96 mmol, 1N in THF) was added dropwise to the above reaction solution at −78° C. The reaction mixture was gradually allowed to reach 25° C. and then stirred for additional 2 hrs. The reaction was quenched with water, extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column (eluted with petroleum ether/EA=5/1~1/1) to give 159-6 (700 mg).

[1049] Step 7: A mixture of 159-6 (700 mg, 2.12 mmol), $B2pin_2$ (1.07 g, 4.25 mmol) and KOAc (624 mg, 6.37 mmol) in 1,4-dioxane (10 mL) was added $Pd(dppf)Cl_2$ (310 mg, 0.42 mmol) was stirred at 80° C. under nitrogen atmosphere for 6 hrs. The reaction was quenched with water, extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column (eluted with petroleum ether/EA=3/1~1/1) to give 159-7 (240 mg).

[1050] Step 8: A mixture of 159-7 (15 mg, 0.05 mmol), 75-7 (20.33 mg, 0.05 mmol), Cs_2CO_3 (33.35 mg, 0.10 mmol) in 1,4-dioxane (0.5 mL) and H_2O (0.1 mL) was treated with $Pd(OAc)_2$ (4.02 mg, 0.017 mmol) and Xantphos (10.36 mg, 0.017 mmol) and stirred at 100° C. under nitrogen atmosphere for 6 hrs. Another 7 batches were run following the same procedure. The reaction mixture was quenched with water and extracted with EA. The combined organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC (Columns: XBridge-1 5 μm 19-150 mm; Mobile phase: ACN/H_2O (0.10% FA); Gradient: 25-70%, ACN, 8 min; flow rate: 60 mL/min) to give 159 (15.60 mg). LCMS (ESI, m/z): $^+$=517.1; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.90-7.83 (m, 2H), 7.62-7.58 (m, 1H), 7.13-7.06 (m, 1H), 6.50-6.40 (m, 2H), 6.13 (s, 1H), 5.58-5.49 (m, 1H), 4.21-4.10 (m, 2H), 3.61 (s, 3H), 3.28-3.17 (m, 2H), 3.00-2.96 (m, 3H), 2.64-2.55 (m, 2H), 2.39 (s, 3H), 2.31 (s, 2H), 1.90-1.79 (m, 2H), 1.59 (d, J=6.8 Hz, 3H).

Example 24 Synthesis of Compound 212



212-1

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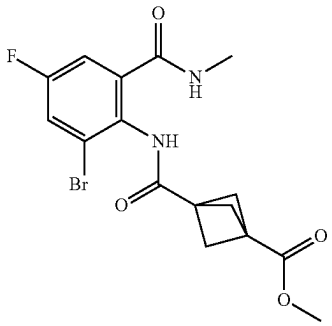
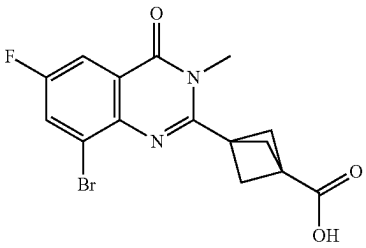


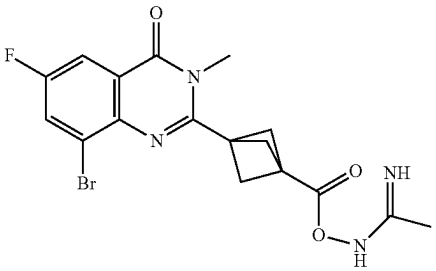
NaOH
step 2

212-2



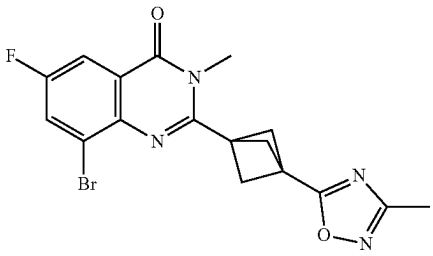
HO—NH
HN
pyBOP, DIEA
step 3

212-3



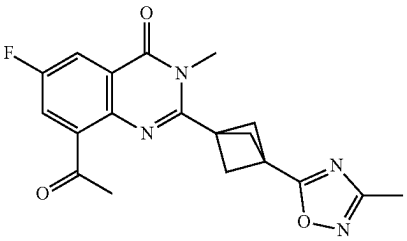
TBAF
step 4

212-4



similar step 4
in example 1

212-5



similar step 6
in example 3

212-6

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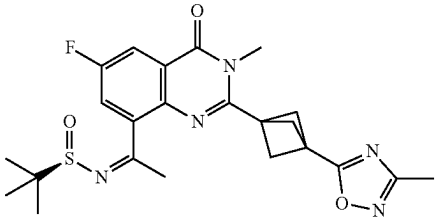
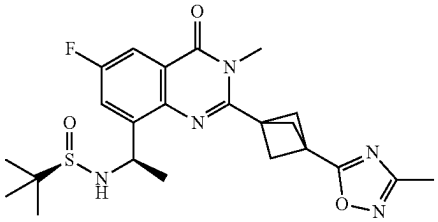


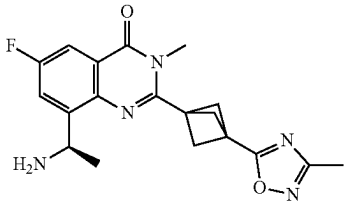
$NaBH_4$,
$CeCl_3 \cdot 7H_2O$
similar step 7
in example 3

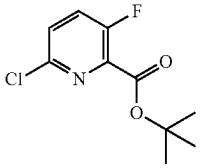
212-7



HCl in EA
similar step 8
in example 3

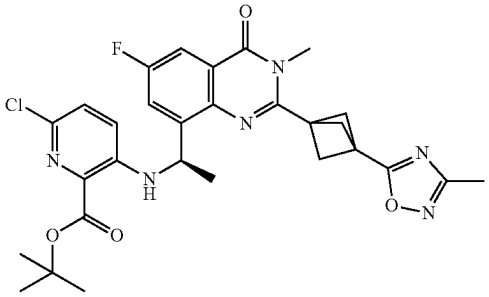
212-8





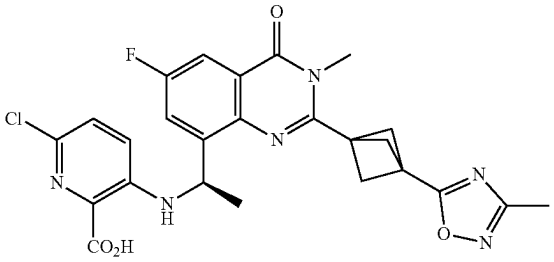
113-1
DIEA, DMAc
step 5

212-9



TFA
DCM
step 6

212-10



212

[1051] Compound 212-1 was prepared from 2-amino-3-bromo-5-fluorobenzoic acid following the procedure for the synthesis of compound 1-1 in example 1.

[1052] Step 1: To a solution of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (3.24 g, 19.02 mmol) in dichloromethane (40 mL) was added oxalyl chloride (1.47 g,

1.16 mmol) at room temperature, then the mixture was stirred for 3 hours. The volatile organics were removed under vacuum. The crude acid chloride was dissolved in dichloromethane (60 mL), followed by the addition of pyridine (4.59 mL, 57.07 mmol) and 212-1 (4.7 g, 19.02 mmol) at 0° C. The reaction mixture was stirred for 2 hours at room temperature before it was diluted with ethyl acetate and saturated sodium bicarbonate aqueous, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20:1) to give 212-2 (5.1 g).

[1053] Step 2: To a mixture of 212-2 (5 g, 12.52 mmol) in methanol (80 mL) was added sodium hydroxide (2.0 g, 50.10 mmol) at room temperature. The mixture was stirred at 70° C. for 2 hours, then concentrated and acidified to pH~2 with 1 M HCl (aq) at 0° C., filtered and washed with water. The collected solid was dried to afford 212-3 (4.3 g).

[1054] Step 3: To a mixture of 212-3 (2200 mg, 5.99 mmol) and N, N-diisopropylethylamine (2.48 mL, 14.98 mmol) in N, N-dimethylformamide (40 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (3741 mg, 7.19 mmol), and the resulting mixture was stirred at room temperature for 20 minutes. To above mixture was added N-(1-azanylideneethyl)hydroxylamine (577 mg, 7.79 mmol), then the reaction mixture was stirred at room temperature for 16 hours before it was diluted with water, filtered, and the solid residue was washed with water. The collected solid was dried to afford 212-4 (2.1 g).

[1055] Step 4: A mixture of 212-4 (1.9 g, 4.49 mmol) in tetrabutylammonium fluoride (18 mL, 1.0 M in tetrahydrofuran) and tetrahydrofuran (15 mL) was stirred at room temperature for 3 hours. The resulting mixture was diluted with water, filtered and the solid residue was washed with water. The collected solid was dried to afford 212-5 (1.7 g).

[1056] Compound 212-6 was prepared from 212-5 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[1057] Compound 212-7 was prepared from 212-6 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

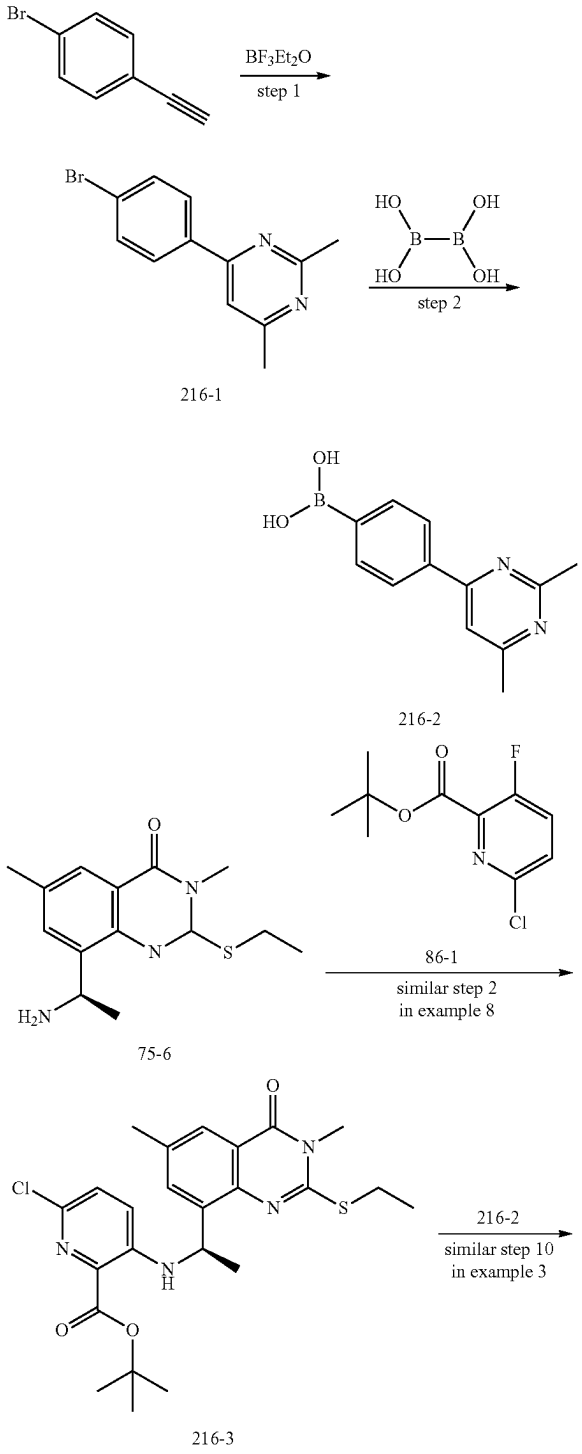
[1058] Compound 212-8 was prepared from 212-7 following the procedure for the synthesis of compound 5-8 in example 3.

[1059] Compound 212-9 was prepared from 212-8 following the procedure for the synthesis of compound 5-9 in example 3.

[1060] Step 5: A mixture of 212-9 (70 mg, 0.19 mmol), N, N-diisopropylethylamine (0.13 mL, 0.76 mmol) and 113-1 (59 mg, 0.26 mmol) in N, N-dimethylformamide (20 mL) was stirred at 110° C. for 16 hours under nitrogen atmosphere before it was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 212-10 (70 mg).

[1061] Step 6: To a mixture of 212-10 (70 mg, 0.12 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1.0 mL) at 0° C. The mixture was stirred at room temperature for 16 hours, concentrate and purified by Prep-HPLC (0.05% FA in water/acetonitrile) to afford 212 (40 mg). LCMS (ESI, m/z): $^{+}$=525.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.33-8.67 (m, 1H), 7.73-7.56 (m, 2H), 7.28-7.17 (m, 1H), 7.09-6.91 (m, 1H), 5.45-5.34 (m, 1H), 3.65 (s, 3H), 2.89-2.80 (m, 6H), 2.35 (s, 3H), 1.65 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −112.33(1F).

Example 25 Synthesis of Compound 216



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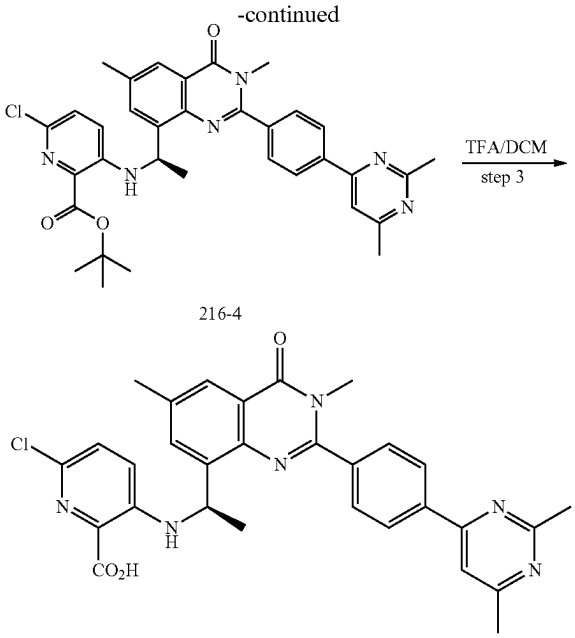


[1062] Step 1: To the solution of 1-bromo-4-ethynylbenzene (1.00 g, 5.52 mmol) in CH_3CN (30 mL) was added BF_3OEt_2 (10.0 g, 33.14 mmol) at 50° C. under N_2, then the mixture was stirred at 50° C. for 8 hrs. The mixture was quenched with water at 0° C. and extracted with ethyl acetate. The organic phase was washed with aqueous $NaHCO_3$, concentrated, and purified by chromatography on a silica gel column (petroleum ether to petroleum ether/ethyl acetate=1/4) to give 216-1 (400 mg).

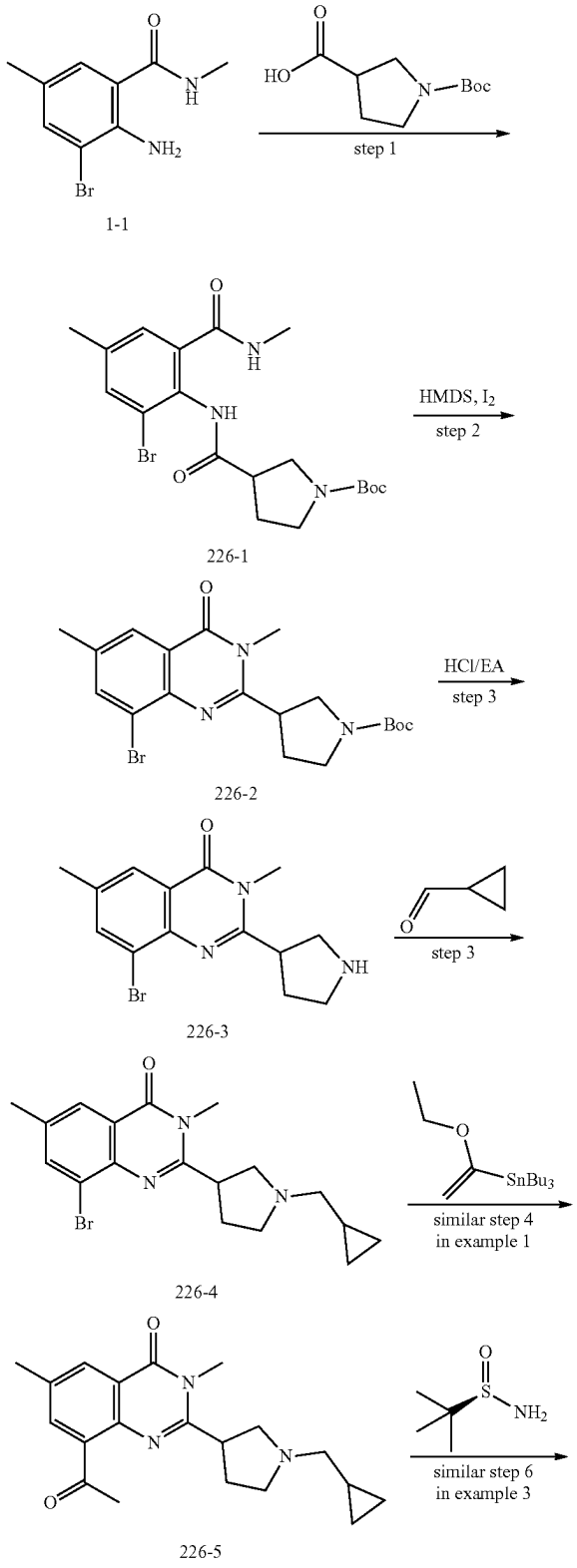
[1063] Step 2: To a mixture of 216-1 (300 mg, 1.14 mmol) in 2-methyltetrahydrofuran (9 mL) and MeOH (4.5 mL) was added tetrahydroxydiboron (153.31 mg, 1.71 mmol), N, N-diisopropylethylamine (147.1 mg, 1.14 mmol) and $(A\text{-}taPhos)_2PdCl_2$ (16.2 mg, 0.023 mmol). The mixture was stirred at 50° C. under N_2 for 3 hours. Then the reaction was concentrated and the residue was purified by column chromatography on silica gel (DCM to DCM/MeOH=10/1) to give 216-2 (150 mg).

[1064] Compound 216-3 was prepared from 75-6 and 86-1 following the procedure for the synthesis of compound 11-5 in example 8.

[1065] Compound 216-4 was prepared from 216-3 and 216-2 following the procedure for the synthesis of compound 5-11 in example 3.

[1066] Step 3: A mixture of 216-4 (100 mg, 0.164 mmol) and TFA (1 mL) in DCM (4 mL) was stirred at rt for 2 h under N_2 atmosphere. The resulting mixture was concentrated and purified by Pre-HPLC (acetonitrile/0.05% FA in water: 5% ~45%) to afford 216 (850 mg). LCMS (ESI, m/z): $[M+H]^+$=555.2; ^1H NMR (400 MHz, MeOH-d_4, ppm): δ 8.36 (d, J=8.0 Hz, 2H), 7.99 (s, 1H), 7.89 (d, J=8.0 Hz, 2H), 7.81 (s, 1H), 7.66 (s, 1H), 7.10-7.02 (m, 2H), 5.61-5.59 (m, 1H), 3.58 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 2.45 (s, 3H), 1.65 (d, J=6.4 Hz, 3H).

Example 26 Synthesis of Compounds 226 and 227



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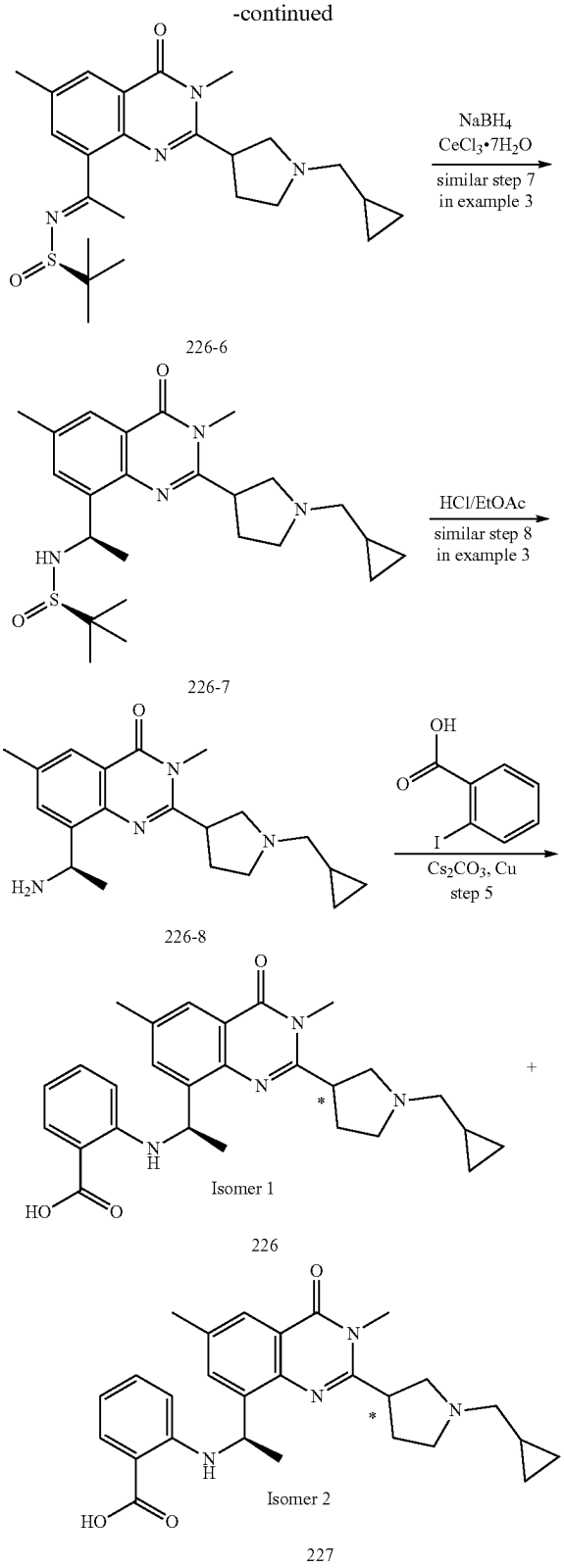


[1067] Step 1: To a mixture of 1-(tert-butoxycarbonyl) pyrrolidine-3-carboxylic acid (3.55 g, 16.4 mmol) and DMAP (2.00 g, 16.4 mmol) in DCM (30 mL) was added methanesulfonyl chloride (2.06 g, 18.0 mmol) dropwise at 0° C. under nitrogen atmosphere. The mixture was stirred at 0° C. for 1 h. Then 1-1 (2.00 g, 8.22 mmol) in dry DCM (20 mL) was added at 0° C. under nitrogen atmosphere. The reaction mixture was gradually allowed to reach 25° C. and then stirred for additional 7 hrs. Another 3 batches were carried out as the above procedure. The combined mixture was quenched with water and extracted with DCM. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column (eluted with DCM/MeOH=60/1~20/1) to give 226-1 (7.0 g).

[1068] Step 2: A mixture of 226-1 (7.00 g, 15.89 mmol), HMDS (5.13 g, 31.79 mmol) and 12 (8.06 g, 31.79 mmol) in DCM (150 mL) was stirred at 40° C. for 4 hrs. The resulting mixture was cooled to room temperature and quenched with $Na_2S_2O_3$ aqueous solution, extracted with DCM. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column (eluted with DCM/MeOH=60/1 ~20/1) to give 226-2 (5.0 g).

[1069] Step 3: A mixture of 226-2 (5.0 g, 11.83 mmol) in HCl/EA (4M, 30 mL) was stirred at 25° C. for 1 h. The mixture was adjusted to pH=7 with $NaHCO_3$(aq) and extracted with DCM. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give 226-3 (3.20 g).

[1070] Step 4: To a stirred mixture of 226-3 (1.60 g, 4.96 mmol) and cyclopropanecarbaldehyde (1.04 g, 14.89 mmol) in MeOH (15 mL) was added CH_3COOH (29.7 mg, 0.496 mmol) at 0° C. under nitrogen atmosphere. The mixture was stirred at 25° C. for 1 h. Sodium triacetoxyborohyride (4.21 g, 19.86 mmol) was added to the above solution at 0° C. under nitrogen atmosphere. The reaction mixture was gradually warmed to 25° C. and then stirred for additional 3 hrs. Another batch was carried out as the above procedure. The combined reaction mixture was quenched with water and extracted with EA. The combined organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated to give 226-4 (2.10 g).

[1071] Compound 226-5 was prepared from 226-4 and tributyl(1-ethoxyvinyl)tin following the procedure for the synthesis of compound 1-4 in example 1.

[1072] Compound 226-6 was prepared from 226-5 and (R)-2-methylpropane-2-sulfinamide following the procedure for the synthesis of compound 5-7 in example 3.

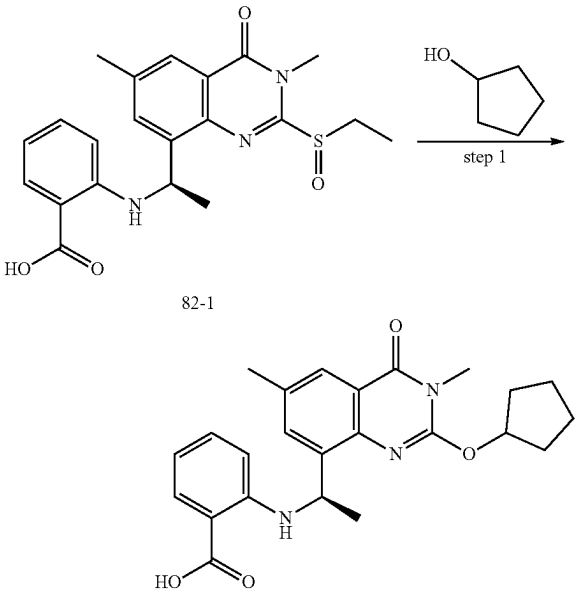
[1073] Compound 226-7 was prepared from 226-6 following the procedure for the synthesis of compound 5-8 in example 3.

[1074] Compound 226-8 was prepared from 226-7 following the procedure for the synthesis of compound 5-9 in example 3.

[1075] Step 5: To a mixture of 226-8 (150 mg, 0.44 mmol) and 2-iodobenzoic acid (218.53 mg, 0.88 mmol) in DMSO (5 mL) was added Cs_2CO_3 (287.09 mg, 0.88 mmol) and copper powder (55.99 mg, 0.88 mmol). Then the resulting mixture was stirred at 110° C. under nitrogen for 16 hrs. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with water, adjusted to pH=2 with HCl (2N) and extracted with EA. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC (Columns: Sunfire 5 μm 19-150 mm; Mobile

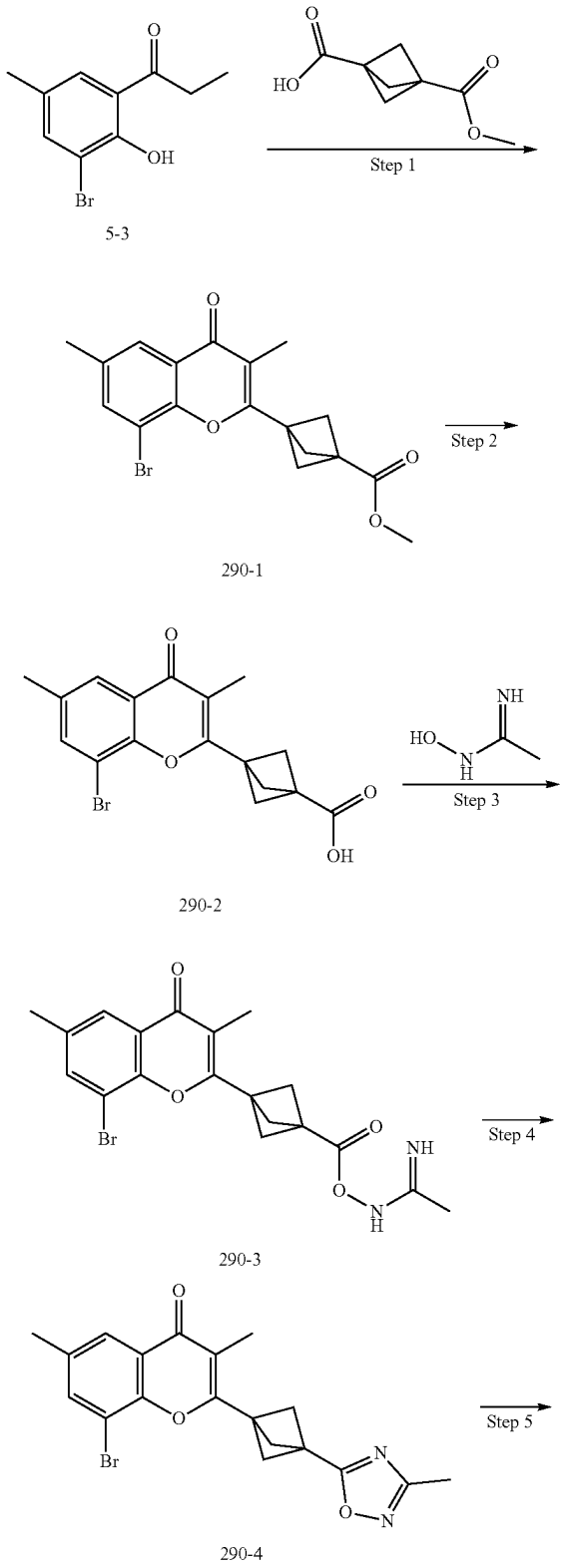
phase: ACN/H_2O (0.1% FA); Gradient: 10-45%, ACN, 8 min; flow rate: 60 mL/min) to get 226 (isomer 1, 21.40 mg) and 227 (isomer 2, 20.50 mg). Compound 226: LCMS (ESI, m/z): $^+$=461.1; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.88 (s, 1H), 7.78 (d, J=7.6 Hz, 1H), 7.62-7.60 (m, 1H), 7.15-7.11 (m, 1H), 6.70-6.60 (m, 1H), 6.51-6.45 (m, 1H), 5.31-5.22 (m, 1H), 4.21-4.15 (m, 1H), 4.05-4.00 (m, 1H), 3.82-3.71 (m, 2H), 3.61 (s, 3H), 3.43-3.33 (m, 1H), 3.19 (d, J=7.2 Hz, 2H), 2.90-2.85 (m, 1H), 2.60-2.52 (m, 1H), 2.42 (s, 3H), 1.71 (d, J=6.8 Hz, 3H), 1.31-1.20 (m, 1H), 0.78-0.70 (m, 2H), 0.50-0.40 (m, 2H). Compound 227: LCMS (ESI, m/z): $^+$=461.1; ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.88 (s, 1H), 7.89 (d, J=8.0 Hz, 1H), 7.66-7.65 (m, 1H), 7.15-7.11 (m, 1H), 6.72 (d, J=8.4 Hz, 1H), 6.47 (t, J=7.6 Hz, 1H), 5.11 (s, 1H), 4.76-4.60 (m, 1H), 4.27-4.20 (m, 1H), 4.02-3.87 (m, 1H), 3.75-3.56 (m, 4H), 3.43-3.31 (m, 2H), 3.18-3.04 (m, 1H), 2.81-2.72 (m, 1H), 2.43 (s, 3H), 2.26-2.12 (m, 1H), 1.77 (d, J=6.8 Hz, 3H), 1.30-1.18 (m, 1H), 0.78-0.66 (m, 2H), 0.52-0.43 (m, 2H).

Example 27 Synthesis of Compound 230



[1076] Step 1: NaH (23.22 mg, 0.58 mmol, 60% wt) was added into cyclopentanol (5 mL) and the mixture was stirred at 25° C. for 10 minutes. Then 82-1 (120 mg, 0.29 mmol) was added slowly under nitrogen atmosphere. The reaction mixture was stirred at 110° C. for 16 hrs under nitrogen atmosphere. The reaction mixture was diluted with water and then treated with 2N HCl until pH=2. The mixture was extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by Prep-HPLC (columns: sunfire 5 μm 19-150 mm, Mobile Phase: ACN-H_2O (0.1% FA), Gradient: 40-80-8gt-500vl) to afford 230 (15.14 mg). LCMS (ESI, m/z): $^+$=422.1; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.63 (s, 1H), 8.43 (s, 1H), 7.79-7.77 (m, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.47 (d, J=2.0 Hz, 1H), 7.19-7.13 (m, 1H), 6.52-6.37 (m, 2H), 5.61-5.57 (m, 1H), 5.40 (s, 1H), 3.39 (s, 3H), 2.32 (s, 3H), 2.08-1.85 (m, 4H), 1.82-1.60 (m, 4H), 1.55 (d, J=6.4 Hz, 3H).

Example 28 Synthesis of Compound 290



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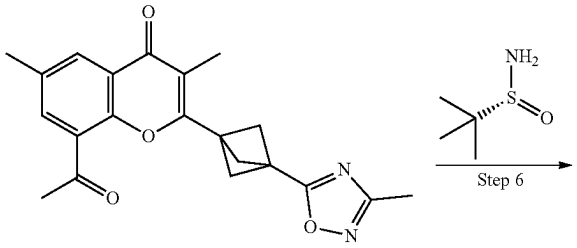
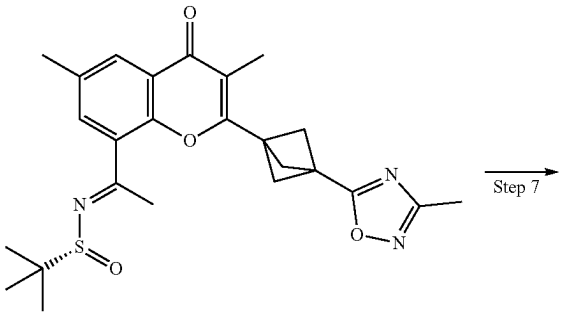


290-5



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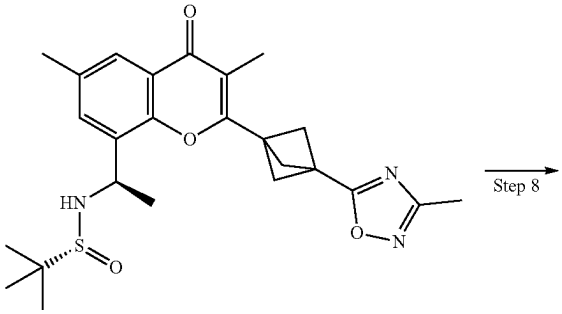

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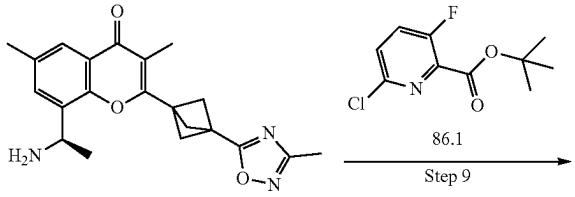
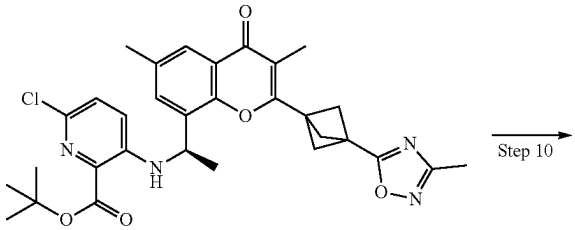


290-8



290-9

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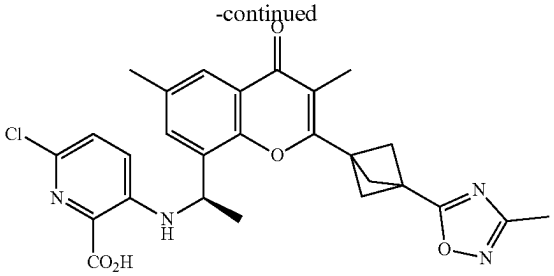


290-9

[1077] Step 1: To a solution of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (3.15 g, 18.5 mmol) in dichloromethane (40 mL) was added oxalyl chloride (5.2 mL, 61.7 mmol) and two drops of N, N-dimethylformamide at room temperature, then stirred for 2 hours. The volatile organics were removed under vacuum. The crude acid chloride was dissolved in pyridine (40 mL), followed by the addition of 5-3 (3 g, 12.34 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.6 g, 37.02 mmol) at room temperature. The reaction mixture was stirred for 2 hours at 80° C. and then diluted with water, filtered and washed with water. The collected solids were dried to afford 290-1 (3.1 g).

[1078] Step 2: To a solution of 290-1 (1.5 g, 3.98 mmol) in tetrahydrofuran (20 mL) was added aqueous lithium hydroxide solution (6.0 mL, 6.0 mmol, 1 M in water) at 0° C. The mixture was stirred at room temperature for 3 hours before acidification to pH~2 with 1 M HCl (aq.) at 0° C. The result solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 290-2 (1.2 g).

[1079] Step 3: To a mixture of 290-2 (1200 mg, 3.30 mmol) and N, N-diisopropylethylamine (1.37 mL, 8.26 mmol) in N, N-dimethylformamide (25 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (2.1 g, 3.97 mmol), stirred at room temperature for 20 minutes. To above mixture was added N-(1-azanylideneethyl)hydroxylamine (0.32 g, 4.30 mmol), then stirred at room temperature for 3 hours and then diluted with water, filtered and washed with water. The collected solids were dried to afford 290-3 (1.3 g).

[1080] Step 4: A mixture of 290-3 (1.3 g, 3.10 mmol) in tetrabutylammonium fluoride (1.0 M tetrahydrofuran) (10 mL) and tetrahydrofuran (10 mL) was stirred at room temperature for 3 hours. The resulting mixture was diluted with water, filtered and washed with water. The collected solids were dried to afford 290-4 (1.1 g).

[1081] Step 5: A mixture of 290-4 (1.1 g, 2.74 mmol), tributyl(1-ethoxyvinyl)tin (1.14 g, 3.15 mmol) and tetrakis (triphenylphosphine)palladium (0.3 g, 0.27 mmol) in dioxane (15 mL) was stirred at 100° C. for 16 hours under N_2 atmosphere before hydrochloric acid (1 M, 10 mL) was added and stirred at 50° C. for 1 hour. The mixture was cooled to room temperature and potassium fluoride solution was added and then stirred at 25° C. for 0.5 hours, filtered, extracted with ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 290-5 (260 mg).

[1082] Step 6: To a mixture of 290-5 (260 mg, 0.72 mmol) and (R)-2-methylpropane-2-sulfinamide (176 mg, 1.45 mmol) in tetrahydrofuran (3 mL) was added titanium tetraisopropanolate (6 mL) at room temperature. The mixture was stirred at 90° C. for 6 hours and then diluted with ethyl acetate and water, filtered and washed with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/ethyl acetate=1:1) to give 290-6 (230 mg).

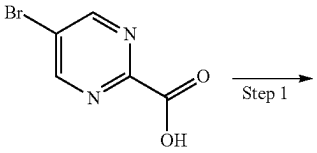
[1083] Step 7: To a mixture of 290-6 (230 mg, 0.49 mmol) and Cerous chloride heptahydrate (366 mg, 0.98 mmol) in methanol (5 mL) was added sodium borohydride (37 mg, 0.98 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour before acidification to pH~5 with saturated ammonium chloride solution at 0° C. The result solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1:4) to give 290-7 (165 mg).

[1084] Step 8: To a mixture of 290-7 (165 mg, 0.20 mmol) in ethyl acetate (4 mL) was added 4M HCl in ethyl acetate (2 mL) at 0° C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was adjusted to pH=12 with $NH_3 \cdot H_2O$ (25% w) and extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 290-8 (125 mg).

[1085] Step 9: A mixture of 290-8 (125 mg, 0.36 mmol), N, N-diisopropylethylamine (0.30 mL, 1.78 mmol) and 86-1 (99 mg, 0.43 mmol) in N, N-dimethylformamide (3 mL) was stirred at 120° C. for 16 hours under nitrogen atmosphere. Then the reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 290-9 (100 mg).

[1086] Step 10: To a mixture of 290-9 (100 mg, 0.17 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL) at 0° C. The mixture was stirred at room temperature for 3 hours and then concentrate and purified by Prep-HPLC (0.05% FA in water/acetonitrile) to afford 290 (55 mg). LCMS (ESI, m/z): $^{+}$=521.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.92-8.37 (m, 1H), 7.75-7.65 (m, 1H), 7.56-7.48 (m, 1H), 7.35-7.20 (m, 1H), 7.10-6.98 (m, 1H), 5.21-5.05 (m, 1H), 2.82 (s, 6H), 2.37-2.32 (m, 6H), 2.06 (s, 3H), 1.64 (d, J=6.4 Hz, 3H).

Example 29 Synthesis of Compound 379



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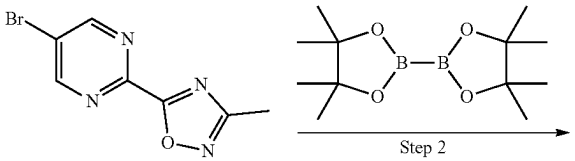
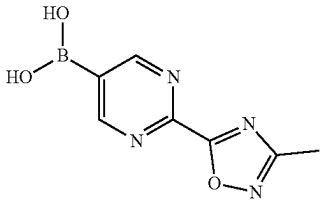
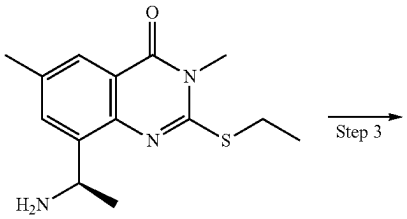


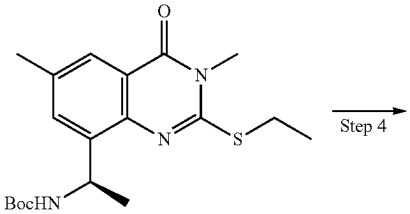
379-1



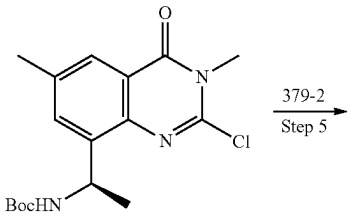
379-2



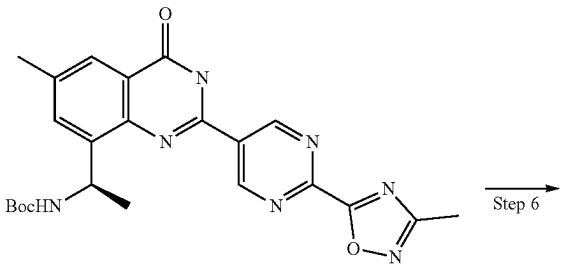
75-6



379-3



379-4



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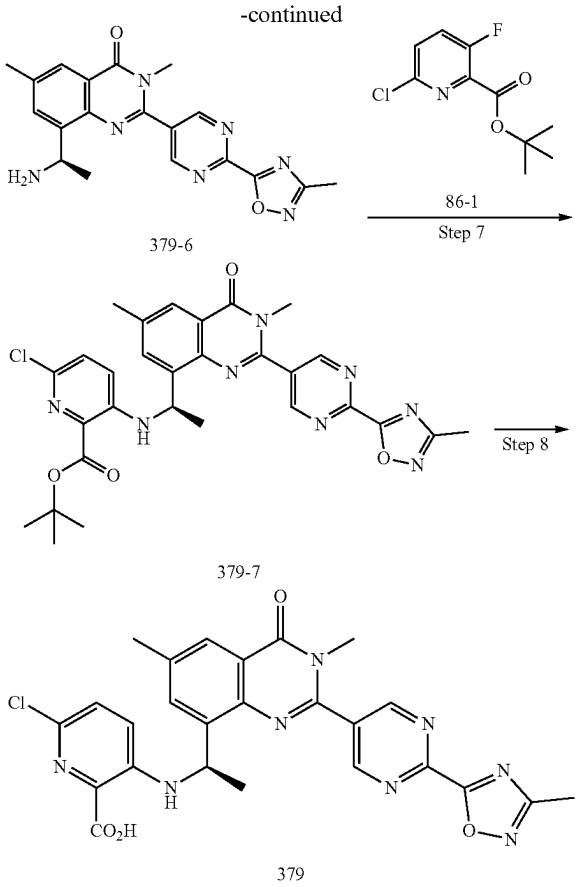


[1087] Step 1: To a mixture of 5-bromopyrimidine-2-carboxylic acid (1.9 g, 9.36 mmol) and N, N-diisopropylethylamine (2.42 g, 18.72 mmol) in N, N-dimethylformamide (40 mL) was added HATU (4.27 g, 11.23 mmol). The reaction was stirred at room temperature for 10 minutes. To the above mixture was added N-hydroxyacetamidine (693.4 mg, 9.36 mmol), then stirred at room temperature for 30 mins. The resulting solution was heated at 110° C. for 30 minutes and then diluted with water and extracted with dichloromethane. The organic layers were concentrated and purified using silica gel column chromatography eluting with dichloromethane to give 379-1 (605 mg).

[1088] Step 2: A mixture of 379-1 (500 mg, 2.07 mmol), bis(pinacolato)diboron (790.0 mg, 3.11 mmol), Pd(dppf)Cl_2 (151 mg, 0.21 mmol) and potassium acetate (610.7 mg, 6.22 mmol) in anhydrous dioxane (5 mL) was degassed and purged three times with N_2. The reaction was stirred at 100° C. for 4 hrs under N_2. The reaction was filtered and purified by C18 flash (eluted with acetonitrile in 0.05% formic acid in water) to give 379-2 (267 mg).

[1089] Step 3: To a stirred solution of 75-6 (1.5 g, 4.7 mmol) in DCM (30 mL) was added TEA (2.6 mL), followed by di-tert-butyl dicarbonate (2.20 mL, 9.56 mmol), then stirred at 30° C. for 2 hrs. The mixture was diluted with DCM and washed with water. Organic layer was concentrated to give a crude which was slurried with petroleum ether, filtered, dried to give 379-3 (1.78 g).

[1090] Step 4: To a solution of 379-3 (1.7 g, 4.503 mmol) in dichloromethane (60 mL) was added sulfuryl chloride (1.82 g, 13.51 mmol) at room temperature. The reaction was stirred at room temperature for 5 mins. The reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane which was washed with brine and dried with anhydrous sodium sulfate to give the crude product 379-4 (1560 mg).

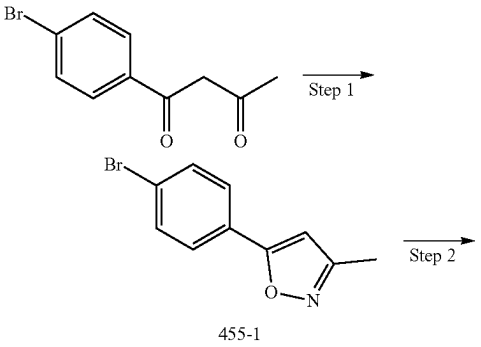
[1091] Step 5: A mixture of 379-4 (200 mg, 0.568 mmol), 379-2 (175.49 mg, 0.85 mmol), potassium phosphate tribasic (362.0 mg, 1.71 mmol) and Pd(dtbpf)Cl_2 (73.3 mg, 0.11 mmol) in dioxane (15 mL) and water (3 mL) was stirred at 95° C. for 16 hours under nitrogen atmosphere. The reaction mixture was diluted with dichloromethane and water. The organic layers were separated, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/ethyl acetate=3/1) to give 379-5 (112 mg).

[1092] Step 6: A mixture of 379-5 (112 mg, 0.24 mmol) in dichloromethane (2 mL) was added hydrogen chloride in ethyl acetate (2.0 mL, 4 M), and stirred at room temperature for 1 hour. The reaction mixture was concentrated to give 379-6 (110 mg, crude) used in the next step directly.

[1093] Step 7: A mixture of 379-6 (100 mg, 0.265 mmol), 86-1 (184.1 mg, 0.80 mmol) and N, N-diisopropylethylamine (205.5 mg, 1.59 mmol) in N, N-dimethylacetamide (5 mL) was stirred at 115° C. for 6 hours under nitrogen atmosphere. The reaction was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20/1) to give 379-7 (156 mg, crude).

[1094] Step 8: To a solution of 379-7 (156 mg, 0.27 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL) at room temperature. The reaction was stirred at room temperature for 3 hrs. The solution was removed and purified by prep-HPLC to give the desired product 379 (58.5 mg). LCMS (ESI, m/z): $^{+}$=533.4; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.53 (s, 2H), 8.78-8.61 (m, 1H), 7.94 (s, 1H), 7.69 (s, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 5.44-5.40 (m, 1H), 3.53 (s, 3H), 2.53 (s, 3H), 2.43 (s, 3H), 1.60 (d, J=6.8 Hz, 3H).

Example 30 Synthesis of Compound 455



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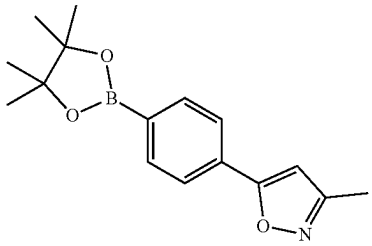
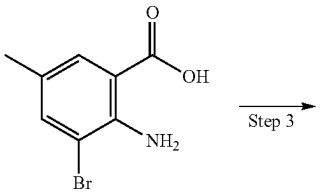
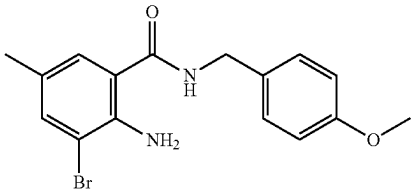


455-2

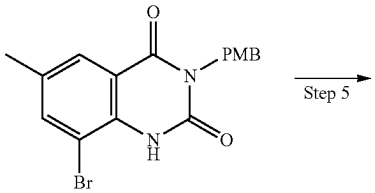


Step 3



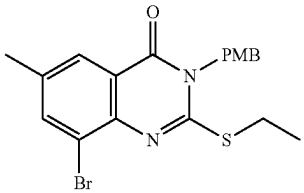
Step 4

455-3



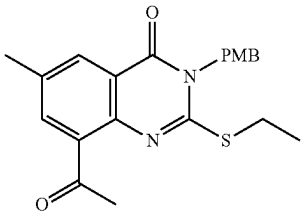
Step 5

455-4



Step 6

455-5



Step 7

455-6

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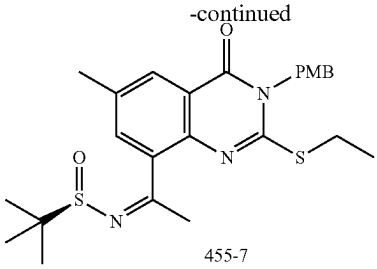
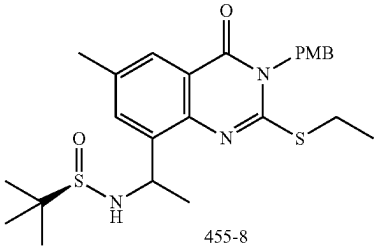


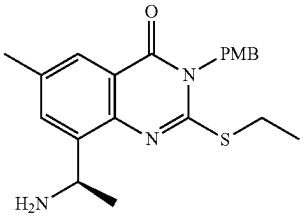
Step 8

455-7



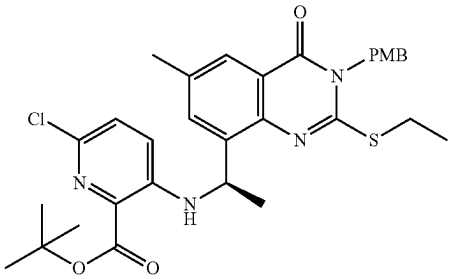
Step 9

455-8



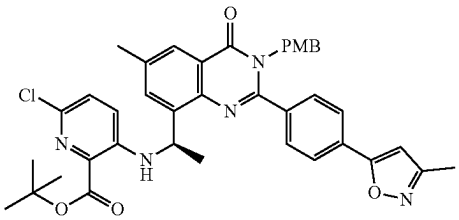
86-1
Step 10

455-9



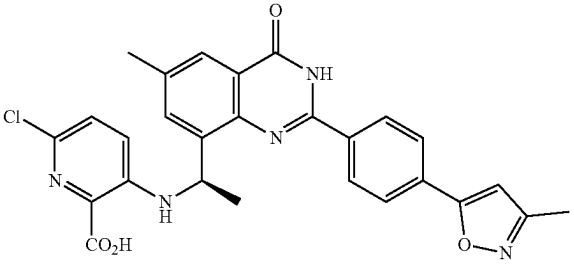
455-2
Step 11

455-10



Step 12

455-11



455

[1095] Step 1: A mixture of 1-(4-Bromophenyl)-1,3-butanedione (2 g, 8.230 mmol) and hydroxyamine hydrochloride (0.7 g, 10.0 mmol) in ethanol (30 mL) was stirred at 80° C. for 2 hours under nitrogen atmosphere. The reaction mixture was concentrated and purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=20/1) to give 445-1 (1.5 g).

[1096] Step 2: To a solution of 455-1 (1.5 g, 6.300 mmol) in dioxane (15 mL) were added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.92 g, 7.56 mmol), dichloropalladium (II) (0.5 g, 0.63 mmol) and potassium acetate (1.9 g, 18.90 mmol), and the reaction was stirred at 100° C. for 2 hours under nitrogen atmosphere. The reaction was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=10/1) to afford 455-2 (1.2 g).

[1097] Step 3: A mixture of 2-amino-3-bromo-5-methylbenzoic acid (10 g, 43.47 mmol), (4-methoxyphenyl) methanamine (8.94 g, 65.20 mmol), O-(7-azabenzotriazol-1-yl)-N, N, N, N-tetramethyluronium hexafluorophosphate (19.8 g, 52.16 mmol) and N, N-diisopropylethylamine (28.7 mL, 173.87 mmol) in N, N-dimethylformamide (50 mL) was stirred at room temperature for 2 h. The resulting mixture was diluted with water and filtered, the cake was dried to afford 455-3 (14 g).

[1098] Step 4: To a mixture of 455-3 (14 g, 40.088 mmol) and N, N-diisopropylethylamine (9.939 mL, 60.132 mmol) in dichloromethane (100 mL) was added trichloromethyl methanoate (4.76 g, 16.035 mmol) at 0° C. The mixture was stirred at 40° C. for 2 hours. The reaction mixture was concentrated and diluted with water, filtered and washed with water. The collected solids were dried to afford 455-4 (13 g).

[1099] Step 5: To a solution of 455-4 (13 g, 34.65 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (10.5 g, 69.29 mmol) and (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (23.4 g, 45.04 mmol) in N, N-dimethylformamide (80 mL) was added sodium ethanethiolate (4.37 g, 51.970 mmol) at 0° C., then stirred at room temperature for 0.5 hours. The mixture was diluted with water, filtered, the cake was washed with water, cake was dried by vacuum to give 455-5 (10 g).

[1100] Step 6: To a solution of 455-5 (10 g, 23.85 mmol) in 1-butanol (200 mL) were added Palladium (II) acetate (0.3 g, 1.19 mmol), 1,1'-Binaphthyl-2,2'-diphenyl phosphine (1.5 g, 2.39 mmol), N, N-diisopropylethylamine (9.5 mL, 57.23 mmol) and 1-(vinyloxy)butane (7.17 g, 71.54 mmol), and the reaction was stirred at 85° C. for 18 hours under nitrogen atmosphere. The mixture was filtered and washed with ethyl acetate, the filtrate was concentrated in vacuo. The residue was dissolved with dichloromethane, hydrochloric acid (2 M) was added and stirred for 1 hour at room temperature, extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether to petroleum ether/ethyl acetate=5/1) to afford 455-6 (7.5 g).

[1101] Step 7: A mixture of 455-6 (7.5 g, 19.61 mmol) and (R)-2-methylpropane-2-sulfinamide (4.75 g, 39.22 mmol) in tetrahydrofuran (50 mL) and titanium tetraisopropanolate (150 mL) was stirred at 85° C. for 16 hours. The mixture was cooled to rt and quenched with brine, stirred for 0.5 h and filtered. The filter cake was washed with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 455-7 (8 g).

[1102] Step 8: To a mixture of 455-7 (8 g, 16.47 mmol) and cerium trichloride heptahydrate (3.1 g, 8.24 mmol) in methanol (100 mL) was added sodium borohydride (1.2 g, 32.95 mmol) in portions at room temperature, and stirred at 20° C. for 1 hour. The reaction mixture was quenched with saturated ammonium chloride (50 mL) and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=3/1) to give 455-8 (7 g).

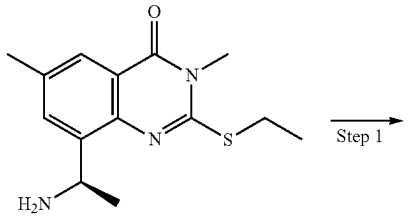
[1103] Step 9: To a mixture of 455-8 (1 g, 2.051 mmol) in ethyl acetate (10 mL) was added hydrochloric acid (2.1 mL, 4 M in ethyl acetate), and stirred at room temperature for 2 hours. The reaction mixture was filtered and washed with ethyl acetate. The collected solids were dried to give 455-9 (750 mg).

[1104] Step 10: A mixture of 455-9 (750 mg, 1.956 mmol), 86-1 (543.62 mg, 2.347 mmol) and N, N-diisopropylethylamine (1.616 mL, 9.778 mmol) in N, N-dimethylacetamide (10 mL) was stirred at 110° C. for 6 hours. The mixture was cooled to room temperature and quenched with water, extracted with ethyl acetate. The organic layer was separated, washed with brine, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=10/1) to give 455-10 (600 mg).

[1105] Step 11: A mixture of 455-2 (102.3 mg, 0.50 mmol), 455-10 (150 mg, 0.25 mmol), copper(I) thiophene-2-carboxylate (96.1 mg, 0.50 mmol) and tetrakis(triphenylphosphine)palladium (58.3 mg, 0.05 mmol) in methanol (10 mL) was stirred at room temperature for 3 hours under nitrogen atmosphere. The resulting mixture was concentrated and purified by silica gel chromatography (petroleum ether to petroleum ether/ethyl acetate=1/1) to afford 455-11 (100 mg).

[1106] Step 12: A mixture of 455-11 (80 mg, 0.116 mmol) in trifluoroacetic acid (5 mL) was stirred at 70° C. for 1.5 hours. The reaction was concentrated in vacuo. The residue was purified by prep-HPLC (acetonitrile/0.05% formic acid in water: 25%~95%) to give 455 (15.1 mg). LCMS (ESI, m/z): $^{+}$=516.0; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.42-8.40 (m, 2H), 8.27 (s, 1H), 8.09-8.05 (m, 2H), 7.90-7.82 (m, 1H), 7.55 (s, 1H), 7.18-7.09 (m, 1H), 7.08-6.97 (m, 1H), 6.69-6.67 (m, 1H), 5.55-5.54 (m, 1H), 2.41-2.36 (m, 3H), 2.36-2.34 (m, 3H), 1.58 (d, J=6.4 Hz, 3H).

Example 31 Synthesis of Compound 506



76-6

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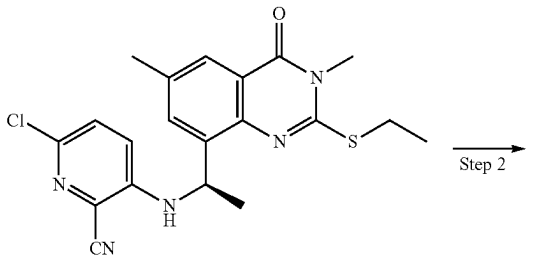
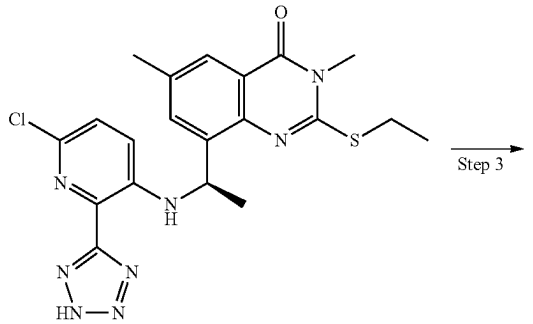
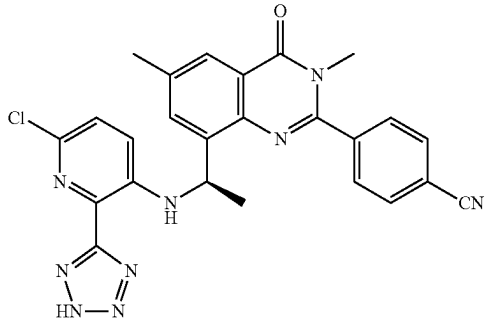


506-1



506-2

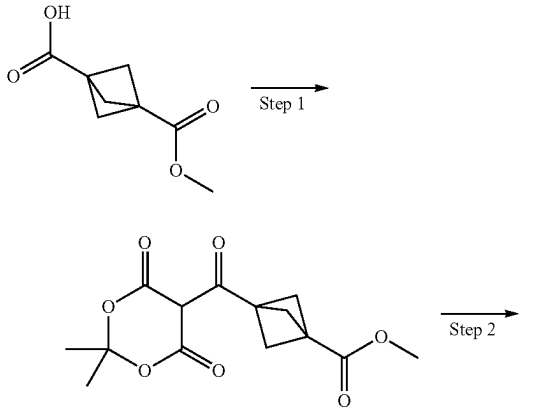


[1107] Step 1: To a mixture of 76-6 (100 mg, 0.36 mmol) in DMAC (5 mL) was added DIEA (0.3 mL, 1.80 mmol) and 6-chloro-3-fluoropyridine-2-carbonitrile (67.7 mg, 0.43 mmol), the mixture was stirred at 120° C. for 4 hours under N_2 atmosphere. The mixture was diluted with ethyl acetate, washed with water, organic layer was concentrated to give a residue which was purified by Combi flash (ethyl acetate in petroleum ether=30%) to give 506-1 (91 mg).

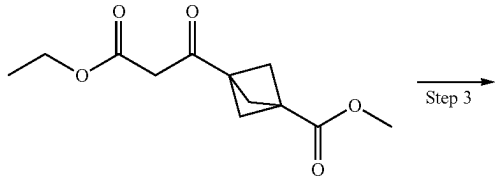
[1108] Step 2: A mixture of 506-1 (180 mg, 0.44 mmol), azidotrimethylsilane (100 mg, 0.87 mmol) and tetrabutylammonium fluoride (68.6 mg, 0.22 mmol) was stirred at 85° C. for 18 hours. The mixture was diluted with ethyl acetate, washed with water, organic layer was concentrated to give a residue which was purified by Combi flash (ethyl acetate in petroleum ether=60%) to give 506-2 (120 mg).

[1109] Step 3: A mixture of 506-2 (120 mg, 0.263 mmol), 4-(dihydroxyboranyl)benzene-1-carbonitrile (116 mg, 0.79 mmol), copper(I) thiophene-2-carboxylate (100.1 mg, 0.53 mmol) and $Pd(PPh_3)_4$ (61 mg, 0.053 mmol) in MeOH (4 mL) was stirred at room temperature for 2 hours under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate, quenched with NH_4Cl, to above mixture was added EDTA (168.7 mg, 0.578 mmol). The mixture was stirred at room temperature for 30 mins under air atmosphere, and then separated and washed with water, brine, dried over sodium filtered and concentrated. The residue was purified by Perp-HPLC (ACN/0.05% FA in water: 15-95%) to give 506 (20 mg). LCMS (ESI, m/z): $[M+H]^+$=498.2; ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 8.27 (brs, 1H), 8.11-8.02 (m, 2H), 8.01-7.95 (m, 2H), 7.94-7.87 (m, 1H), 7.76-7.60 (m, 1H), 7.39-7.22 (m, 1H), 7.16-7.01 (m, 1H), 5.63-5.39 (m, 1H), 3.37 (s, 3H), 2.39 (s, 3H), 1.66 (d, J=6.4 Hz, 3H).

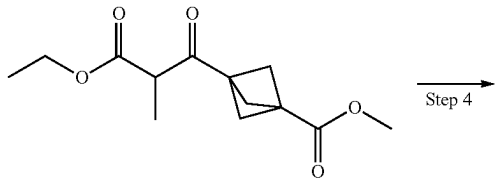
Example 32 Synthesis of Compound 527



527-1



527-2



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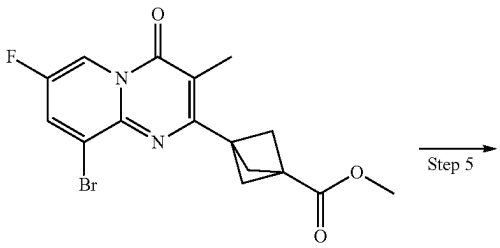

527-4

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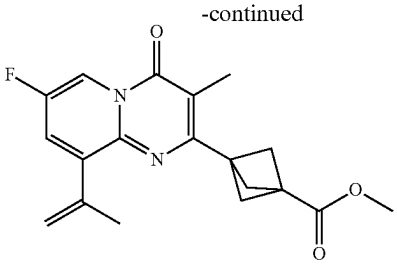
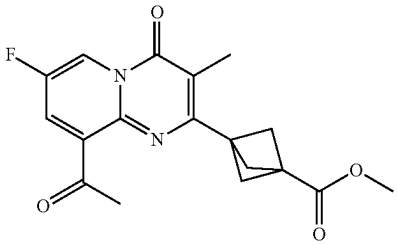


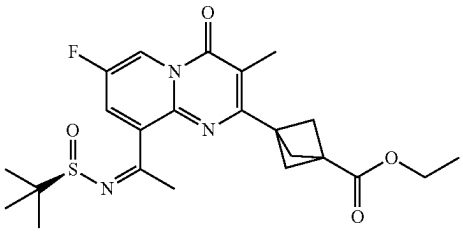
527-5

Step 6



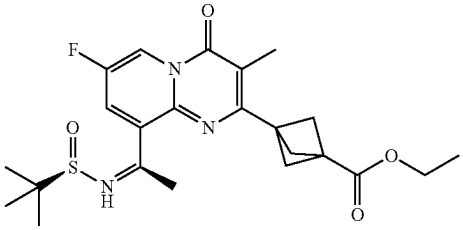
527-6

Step 7



527-7

Step 8



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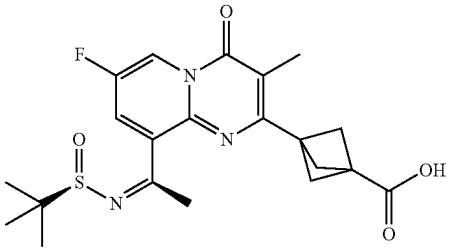
Step 9



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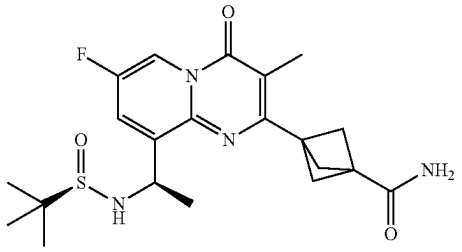
Step 10



527-10

Step 11

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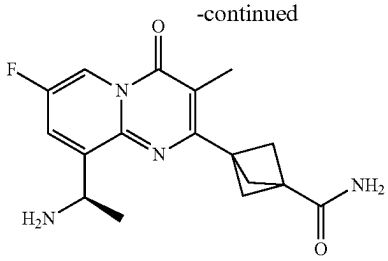

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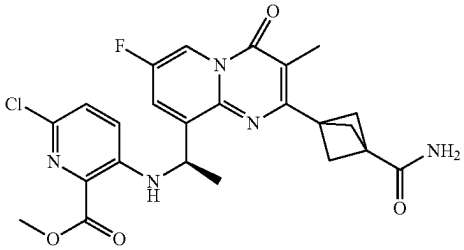
Step 12



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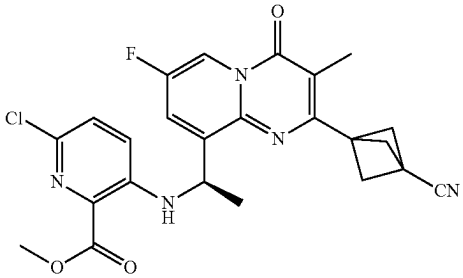
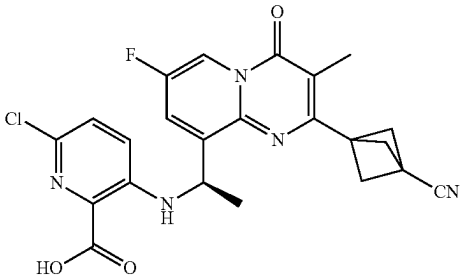
Step 13



527-13

Step 14



527

[1110] Step 1: To a solution of 3-(methoxycarbonyl) bicyclo[1.1.1]pentane-L-carboxylic acid (15 g, 88.2 mmol) in dichloromethane (150 mL) were added 2,2-dimethyl-1,3-dioxane-4,6-dione (15.25 g, 105.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20.3 g, 105.8 mmol), and 4-dimethylaminopyridine (16.2 g, 132.2 mmol). The reaction mixture was stirred at room temperature overnight under nitrogen atmosphere. The reaction mixture was diluted with dichloromethane and 5% potassium bisulfate aqueous solution. The organic layer was separated, washed with further brine, the organic layer was collected, concentrated in vacuo and dried to afford 527-1 (25 g, crude).

[1111] Step 2: The solution of 527-1 (25 g, 84.4 mmol) in ethanol (100 mL) was stirred at 90° C. for 3 hours. The reaction was concentrated in vacuo to afford 527-2 (20 g, crude).

[1112] Step 3: To a solution of 527-2 (20 g, 83.2 mmol) in acetone (150 mL) were added iodomethane (11.82 g, 83.2 mmol) and potassium carbonate (13.8 g, 99.9 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with further brine and concentrated. The residue was purified by silica gel chromatography (petroleum ether to petroleum ether/ethyl acetate=10/1) to afford 527-3 (15 g).

[1113] Step 4: A mixture of 3-bromo-5-fluoropyridin-2-amine (11.27 g, 59.0 mmol), pyridinium p-toluenesulfonate (1.5 g, 5.9 mmol) and 527-3 (15 g, 59.0 mmol) was heated at 130° C. for 48 hours. The reaction mixture was concentrated and purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=3/1) to afford 527-4 (7 g).

[1114] Step 5: A mixture of 527-4 (6.8 g, 17.8 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (6.00 g, 35.7 mmol), 1,1'-bis(di-t-butylphosphino) ferrocene palladium dichloride (1.2 g, 1.8 mmol) and potassium carbonate (4.9 g, 35.7 mmol) in dioxane (50 mL) and water (10 mL) was stirred at 100° C. for 2 hours under nitrogen atmosphere. The mixture was diluted with water and extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and evaporated, the residue was purified by (petroleum ether to petroleum ether/ethyl acetate=10/1) to give 527-5 (5 g).

[1115] Step 6: The mixture of 527-5 (5 g, 14.6 mmol) and potassium osmate (VI) dihydrate (0.3 g, 0.73 mmol) in dioxane (20 mL) and water (10 mL) was stirred at room temperature for 20 minutes. To the above mixture was added sodium periodate (7.8 g, 36.5 mmol), the resulting mixture was stirred at room temperature for 1 hour. The reaction was quenched with saturated sodium thiosulfate, filtered and washed with dichloromethane, diluted with dichloromethane and water. The organic layer was separated, washed with further brine, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=10/1) to afford 527-6 (2.5 g).

[1116] Step 7: A mixture of 527-6 (2.5 g, 7.26 mmol) and (R)-2-methylpropane-2-sulfinamide (1.76 g, 14.5 mmol) in tetrahydrofuran (10 mL) and titanium tetraethanolate (70 mL) was stirred at 90° C. for 16 hours. The mixture was cooled to rt and quenched with brine, stirred for 0.5 hour and filtered. The filter cake was washed with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 527-7 (2.5 g, crude).

[1117] Step 8: To a mixture of 527-7 (2.4 g, 5.2 mmol) and cerium trichloride heptahydrate (0.6 g, 2.6 mmol) in methanol (30 mL) was added sodium borohydride (0.4 g, 10.4 mmol)) in portions at room temperature, and stirred at 20° C. for 1 hour. The reaction mixture was quenched with saturated ammonium chloride and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1/1) to give 527-8 (1.5 g).

[1118] Step 9: To a solution of 527-8 (1 g, 2.16 mmol) in tetrahydrofuran (2 mL) and methanol (2 mL) was added water (1 mL). The mixture was stirred at 25° C. for 1 hour. The reaction mixture was adjusted to pH~3 with 2 M hydrochloric acid, diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated to give 527-9 (800.0 mg, crude).

[1119] Step 10: To a mixture of 527-9 (800 mg, 1.84 mmol) in N, N-dimethylformamide (10 mL) was added O-(7-Azabenzotriazol-1-yl)-N, N, N, N-tetramethyluronium hexafluorophosphate (1047.7 mg, 2.76 mmol), N, N-diisopropylethylamine (1.8 mL, 11.0 mmol) and ammonium chloride (491.3 mg, 9.19 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=10/1) to give 527-10 (700 mg).

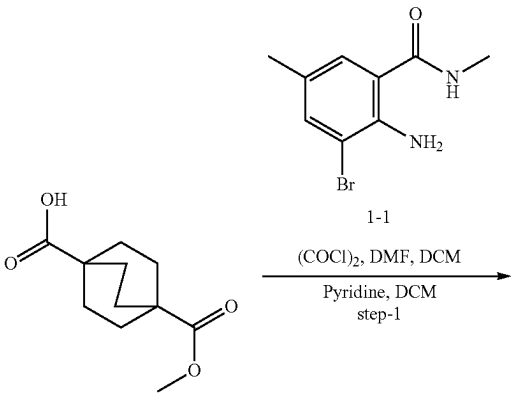
[1120] Step 11: To a mixture of 527-10 (700 mg, 1.61 mmol) in ethyl acetate (10 mL) was added hydrochloric acid (0.48 mL, 4 M in ethyl acetate), and stirred at room temperature for 2 hours. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was adjusted to pH=12 with aqueous ammonia (25%) and extracted with ethyl acetate. The combined extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 527-11 (400 mg, crude).

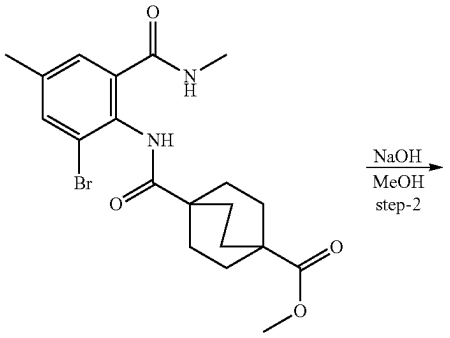
[1121] Step 12: A mixture of 527-11 (400 mg, 1.21 mmol), 11-1 (275.4 mg, 1.45 mmol) and N, N-diisopropylethylamine (1.0 mL, 6.05 mmol) in N, N-dimethylacetamide (5 mL) was stirred at 110° C. for 6 hours. The mixture was cooled to room temperature and quenched with water, extracted with ethyl acetate. The organic layer was separated, washed with brine, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=10/1) to give 527-12 (350 mg).

[1122] Step 13: To a solution of 527-12 (350 mg, 0.700 mmol) in 1,2-dichloroethane (10 mL) was added phosphorus oxychloride (0.169 mL, 1.820 mmol). The mixture was stirred at 85° C. for 1 hour. The mixture was diluted with sodium bicarbonate aqueous and extracted with dichloromethane, dried over anhydrous sodium sulfate, then it was filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether to petroleum ether/ethyl acetate=1/1) to afford 527-13 (250 mg).

[1123] Step 14: To a mixture of 527-13 (50 mg, 0.104 mmol) in tetrahydrofuran (4 mL) and water (2 mL) was added sodium hydroxide (12.5 mg, 0.311 mmol), and stirred at room temperature for 1 hour. The reaction was adjusted to pH~3 with 2 M hydrochloric acid, diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC (acetonitrile/0.05% formic acid in water: 25%~95%) to give 527 (41.5 mg). LCMS (ESI, m/z): $^{+}$=468.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.01 (brs, 1H), 9.07-8.69 (m, 2H), 8.04-7.90 (m, 1H), 7.41-7.20 (m, 1H), 7.14-6.96 (m, 1H), 5.28-5.25 (m, 1H), 2.85-2.71 (m, 6H), 2.22 (s, 3H), 1.68 (d, J=6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −133.40 (1F).

Example 33 Synthesis of Compound 309





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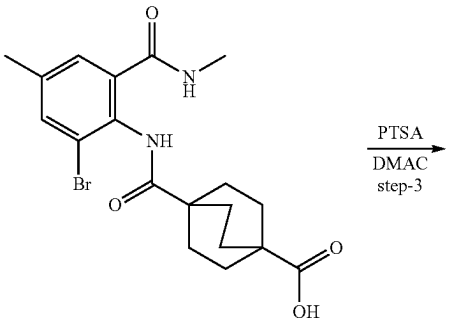

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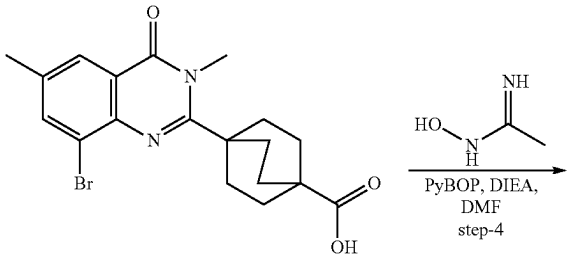

309-3

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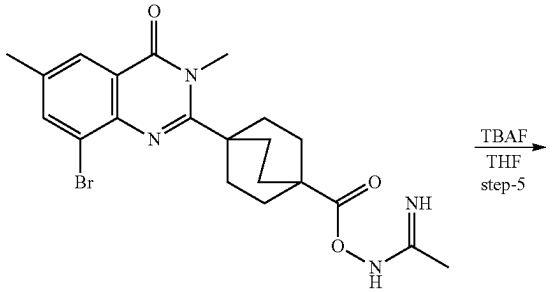

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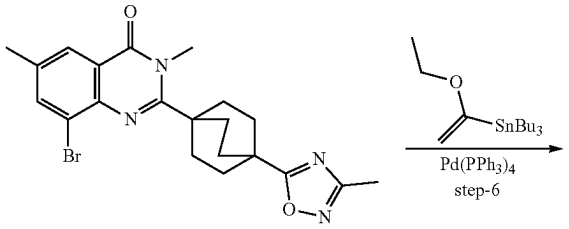

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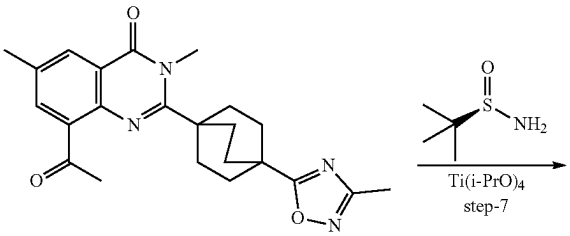

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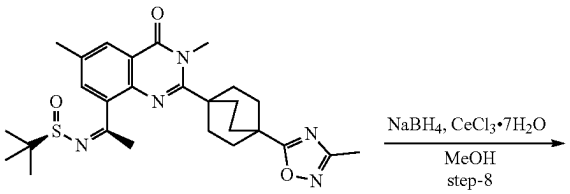

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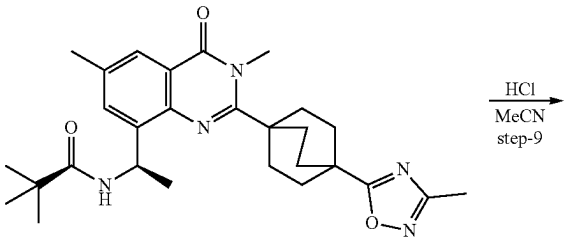

309-8

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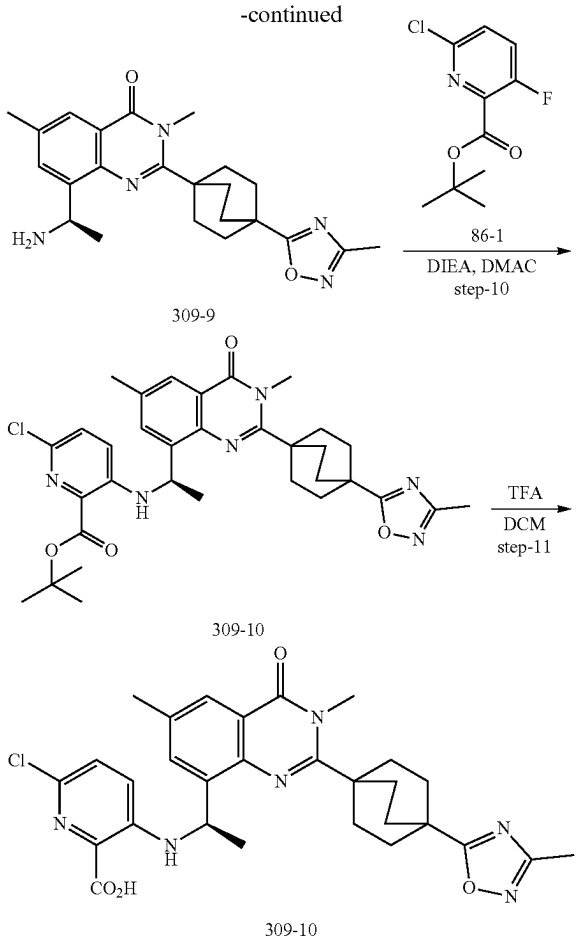


[1124] Step 1: To a solution of 4-(methoxycarbonyl)bicyclo octane-1l-carboxylic acid (6.60 g, 31.1 mmol)) in dichloromethane (40 mL) was added oxalyl chloride (6.58 mL, 77.7 mmol) at room temperature, then the reaction moisture was stirred for 3 hours. The volatile organics were removed under vacuum to give a crude residue which was dissolved in dichloromethane (60 mL), followed addition of pyridine (6.26 mL, 77.7 mmol) and 1-1 (6.3 g, 25.9 mmol) at 0° C. The resulting reaction mixture was stirred for 2 hours at room temperature, and then diluted with saturated sodium bicarbonate aqueous, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude 309-1 (6.9 g).

[1125] Step 2: To a mixture of 309-1 (6.5 g, 14.86 mmol) in MeOH (50 mL) was added NaOH (2.37 g, 59.4 mmol) at room temperature. The mixture was stirred at 60° C. for 4 hours. The mixture was diluted with water, extracted with ethyl acetate. Aqueous layer was adjusted pH <7 with HCl (2 M), filtered, the collected solid was washed with water and dried to give a crude 309-2 (3.3 g).

[1126] Step 3: To a solution of 309-2 (3.3 g, 7.8 mmol) in DMAC (30 mL) was added p-toluenesulfonic acid monohydrate (5.9 g, 31.2 mmol) at room temperature. The mixture was stirred at 140° C. for 16 hours. The mixture was diluted with water, filtered, the cake was washed with water and dried to give 309-3 (1.01 g, crude).

[1127] Step 4: To a mixture of 309-3 (1 g, 2.47 mmol) and ethyldiisopropylamine (1.02 mL, 6.17 mmol) in DMF (10 mL) was added PyBOP (1.67 g, 3.21 mmol), the reaction mixture was stirred at room temperature for 20 minutes. To the above mixture was added N-(1-azanylideneethyl)hydroxylamine (237.62 mg, 3.21 mmol), the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with water, organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude 309-4 (967 mg).

[1128] Step 5: A solution of 309-4 (967 mg, 2.1 mmol) in TBAF (5 mL, 1 M in THF) was stirred at room temperature for 0.5 hours. The mixture was diluted with ethyl acetate, washed with water, organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue which was purified by Combi flash (ethyl acetate in petroleum ether=100%) to give 309-5 (1.05 g).

[1129] Step 6: A mixture of 309-5 (980 mg, 2.21 mmol), tributyl(1-ethoxyvinyl)-x4-stannane (918 mg, 2.5 mmol) and $Pd(PPh_3)_4$ (255.4 mg, 0.22 mmol) in dioxane (10 mL) was stirred at 100° C. overnight under nitrogen atmosphere. Then HCl solution (1 M, 10 mL) was added into the above reaction mixture and the resulting mixture was stirred at 50° C. for 1 hour. The mixture was diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue which was purified by Combi flash (ethyl acetate in petroleum ether=0~100%) to give 309-6 (340 mg).

[1130] Step 7: A mixture of 309-6 (340 mg, 0.84 mmol) and (R)-(2-methylprop-2-yl)(oxo)-λ4-sulfanamine (203 mg, 1.67 mmol) in titanium tetraisopropanolate (6 mL, 0.84 mmol) and THF (3 mL) was stirred at 85° C. for 6 hours under nitrogen atmosphere. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1:1) to give 309-7 (250 mg).

[1131] Step 8: To a mixture of 309-7 (250 mg, 0.49 mmol) and Cerium trichloride heptahydrate (366.5 mg, 0.98 mmol) in MeOH (5 mL) was added NaBH4 (37.6 mg, 0.99 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour before acidification to pH~5 with saturated ammonium chloride solution at 0° C. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1:4) to give 309-8 (246 mg).

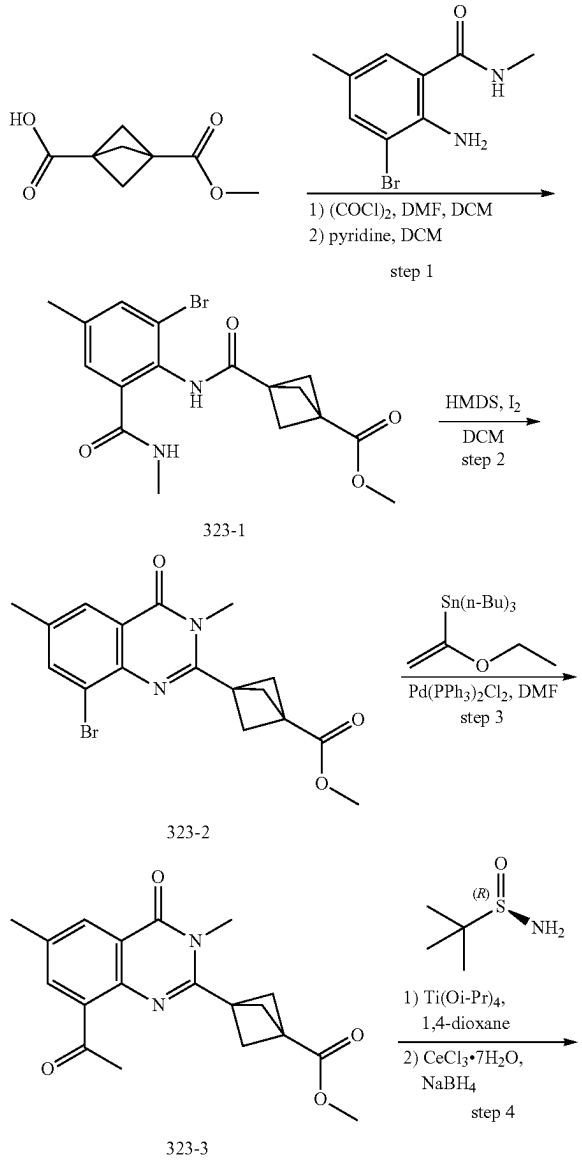
[1132] Step 9: To a mixture of 309-8 (246 mg, 0.48 mmol) in acetonitrile (2 mL) was added HCl in ethyl acetate (0.24 mL, 4 M), the mixture was stirred at 0° C. for 0.5 h. The mixture was diluted with water and adjusted pH>7, extracted with ethyl acetate, organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue which was purified by Combi flash (ethyl acetate in petroleum ether=100%) to give 309-9 (144 mg).

[1133] Step 10: To a mixture of 309-9 (144 mg, 0.35 mmol) in DMAC (3 mL) was added DIEA (137 mg, 1.06 mmol) and 86-1 (163.71 mg, 0.71 mmol), the mixture was stirred at 120° C. for 6 hours. The mixture was diluted with ethyl acetate, washed with water, organic layer was dried

over anhydrous sodium sulfate, filtered and concentrated to give a residue which was purified by Combi flash (ethyl acetate in petroleum ether=100%) to give 309-10 (150 mg).

[1134] Step 11: To a solution of 309-10 (150 mg, 0.24 mmol) in DCM (2 mL) was added TFA (1 mL) at room temperature, the mixture was stirred at room temperature for 2 hours. The mixture was concentrated to give a residue which was purified by Pre-HPLC (0.05% FA in water/acetonitrile) to give 309 (73 mg). LCMS (ESI, m/z): $^{+}$=563.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.58-8.42 (brs, 1H), 7.84-7.79 (m, 1H), 7.61-7.56 (m, 1H), 7.36-7.28 (m, 1H), 7.06-6.97 (m, 1H), 5.51-5.37 (m, 1H), 3.70 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H), 2.31-2.17 (m, 6H), 2.09-2.03 (m, 6H), 1.67-1.57 (m, 3H).

Example 34 Synthesis of Compound 323



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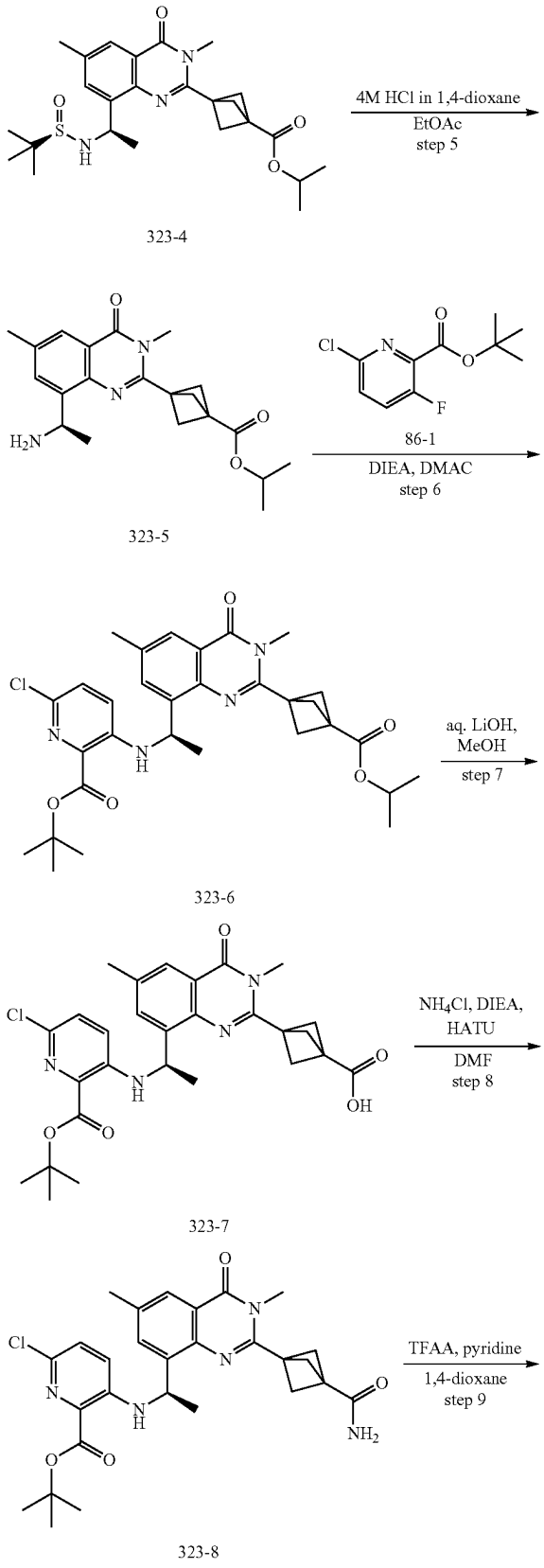

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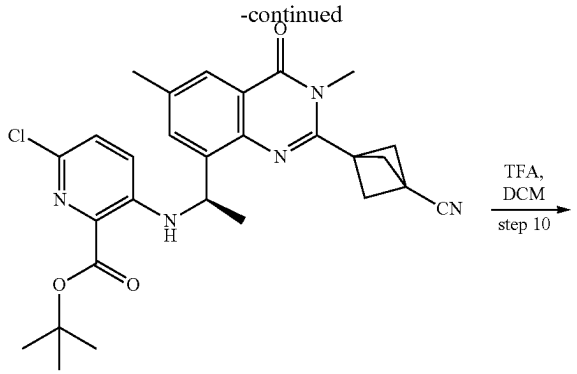
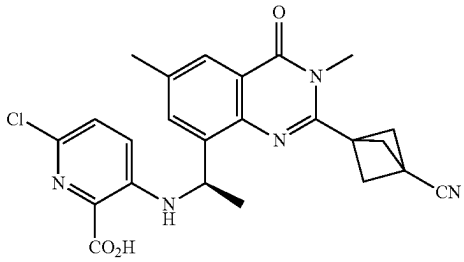


323-8



323

[1135] Step 1: To a solution of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (60 g, 352.61 mmol) in DCM (600 mL) and DMF (10 mL) was added dropwise oxalyl chloride (29.8 mL, 352.61 mmol) and the mixture was stirred for 1 h at 25° C. Then to a solution of 1-1 (60.0 g, 246.81 mmol) in DCM (600 mL) was added pyridine (99.3 mL, 1.23 mol), followed the above reaction mixture solution at 0° C. The reaction mixture was stirred for 2 hours at room temperature. The mixture was quenched with saturated aqueous sodium bicarbonate, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20:1) to give 323-1 (90 g).

[1136] Step 2: A mixture of 323-1 (80 g, 202.40 mmol), 12 (102.7 g, 404.81 mmol) and HMDS (130.7 g, 809.61 mmol) in DCM (500 mL) was stirred at 40° C. for 1 h. The reaction mixture was cooled to room temperature and quenched with aq. $Na_2S_2O_3$ solution. The organic phase was separated and the aqueous phase was extracted with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford 323-2 (70.0 g).

[1137] Step 3: A mixture of 323-2 (30 g, 70.22 mmol), tributyl(1-ethoxyvinyl)-λ4-stannane (40.3 mL, 119.29 mmol) and bis(triphenylphosphine)palladium(II) chloride (8.4 g, 11.93 mmol) in DMF (300 mL) was degassed three times under nitrogen gas and stirred at 120° C. for 1 h. The reaction mixture was cooled to room temperature and 10% aq. KF solution (600 mL) was added. The resulting mixture was stirred for 30 min. Then aq. HCl solution (6 M) was added and the mixture was stirred at 50° C. for 5 h. The mixture was basified pH to 7.0 with sat. aq. $NaHCO_3$ solution, extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash silica gel column eluted with 0 to 36% EtOAc in petroleum ether to give 323-3 (12 g).

[1138] Step 4: A solution of 323-3 (5 g, 14.69 mmol), (R)-(2-methylprop-2-yl) (oxo)-λ4-sulfanamine (3.56 g, 29.38 mmol) and titanium tetraisopropanolate (20.9 g, 73.45 mmol) in 1,4-dioxane (50 mL) was stirred at 65° C. for 40 h. The reaction mixture was cooled to 0° C., then Cerium trichloride heptahydrate (1.8 g, 7.35 mmol) and NaBH4 (0.8 g, 22.03 mmol) were added and the resulting mixture was stirred at 25° C. for 1 h. The reaction mixture was quenched with H_2O, extracted with EtOAc. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with 5-60% ethyl acetate/petroleum) to yield 323-4 (6 g).

[1139] Step 5: The mixture of 323-4 (1.3 g, 2.83 mmol) and HCl solution (4.95 mL, 4 M in 1,4-dioxane) in EtOAc (5 mL) was stirred at 25° C. for 1 h. The suspension was diluted with EtOAc (50 mL), washed with diluted. aq. $NH_{40}H$ solution, water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give crude 323-5 (900 mg), which was used directly for next step.

[1140] Step 6: To a solution of 323-5 (900 mg, 2.44 mmol) and 2-methylpropan-2-yl 6-chloro-3-fluoropyridine-2-carboxylate (1128.59 mg, 4.87 mmol) in DMAC (10 mL) was added DIPEA (1.610 mL, 9.74 mmol) and the reaction mixture was stirred at 110° C. for 16 h. The reaction mixture was cooled to room temperature, quenched with H_2O, extracted with EtOAc. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with 5-60% ethyl acetate/petroleum) to yield 323-6 (1.2 g).

[1141] Step 7: To a solution of 323-6 (220 mg, 0.39 mmol) in MeOH (5 mL) and H_2O (5 mL) was added LiOH (81.4 mg, 1.94 mmol) and the reaction mixture was stirred at 25° C. for 16 h. The solution was purified by C18 reverse phase column (Acetonitrile; 0.05% TFA in water: 0 to 100%) to afford 323-7 (180 mg).

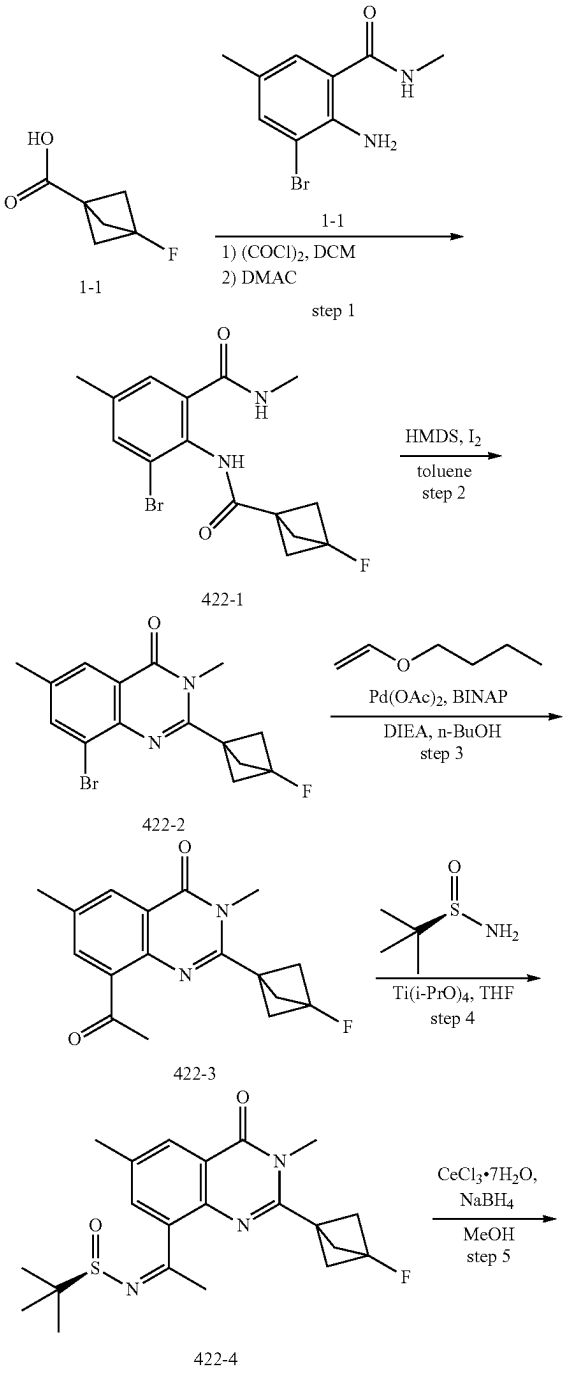
[1142] Step 8: To a solution of 323-7 (400 mg, 0.74 mmol) in DMF (5 mL) were added HATU (338.6 mg, 0.89 mmol), TEA (0.31 mL, 2.23 mmol) and NH_4Cl (79.4 mg, 1.48 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated, the residue was purified by C18 reverse phase column (acetonitrile; 0.1% FA in water: 0%~70%, keep at 50%) to afford 323-8 (178 mg).

[1143] Step 9: To a solution of 323-8 (80 mg, 0.15 mmol) in 1,4-dioxane (2 mL) were added pyridine (0.024 mL, 0.30 mmol) and TFAA (0.025 mL, 0.18 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with water, extracted with EtOAc. The combined organic layers were washed with saturated aq. NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by C18 reverse phase column (acetonitrile; 0.1% FA in water: 0%~70%) to afford 323-9 (70 mg).

[1144] Step 10: A solution of 323-9 (90 mg, 0.17 mmol) in DCM (4 mL) and TFA (1 mL) was stirred at 25° C. for 3 hours. The reaction was diluted with EtOAc (50 mL), washed with saturated aq. $NaHCO_3$ solution and further

saturated NaCl solution. Organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by C18 reverse phase column (acetonitrile; 0.1% FA in water: 0%~70%) to afford 323 (21.9 mg). LCMS (ESI, m/z): $^+$=464.4; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.39 (d, J=8.0 Hz, 1H), 7.95 (s, 1H), 7.47 (s, 1H), 7.13 (d, J=6.0 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 5.39-5.28 (m, 1H), 3.68 (s, 3H), 2.95-2.78 (m, 6H), 2.41 (s, 3H), 1.68 (d, J=8.0 Hz, 3H).

Example 35 Synthesis of Compound 422



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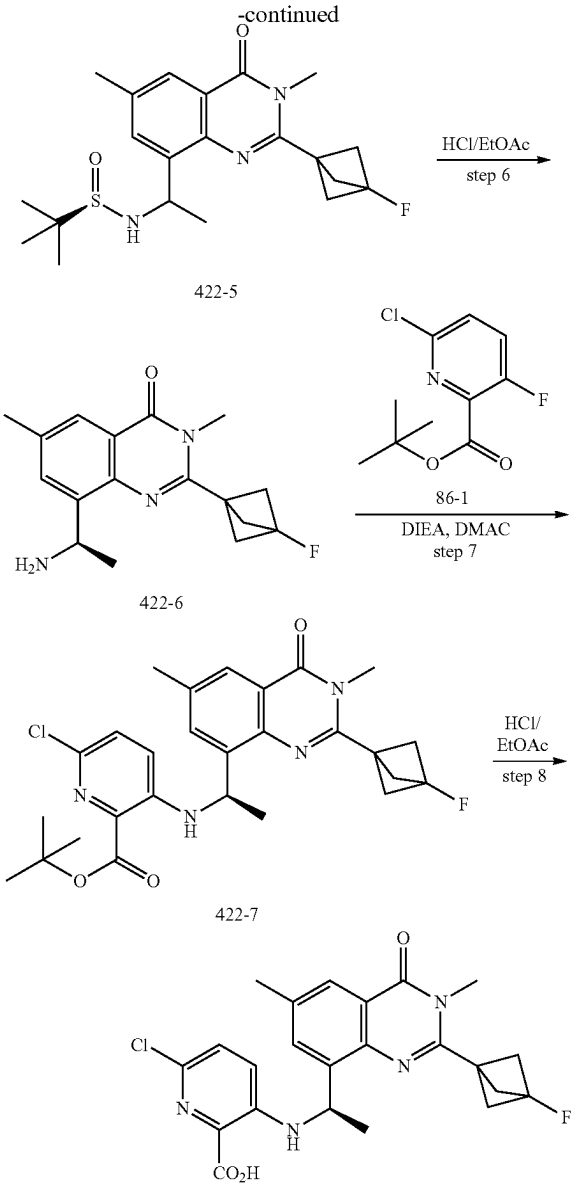


[1145] Step 1: To a solution of 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid (1.09 g, 8.39 mmol) in dichloromethane (10 mL) was added oxalyl chloride (1.8 mL, 20.98 mmol) and 2 drops of DMF at room temperature and the reaction mixture was stirred for 1 hour. Then the above reaction mixture was added to a solution of 1-1 (1.7 g, 6.99 mmol) in N, N-dimethylacetamide (10 mL) at room temperature. The resulting reaction mixture was stirred for 0.5 hours at room temperature. The mixture was diluted with water, filtered, the cake was washed with water, the collected cake was dried to give 422-1 (1.2 g, crude).

[1146] Step 2: To a solution of 422-1 (1 g, 2.82 mmol) in toluene (15 mL) were added hexamethyldisilazane (1.4 g, 8.45 mmol) and iodine (0.7 g, 2.82 mmol) at room temperature. The mixture was stirred at 120° C. for 2 hours. The mixture was cooled to room temperature, then quenched

with aqueous sodium thiosulfate, extracted with ethyl acetate. The organic layer was separated, washed with brine, and concentrated in vacuo to give 422-2 (900 mg, crude).

[1147] Step 3: To a solution of 422-2 (850 mg, 2.52 mmol) in 1-butanol (10 mL) were added Palladium (II) acetate (17.0 mg, 0.076 mmol), 1,1'-binaphthyl-2,2'-diphenyl phosphine (94.2 mg, 0.15 mmol), N, N-diisopropylethylamine (1.0 mL, 6.05 mmol) and 1-(vinyloxy) butane (757.5 mg, 7.56 mmol). The reaction mixture was stirred at 85° C. for 16 hours under nitrogen atmosphere. The mixture was filtered and washed with ethyl acetate, the filtrate was concentrated in vacuo. The residue was dissolved with dichloromethane and hydrochloric acid (2 M) and stirred for 1 hour at room temperature. The resulting mixture was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether to petroleum ether/ethyl acetate=3/1) to afford 422-3 (650 mg).

[1148] Step 4: A mixture of 422-3 (650 mg, 2.16 mmol) and (R)-2-methylpropane-2-sulfinamide (524.62 mg, 4.33 mmol) in tetrahydrofuran (10 mL) and titanium tetraisopropanolate (40 mL) was stirred at 90° C. for 16 hours. The mixture was cooled to rt and then quenched with brine, stirred for 0.5 hours and filtered. The filter cake was washed with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 422-4 (700 mg, crude).

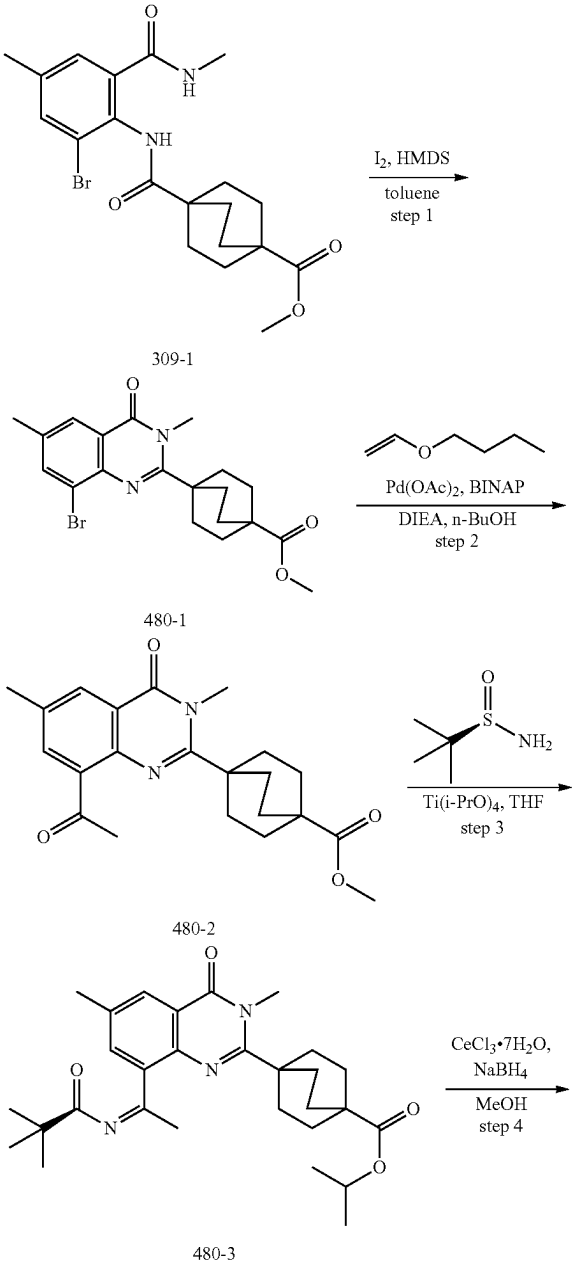
[1149] Step 5: To a mixture of 422-4 (600 mg, 1.48 mmol) and Cerium trichloride heptahydrate (277.3 mg, 0.74 mmol) in methanol (15 mL) was added sodium borohydride (112.5 mg, 2.974 mmol) in portions at room temperature, and stirred at 20° C. for 16 hours. The reaction mixture was quenched with saturated ammonium chloride and filtered. The filter cake was washed with dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reversed phase chromatography (0.05% formic acid in water/acetonitrile) to give 422-5 (250 mg).

[1150] Step 6: To a mixture of 422-5 (250 mg, 0.62 mmol) in ethyl acetate (8 mL) was added hydrochloric acid (0.62 mL, 4 M in ethyl acetate), and stirred at room temperature for 2 hours. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was adjusted to pH=12 with aqueous ammonia (w/w, 25%) and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 422-6 (120 mg, crude).

[1151] Step 7: A mixture of 422-6 (120 mg, 0.40 mmol), 86-1 (110.7 mg, 0.48 mmol) and N, N-diisopropylethylamine (0.33 mL, 1.99 mmol) in N, N-dimethylacetamide (5 mL) was stirred at 110° C. for 6 hours. The mixture was cooled to room temperature and then quenched with water, extracted with ethyl acetate. The organic layer was separated, washed with brine, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=5/1) to give 422-7 (150 mg).

[1152] Step 8: To a mixture of 422-7 (150 mg, 0.29 mmol) in ethyl acetate (10 mL) was added HCl solution (0.29 mL, 4 M in ethyl acetate), and stirred at room temperature for 3 hours. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC (acetonitrile/0.05% formic acid in water: 25%~95%) to give 422 (83.9 mg). LCMS (ESI, m/z): $^{+}$=457.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.96-8.41 (m, 1H), 7.87-7.72 (m, 1H), 7.69-7.58 (m, 1H), 7.37-7.23 (m, 1H), 7.23-7.03 (m, 1H), 5.52-5.12 (m, 1H), 3.57 (s, 3H), 2.80-2.58 (m, 6H), 2.38 (s, 3H), 1.63 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −148.35 (1F).

Example 36 Synthesis of Compound 480



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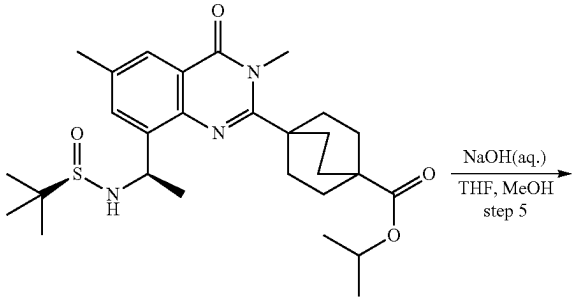

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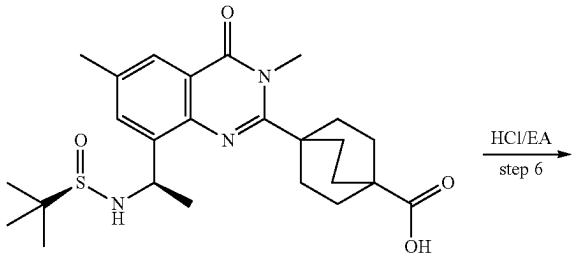

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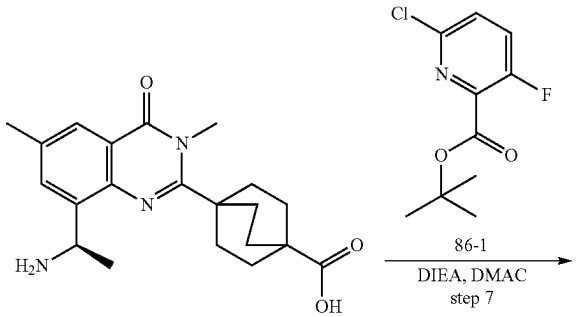
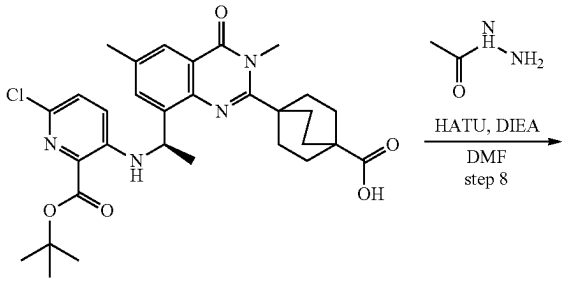
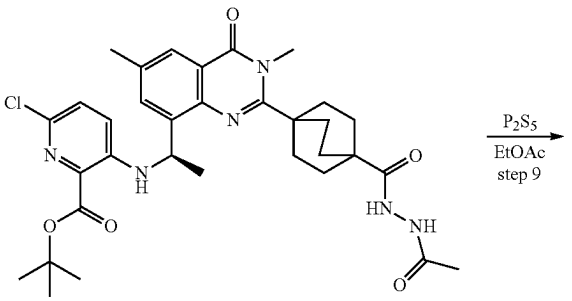


480-6



480-7



480-8

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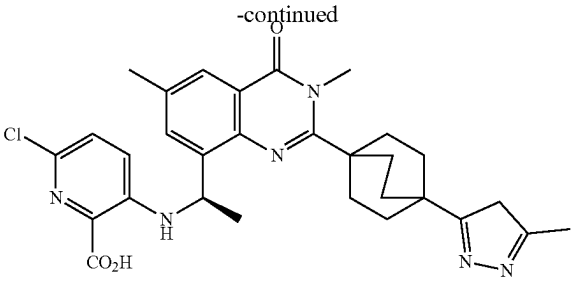


480

[1153] Step 1: To a solution of 309-1 (50 g, 114.33 mmol) in toluene (200 mL) were added Iodine (29 g, 114.3 mmol) and HMDS (71.5 mL, 342.9 mmol) at rt. The reaction was stirred at 120° C. for 2 hours, and then quenched with saturated $NaHSO_3$ aqueous solution, extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was dried over vacuo to give 480-1 (38 g, crude).

[1154] Step 2: To a solution of 480-1 (6.00 g, 14.31 mmol) in 1-butanol (120 mL) was added palladium (II) acetate (321.2 mg, 1.43 mmol), 1,1'-binaphthyl-2,2'-diphenyl phosphine (1.78 g, 2.86 mmol), 1-(vinyloxy) butane (4.30 g, 42.95 mmol) and N, N-diisopropylethylamine (5.9 mL, 35.77 mmol). The mixture was stirred at 85° C. for 22 hours under N_2 atmosphere. HCl aqueous solution (1 M) was added into the reaction mixture, and the resulting mixture was stirred at room temperature for 15 mins. The mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (50% ethyl acetate in petroleum ether) to afford 480-2 (3 g).

[1155] Step 3: To a solution of 480-2 (4.1 g, 10.72 mmol) in tetrahydrofuran (20 mL) and titanium tetraisopropanolate (40 mL) was added (R)-(2-methylprop-2-yl)(oxo)-λ4-sulfanamine (1.95 g, 16.08 mmol). The mixture was stirred at 90° C. for 16 hours under N_2 atmosphere. The mixture was diluted with water and extracted with ethyl acetate, organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to afford 480-3 (3.5 g, crude).

[1156] Step 4: To a solution of 480-3 (3.50 g, 6.81 mmol) in methanol (45 mL) was added Cerium trichloride heptahydrate (5.08 g, 13.63 mmol) and sodium cyanoborohydride (515.5 mg, 13.63 mmol). The mixture was stirred at 25° C. for 30 mins. The mixture was diluted with water and extracted with ethyl acetate, organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (85% ethyl acetate in petroleum ether) to afford 480-4 (1.5 g).

[1157] Step 5: To a solution of 480-4 (500 mg, 0.97 mmol) in methanol (12 mL) and tetrahydrofuran (12 mL) was added sodium hydroxide aqueous solution (4.85 mL, 19.39 mmol, 4 M). The mixture was stirred at 25° C. for 16 hours. The mixture was extracted with tert-butyl methyl ether. The water phase was adjusted to pH=2, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated to afford 480-5 (423 mg, crude).

[1158] Step 6: A solution of 480-5 (400 mg, 0.845 mmol) in HCl solution (8 mL, 4 M in ethyl acetate) was stirred at 25° C. for 16 hours. The mixture was adjusted to pH=9 with saturated sodium bicarbonate (aq.) solution, and extracted

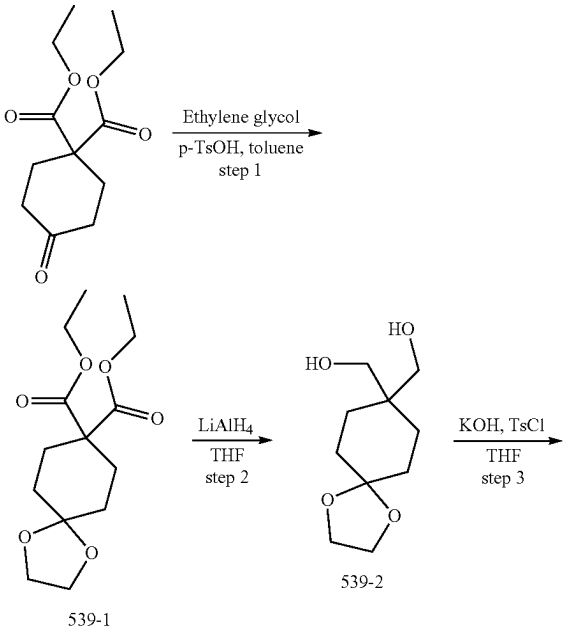
with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated to afford 480-6 (285 mg, crude).

[1159] Step 7: To a solution of 480-6 (285 mg, 0.77 mmol) in N, N-dimethylacetamide (20 mL) were added 86-1 (268.04 mg, 1.16 mmol) and N, N-diisopropylethylamine (349.0 mg, 2.70 mmol). The mixture was stirred at 110° C. for 6 hours. The mixture was diluted with water and extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (85% ethyl acetate in petroleum ether) to afford 480-7 (150 mg, crude).

[1160] Step 8: To a solution of 480-7 (90 mg, 0.16 mmol) in N, N-dimethylformamide (3 mL) was added HATU (64.8 mg, 0.17 mmol), acetohydrazide (11.48 mg, 0.16 mmol) and N, N-diisopropylethylamine (0.077 mL, 0.47 mmol). The mixture was stirred at 25° C. for 2 hours. The mixture was diluted with saturated sodium carbonate (aq.) solution and extracted with ethyl acetate, organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to afford 480-8 (85 mg, crude).

[1161] Step 9: To a solution of 480-8 (85 mg, 0.13 mmol) in ethyl acetate (5 mL) was added Phosphorus pentasulfide (118.6 mg, 0.53 mmol). The mixture was stirred at 75° C. for 16 hours. The mixture was diluted with saturated sodium bicarbonate (aq.) solution and extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated, the residue was purified by prep-HPLC (7000 ACN in FA) to afford 480 (19.57 mg). LCMS (ESI, m/z): $^{+}$=579.2. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.99 (brs, 1H), 8.50 (s, 1H), 7.81 (s, 1H), 7.59 (s, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.04 (d, J=8.8 Hz, 1H), 5.50-5.37 (m, 1H), 3.72 (s, 3H), 2.70 (s, 3H), 2.38 (s, 3H), 2.30 (dd, J=19.2, 10.4 Hz, 6H), 2.07 (t, J=7.6 Hz, 6H), 1.63 (d, J=6.4 Hz, 3H).

Example 37 Synthesis of Compound 539



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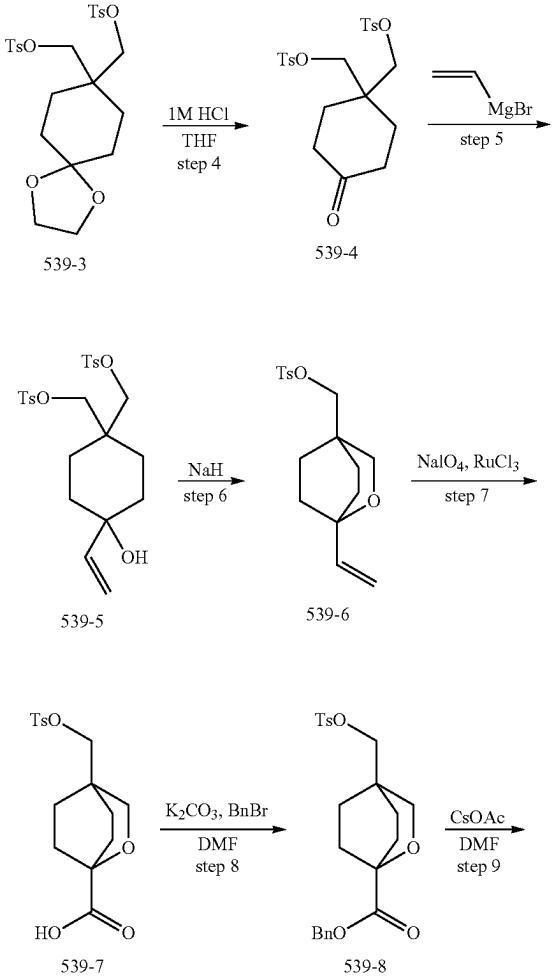

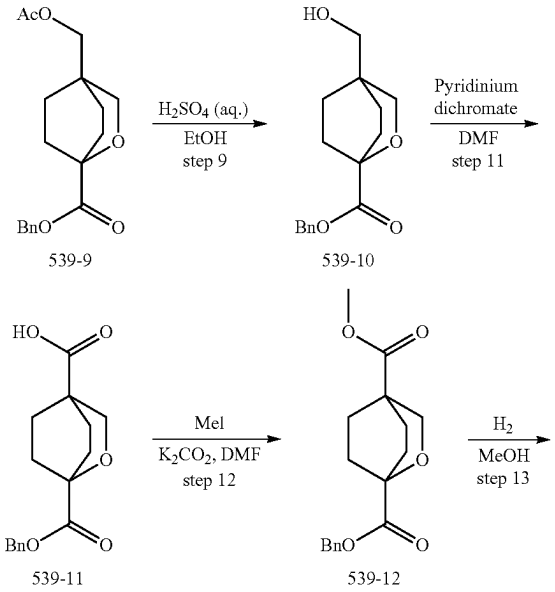

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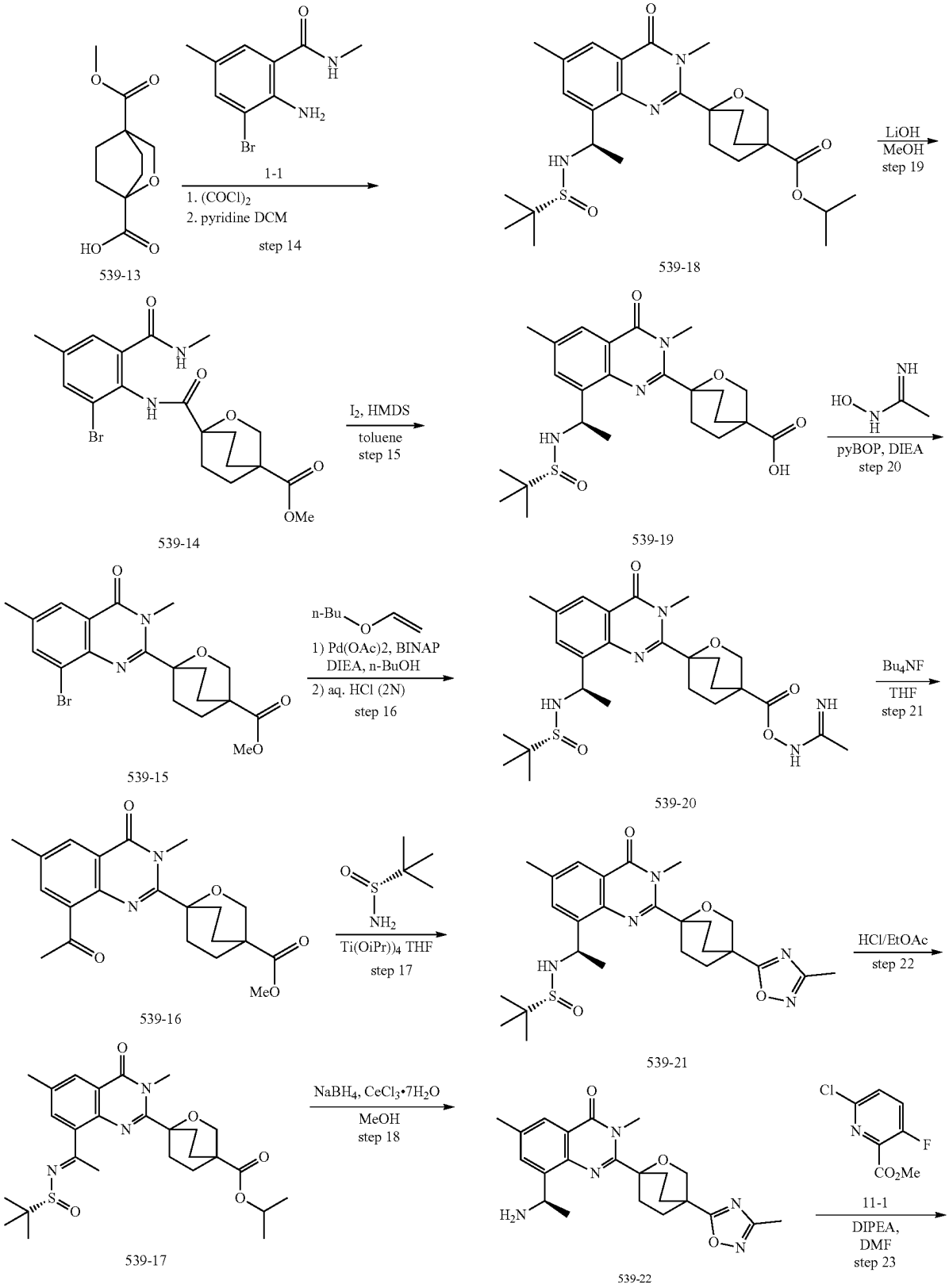
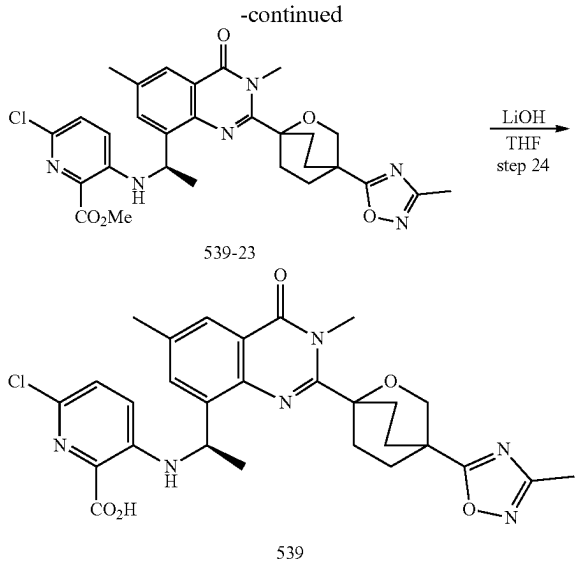

1-1
1. (COCl)2
2. pyridine DCM
step 14
539-13
539-14
I2, HMDS
toluene
step 15
539-15
n-Bu
1) Pd(OAc)2, BINAP
DIEA, n-BuOH
2) aq. HCl (2N)
step 16
539-16
Ti(OiPr))4 THF
step 17
539-17
NaBH4, CeCl3•7H2O
MeOH
step 18
539-18
LiOH
MeOH
step 19
539-19
pyBOP, DIEA
step 20
539-20
Bu4NF
THF
step 21
539-21
HCl/EtOAc
step 22
539-22
11-1
DIPEA,
DMF
step 23

-continued



[1162] Step 1: A mixture of ethyl 1-(ethoxycarbonyl)-4-oxocyclohexane-1-carboxylate (50 g, 206.38 mmol), ethylene glycol (13.8 mL, 247.66 mmol) and p-toluenesulfonic acid monohydrate (0.4 g, 2.06 mmol) in toluene (500 mL) was stirred at 110° C. for 16 hours under nitrogen atmosphere. The mixture was poured into saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=5/1) to give 539-1 (51 g).

[1163] Step 2: To a mixture of lithium aluminum hydride (13.9 g, 365.15 mmol) in tetrahydrofuran (500 mL) was added dropwise a solution of 539-1 (51 g, 178.12 mmol) in tetrahydrofuran (500 mL) at −20° C. The mixture was stirred at 0° C. for 3 hours. The reaction was quenched with water (14 mL), 30% sodium hydroxide solution (14 mL) and water (42 mL) at 0° C. and the resulting mixture was stirred at room temperature overnight. The reaction mixture was filtered and concentrated. The crude product was stirred in petroleum ether/ethyl acetate=5/1 at room temperature for 30 minutes. The collected solids via filtration were dried to afford 539-2 (28.7 g, crude).

[1164] Step 3: To a mixture of 539-2 (27.8 g, 137.45 mmol) and potassium hydroxide (61.7 g, 1099.63 mmol) in tetrahydrofuran (500 mL) was added 4-methylbenzenesulfonyl chloride (53.72 g, 281.78 mmol) at 0° C. The mixture was stirred at room temperature for 3 hours, filtered and washed with tetrahydrofuran. The organic phase was concentrated to give 539-3 (65 g, crude).

[1165] Step 4: To a mixture of 539-3 (65 g, 127.30 mmol) in tetrahydrofuran (500 mL) was added HCl aqueous solution (250 mL, 1 M) at room temperature. The mixture was stirred at 70° C. for 16 hours. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was stirred in petroleum ether/ethyl acetate=10/1 at room temperature for 30 minutes. The collected solids via filtration were dried to afford 539-4 (51 g, crude).

[1166] Step 5: To a solution of bromo(vinyl)magnesium (128.60 mL, 128.60 mmol) was added a solution of 539-4 (30 g, 64.30 mmol) in tetrahydrofuran (300 mL) at −78° C. The mixture was stirred at 0° C. for 2 hours and then quenched with saturated ammonium chloride solution at 0° C. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-5 (32 g, crude), which was used directly in the next step.

[1167] Step 6: To a solution of 539-5 (31.8 g, 64.29 mmol) in 1,2-dimethoxy-ethan (1200 mL) was added sodium hydride (5.1 g, 128.58 mmol) at 0° C., then stirred at room temperature for 30 min under N_2 atmosphere. The mixture was stirred at 85° C. for 16 hours under N_2 atmosphere and then quenched with saturated ammonium chloride solution at 0° C. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=10/1) to give 539-6 (17 g).

[1168] Step 7: To a mixture of 539-6 (18.4 g, 57.07 mmol) in water (200 mL), acetonitrile (200 mL) and dichloromethane (200 mL) were added ruthenium(III) chloride (0.6 g, 2.85 mmol) and sodium periodate (48.8 g, 228.27 mmol) at 0° C. The mixture was stirred at room temperature for 16 hours and then quenched with HCl (aq. 1 M). The resulting solution was filtered and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-7 (20 g, crude), which was used directly in the next step.

[1169] Step 8: To a mixture of 539-7 (19.4 g, 56.99 mmol) and potassium carbonate (15.8 g, 113.99 mmol) in N, N-dimethylformamide (200 mL) was added (bromomethyl) benzene (9.75 g, 56.99 mmol) at 0° C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 539-8 (20.5 g).

[1170] Step 9: A mixture of 539-8 (20.4 g, 47.39 mmol) and cesium acetate (20.0 g, 104.25 mmol) in N, N-dimethylformamide (250 mL) was stirred at 110° C. for 16 hours under nitrogen atmosphere. The reaction mixture was diluted with H_2O. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-9 (14 g).

[1171] Step 10: To a solution of 539-9 (12.5 g, 39.26 mmol) in ethanol (112 mL) was added H_2SO_4 (aq.) (75 mL, 18.75 mmol, 0.25 M) at room temperature, then stirred at 55° C. for 16 hours under N_2 atmosphere. The reaction mixture was diluted with saturated sodium bicarbonate aqueous, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1/2) to give 539-10 (6.2 g).

[1172] Step 11: A mixture of 539-10 (6.2 g, 22.44 mmol) and pyridinium dichromate (21.1 g, 56.09 mmol) in N, N-dimethylformamide (80 mL) was stirred at 40° C. for 3

hours under nitrogen atmosphere. The reaction mixture was diluted with H_2O, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20:1) to give 539-11 (4 g).

[1173] Step 12: To a mixture of 539-11 (2 g, 6.89 mmol) and potassium carbonate (1.9 g, 13.78 mmol) in N, N-dimethylformamide (30 mL) was added Iodomethane (1.5 g, 10.33 mmol) at 0° C. The mixture was stirred at rt for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=3/1) to give 539-12 (2 g).

[1174] Step 13: To a solution of 539-12 (2 g, 6.57 mmol) in methanol (40 mL) was added Pd/C (400 mg, 5% w/w). The mixture was stirred at room temperature for 16 hours under hydrogen atmosphere. The mixture was filtered through a celite pad and washed with methanol, the filtrate was concentrated to give 539-13 (1.4 g).

[1175] Step 14: To a solution of 539-13 (1.4 g, 6.54 mmol) in dichloromethane (20 mL) was added oxalyl chloride (2.2 mL, 26.1 mmol) and two drops N, N-dimethylformamide and at room temperature, then the reaction mixture was stirred for 3 hours. The volatile organics were removed under vacuum. The crude residue was dissolved in dichloromethane (10 mL), and to the above solution was added pyridine (2.10 mL, 26.14 mmol) and 1-1 (1.51 g, 6.20 mmol) at 0° C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted water, extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20:1) to give 539-14 (2.6 g).

[1176] Step 15: To a mixture of 539-14 (2.6 g, 5.92 mmol) in toluene (40 mL) was added hexamethyldisilazane (2.4 g, 14.80 mmol) and Iodine (1.8 g, 7.10 mmol) at room temperature. The mixture was stirred at 110° C. for 1 hour and then quenched with saturated $Na_2S_2O_3$ aqueous solution, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=4/1) to give 539-15 (1.8 g).

[1177] Step 16: A mixture of 539-15 (1.6 g, 3.80 mmol), N, N-diisopropylethylamine (1.5 g, 9.12 mmol), BINAP (237 mg, 0.38 mmol), $Pd(OAc)_2$ (43 mg, 0.19 mmol) and 1-(vinyloxy)butane (1.14 g, 11.39 mmol)) in 1-butanol (16 mL) was stirred at 85° C. for 16 hours under nitrogen atmosphere. Then HCl aqueous solution (20 mL, 2 M) was added into the mixture and the resulting mixture was stirred at room temperature for 1 hour and filtered. The filtrate was extracted with ethyl acetate. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=2/1) to give 539-16 (1.4 g).

[1178] Step 17: To a mixture of 539-16 (1.35 g, 3.51 mmol) and (R)-2-methylpropane-2-sulfinamide (0.64 g, 5.27 mmol) in tetrahydrofuran (6 mL) was added titanium tetraisopropanolate (12 mL) at room temperature. The mixture was stirred at 85° C. for 16 hours and then diluted with water, extracted with ethyl acetate and washed with water. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-17 (2.0 g, crude).

[1179] Step 18: To a mixture of 539-17 (2.0 g, 3.87 mmol) and cerium chloride heptahydrate (2.6 g, 6.98 mmol) in methanol (30 mL) was added sodium borohydride (0.3 g, 6.98 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour and acidified pH~5 with saturated ammonium chloride solution at 0° C., extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20:1) to give 539-18 (980 mg).

[1180] Step 19: To a mixture of 539-18 (980 mg, 1.89 mmol) in methanol (10 mL) was added a solution of lithium hydroxide aqueous solution (9.5 mL, 9.5 mmol, 1 M) at room temperature. The mixture was stirred at 50° C. for 2 hours and acidified pH~3 with HCl (aq. 1 M) at 0° C. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-19 (900 mg).

[1181] Step 20: To a mixture of 539-19 (550 mg, 1.16 mmol) and N, N-diisopropylethylamine (374 mg, 2.89 mmol) in N, N-dimethylformamide (8 mL) was added PyBOP (722 mg, 1.39 mmol), the reaction mixture was stirred at room temperature for 20 minutes. To the above reaction mixture was added N-(1-azanylideneethyl)hydroxylamine (111 mg, 1.50 mmol), then the reaction mixture was stirred at room temperature for 1 hour. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-20 (800 mg, crude).

[1182] Step 21: To a mixture of 539-20 (500 mg, 0.94 mmol) in tetrahydrofuran (3 mL) was added TBAF solution (3 mL, 1 M in THF) at 0° C. The mixture was stirred at room temperature for 20 min and acidified pH~5 with saturated ammonium chloride solution at 0° C. The resulting solution was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1/4) to give 539-21 (410 mg).

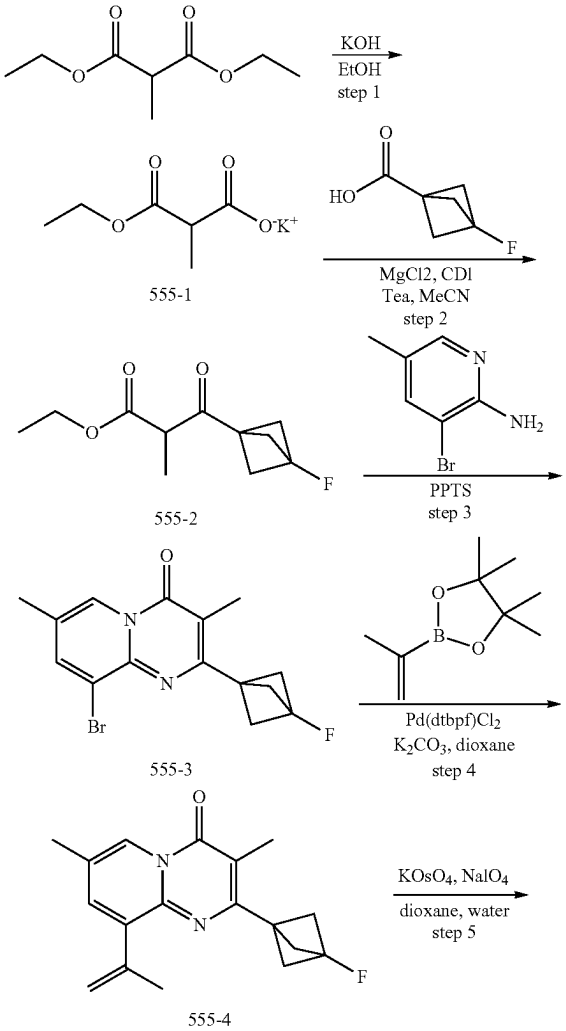
[1183] Step 22: To a mixture of 539-21 (410 mg, 0.80 mmol) in ethyl acetate (4 mL) was added HCl solution (4 mL, 4 M in ethyl acetate) at 0° C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The aqueous phase was adjusted to pH=12 with $NH_3 \cdot H_2O$ (25% w/w) and extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 539-22 (315 mg).

[1184] Step 23: A mixture of 539-22 (310 mg, 0.76 mmol), N, N-diisopropylethylamine (0.50 mL, 3.03 mmol) and 11-1 (215 mg, 1.14 mmol) in N, N-dimethylformamide (3 mL) was stirred at 120° C. for 16 hours under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered

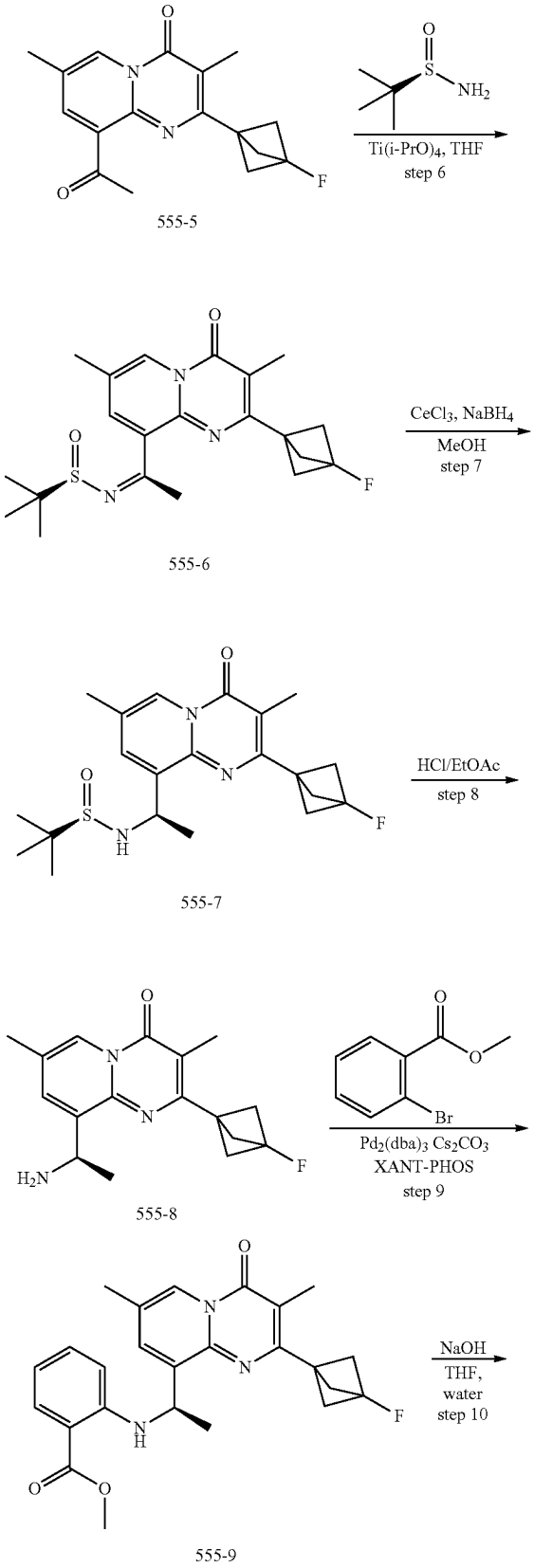
and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=1/1) to give 539-23 (400 mg).

[1185] Step 24: To a mixture of 539-23 (400 mg, 0.69 mmol) in tetrahydrofuran (5 mL) was added lithium hydroxide (1.38 mL, 1.38 mmol, 1 M in water) at room temperature. The mixture was stirred at 40° C. for 2 hours and acidified to pH~3 with HCl (aq. 1 M) at 0° C. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC (acetonitrile/0.05% FA in water: 10%~95%) to give 539 (272 mg). LCMS (ESI, m/z): $^{+}$=565.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.00 (brs, 1H), 8.50-8.37 (m, 1H), 7.87-7.79 (m, 1H), 7.66-7.57 (m, 1H), 7.38-7.30 (m, 1H), 7.12-7.00 (m, 1H), 5.48-5.30 (m, 1H), 4.28-4.16 (m, 2H), 3.78 (s, 3H), 2.72-2.53 (m, 2H), 2.48-2.41 (m, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 2.30-2.19 (m, 5H), 1.63 (d, J=6.4 Hz, 3H).

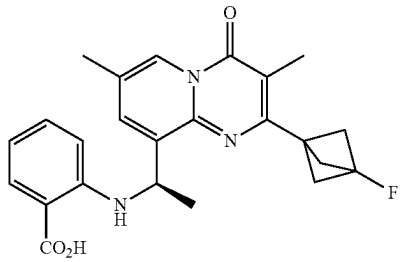
Example 38 Synthesis of Compound 555



-continued



-continued



555

[1186] Step 1: To a mixture of KOH (17.9 g, 287 mmol) in EtOH (500 mL) were added ethyl 3-ethoxy-2-methyl-3-oxopropanoate (50 g, 287 mmol), and the reaction was stirred at 80° C. overnight. The mixture was allowed to cool down to rt. The resulting mixture was concentrated under reduced pressure. The residue was treated with diisopropyl ether and stirred for 10 mins. The precipitated solid was collected by filtration and washed with diisopropyl ether, dried to give 555-1 (45 g, crude), which was used directly in the next step.

[1187] Step 2: To a solution of 555-1 (22.6 g, 122 mmol) and magnesium chloride (14.6 g, 153 mmol) in ACN (100 mL) was added TEA (27.3 mL, 196 mmol). The reaction mixture was stirred 20° C. for 1.0 hour. To the mixture was added a mixture of 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid (8.0 g, 61 mmol) and CDI (11.0 g, 67 mmol) in MeCN (80.0 mL) which was premixed at 20° C. for 1.0 hour, the resulting mixture was stirred at 80° C. for 16 hours. The mixture was filtered, and the filter cake was washed with DCM, the combined filtrate was concentrated under vacuum. The residue was purified by silica gel column (5-10% ethyl acetate in petroleum ether) to give 555-2 (7.1 g).

[1188] Step 3: A mixture of 555-2 (1.2 g, 5.7 mmol), pyridinium p-toluenesulfonate (143.1 mg, 0.5 mmol) and 3-bromo-5-methylpyridin-2-amine (1.1 g, 5.6 mmol) was stirred at 130° C. for 16 hours. The reaction was purified by prep-HPLC (acetonitrile/0.05% FA in water: 5%~80%) to afford 555-3 (500 mg).

[1189] Step 4: A mixture of 555-3 (500 mg, 1.5 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (373.77 mg, 2.224 mmol), Pd(dtbpf)Cl_2 (96.9 mg, 0.15 mmol) and K_2CO_3 (409.9 mg, 3.0 mmol) in dioxane (5.0 mL) and water (1.0 mL) was stirred at 100° C. for 1.0 hour under nitrogen atmosphere. The mixture was diluted with water and extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and evaporated, the residue was purified by flash column chromatography (25% ethyl acetate in petroleum ether) to give 555-4 (320 mg).

[1190] Step 5: The mixture of 555-4 (320 mg, 1.1 mmol) and Potassium osmate (VI) dihydrate (19.8 mg, 0.05 mmol) in dioxane (4.0 mL) and water (2.0 mL) was stirred at room temperature for 1.0 hour under air atmosphere. To the above mixture was added sodium periodate (573.5 mg, 2.7 mmol), the resulting mixture was stirred at room temperature for 1.0 hour. The reaction mixture was diluted with water and extracted with EtOAc, washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in petroleum ether) to give 555-5 (160 mg).

[1191] Step 6: The mixture of 555-5 (160 mg, 0.5 mmol) and (R)-2-methylpropane-2-sulfinamide (129.1 mg, 1.06 mmol) in THF (0.5 mL) and titanium tetraisopropanolate (1.0 mL, 0.53 mmol) was stirred at 110° C. overnight under N_2 atmosphere. The mixture was diluted with water, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated to give 555-6 (160 mg, crude), which was used directly in the next step.

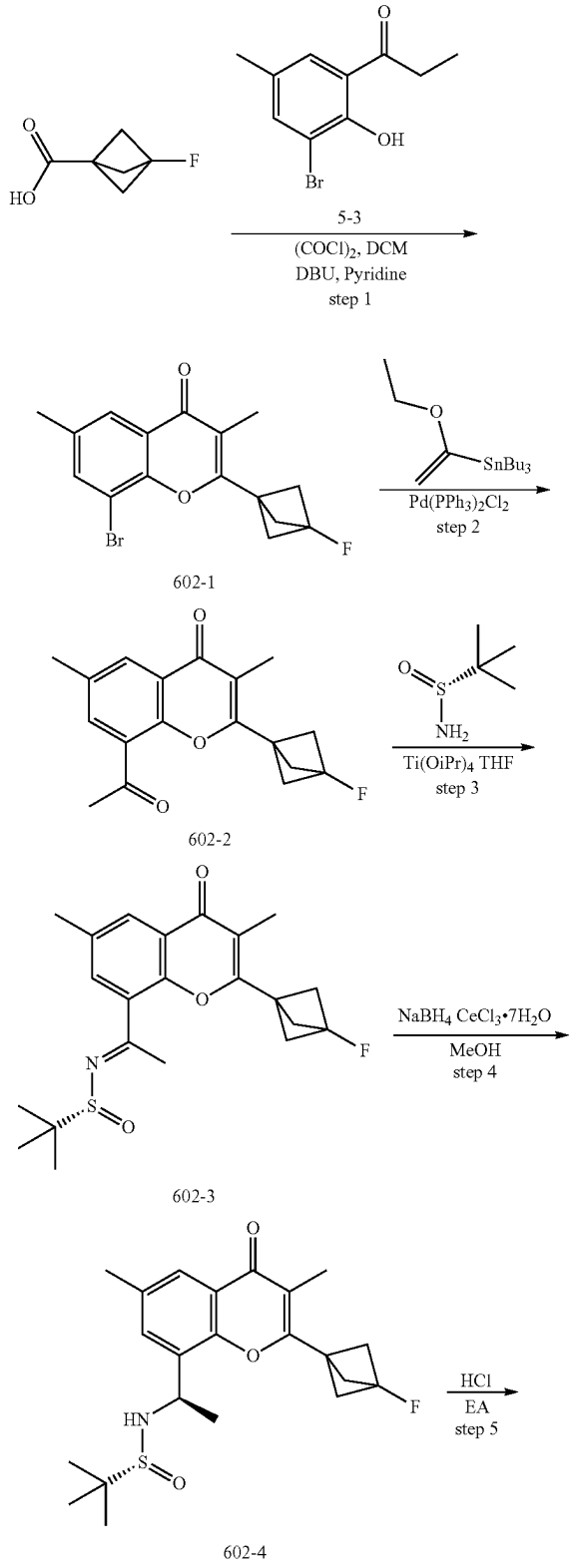
[1192] Step 7: To a mixture of 555-6 (160 mg, 0.4 mmol) and cerium (III) chloride heptahydrate (295.5 mg, 0.8 mmol) in MeOH (3.0 mL) was added NaBH4 (30.0 mg, 0.8 mmol) at rt. The mixture was stirred at rt for 30 mins. The reaction mixture was acidified pH~5 with saturated ammonium chloride solution at 0° C. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (1% MeOH in DCM) to give 555-7 (100 mg).

[1193] Step 8: To a solution of 555-7 (100 mg, 0.25 mmol) in DCM (3.0 mL) was added HCl solution (1.5 mL, 4 M in EtOAc), the mixture was stirred at it for 30 mins. The reaction solution was diluted with water and extracted twice with DCM. Aqueous phase was adjusted pH to 7 with $NaHCO_3$ solution, then extracted three times with DCM. The collected organic layer was washed brine, then dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give 555-8 (70 mg).

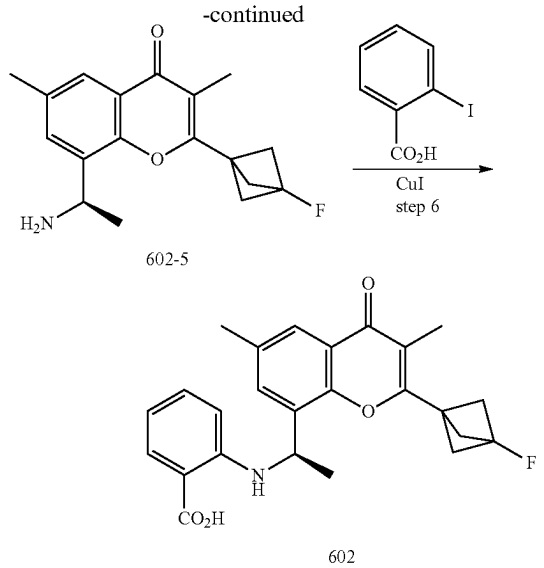
[1194] Step 9: To a solution of 555-8 (100 mg, 0.3 mmol) and methyl 2-bromobenzoate (71.3 mg, 0.3 mmol) in dioxane (2.0 mL) was added Cs_2CO_3 (540.6 mg, 1.6 mmol), XANT-PHOS (38.4 mg, 0.06 mmol) and $Pd_2(dba)_3$ (30.4 mg, 0.03 mmol) at 25° C., the mixture was stirred at 110° C. for 12 hrs. After cooling to room temperature, water was added into the mixture and it was extracted with EtOAc, the combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography (20% EtOAc in PE) to give 555-9 (100 mg).

[1195] Step 10: To a solution of 555-9 (100 mg, 0.2 mmol) in MeOH (1.0 mL), THF (2.0 mL) and water (1.0 mL) was added NaOH (46.0 mg, 1.1 mmol) at 25° C., the mixture was stirred at 50° C. for 3.0 hrs. The water layer was adjusted pH to 5 with HCl (1 M), extracted with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated, the residue was purified by prep-HPLC (acetonitrile/0.05% FA in water: 5%~65%) to give 555 (60 mg). LCMS (ESI, m/z): $^+$=422.2; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.78-8.55 (m, 2H), 7.86-7.76 (m, 1H), 7.67 (s, 1H), 7.24-7.13 (m, 1H), 6.55-6.47 (m, 1H), 6.46-6.35 (m, 1H), 5.39-5.21 (m, 1H), 2.63-2.54 (m, 6H), 2.31 (s, 3H), 2.21 (s, 3H), 1.67-1.59 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −145.51 (1F).

Example 39 Synthesis of Compound 602



-continued



[1196] Step 1: To a solution of 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid (642 mg, 4.94 mmol) in dichloromethane (15 mL) was added oxalyl chloride (0.45 mL, 5.35 mmol) and a drop of N, N-dimethylformamide at room temperature, then the reaction was stirred for 2 hours. The above reaction mixture was dissolved in pyridine (10 mL), followed by the addition of 5-3 (1.0 g, 4.11 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.9 g, 12.34 mmol) at room temperature. The reaction mixture was stirred for 2 hours at 80° C. and then diluted with water, filtered and washed with water. The collected solids were dried to afford 602-1 (800 mg).

[1197] Step 2: A mixture of 602-1 (700 mg, 2.08 mmol), bis(triphenylphosphine)palladium(II) chloride (146 mg, 0.21 mmol) and tributyl(1-ethoxyvinyl)tin (900 mg, 2.49 mmol) in dioxane (10 mL) was stirred at 100° C. for 16 hours under N_2 atmosphere. To the mixture was added hydrochloric acid (1 M) and stirred at 50° C. for 1 hour. The mixture was cooled to room temperature, potassium fluoride solution was added and the resulting mixture was stirred at 25° C. for 0.5 hours. The reaction mixture was extracted with ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether to petroleum ether/ethyl acetate=3/1) to give 602-2 (400 mg).

[1198] Step 3: To a mixture of 602-2 (400 mg, 1.33 mmol) and (R)-2-methylpropane-2-sulfinamide (242 mg, 2.00 mmol) in tetrahydrofuran (3 mL) was added titanium tetraisopropanolate (6 mL) at room temperature. The mixture was stirred at 85° C. for 16 hours and then diluted with water and extracted with ethyl acetate, filtered and wash with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=40:1) to give 602-3 (520 mg).

[1199] Step 4: To a mixture of 602-3 (520 mg, 1.29 mmol) and Cerium chloride heptahydrate (960 mg, 2.58 mmol) in methanol (20 mL) was added sodium borohydride (98 mg, 2.58 mmol) at room temperature. The mixture was stirred at

room temperature for 1 hour before acidification pH~5 with saturated ammonium chloride solution at 0° C. The result solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane to dichloromethane/methanol=20:1) to give 602-4 (400 mg).

[1200] Step 5: To a mixture of 602-4 (400 mg, 0.99 mmol) in ethyl acetate (4 mL) was added HCl solution (4 mL, 4 M in ethyl acetate) at 0° C. The mixture was stirred at room temperature for 1 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The aqueous phase was adjusted to pH=12 with NH_3H_2O (25% w/w) and extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 602-5 (280 mg).

[1201] Step 6: To a mixture of 602-5 (110 mg, 0.37 mmol), potassium carbonate (151 mg, 1.10 mmol) and 2-iodobenzoic acid (181 mg, 0.73 mmol) in dimethyl sulfoxide (4 mL) was added cuprous iodide (14 mg, 0.073 mmol) and sarcosine (13 mg, 0.15 mmol) at room temperature under N_2 atmosphere. The mixture was stirred at 40° C. for 16 hours. Acidification to pH~5 with saturated ammonium chloride solution at 0° C., extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC (acetonitrile/0.05% FA in water: 15%-95%) to give 602 (80 mg). LCMS (ESI, m/z): $^{+}$=422.0; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.76 (brs, 1H), 8.38-8.37 (m, 1H), 7.82-7.79 (m, 1H), 7.70 (s, 1H), 7.55 (s, 1H), 7.28-7.21 (m, 1H), 6.59-6.47 (m, 2H), 5.13-5.03 (m, 1H), 2.71-2.64 (m, 6H), 2.35 (s, 3H), 2.01 (s, 3H), 1.62 (d, J=6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −145.62 (1F).

[1202] The preparation of the intermediates in Table 1 below can be carried out by referring to the similar methods in the above-mentioned examples, the relevant characterization data was as follows:

TABLE 1

Intermediates

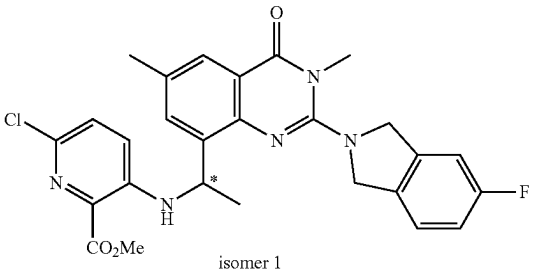
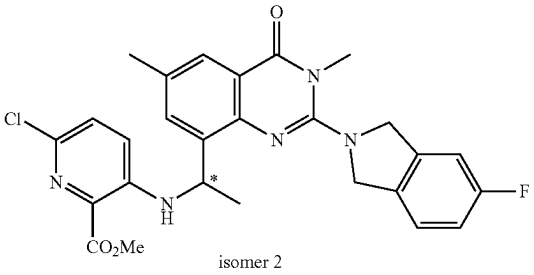
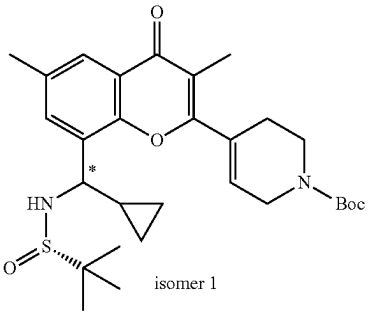
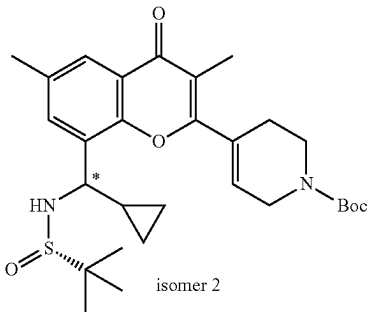
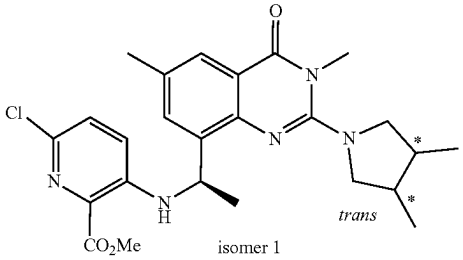
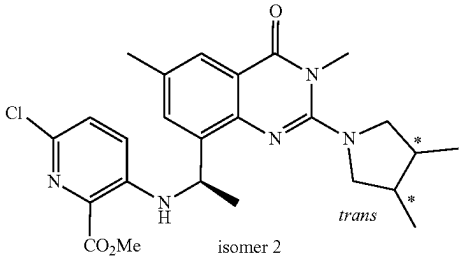
Intermediate	Structure	LCMS (ESI, m/z): [M + H]$^{+}$	Chiral purity and Analytical method
20-1	 isomer 1	522.2	Chiral SFC analysis: >99% ee. Retention time 3.079 min on Chiralcel OJ-3 150 × 4.6 mm I.D., 3 um; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), 1500 psi, 2.5 mL/min.
20-2	 isomer 2	522.4	Chiral SFC analysis: 99.4% ee. Retention time 4.199 min on Chiralcel OJ-3 150 × 4.6 mm I.D., 3 um; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), 1500 psi, 2.5 mL/min.
313-1	 isomer 1	529.2	Chiral SFC analysis: 100% ee. Retention time 0.873 min on ChiralPak AD, 150 × 4.6 mm I.D., 3μ; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), 100 bar, 2.5 mL/min.

TABLE 1-continued

Intermediates			
Intermediate	Structure	LCMS (ESI, m/z): [M + H]$^+$	Chiral purity and Analytical method
313-2	 isomer 2	529.2	Chiral SFC analysis: 99.0% ee. Retention time 1.371 min on ChiralPak AD, 150 × 4.6 mm I.D., 3μ; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), 100 bar, 2.5 mL/min.
540-p1	 isomer 1	522.2	Chiral SFC analysis: 99.84% ee. Retention time 3.989 min on ChiralCel OD, 150 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO_2 and B for Ethanol (0.05% DEA), 100 bar, 2.5 mL/min.
540-p2	 isomer 2	522.4	Chiral SFC analysis: 97.06% ee. Retention time 3.989 min on ChiralCel OD, 150 × 4.6 mm I.D., 3 μm; Mobile phase: A for CO_2 and B for Ethanol (0.05% DEA), 100 bar, 2.5 mL/min.

[1203] The preparation of the compounds in Table 2 below can be carried out by referring to the similar methods in the above-mentioned examples, the relevant characterization data was as follows:

TABLE 2

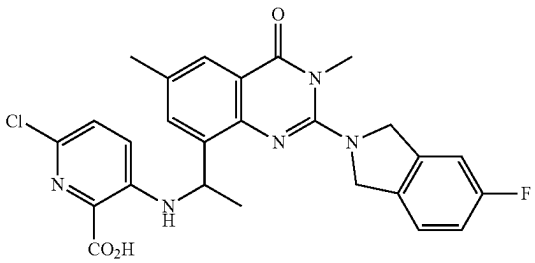
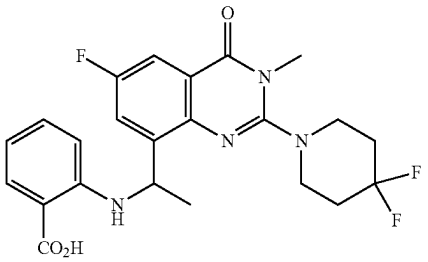
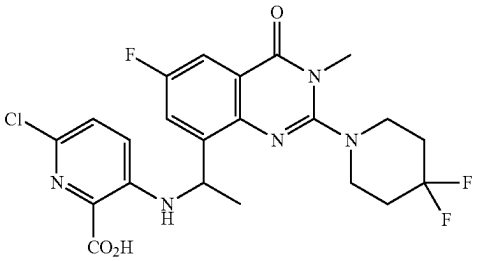
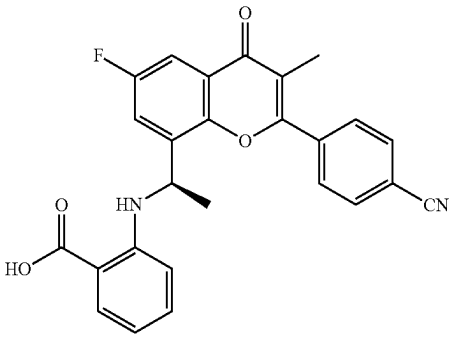
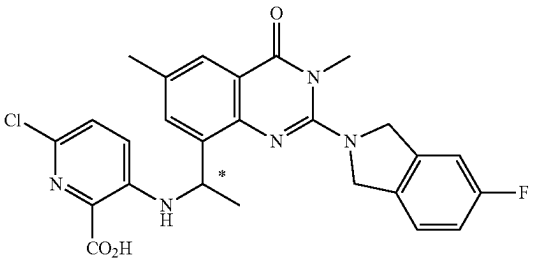
Characterization of exemplary compounds.			
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
12		508.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.95 (brs, 1H), 8.54-8.26 (m, 1H), 7.79-7.64 (m, 1H), 7.49-7.36 (m, 2H), 7.34-7.22 (m, 2H), 7.20-7.10 (m, 1H), 7.09-7.00 (m, 1H), 5.47-5.33 (m, 1H), 5.12-4.93 (m, 4H), 3.59 (s, 3H), 2.32 (s, 3H), 1.60 (d, 3H, J = 6.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −115.74 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
14		461.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.45-8.43 (m, 1H), 7.80 (dd, J = 8.0, 1.6 Hz, 1H), 7.59 (dd, J = 8.4, 2.8 Hz, 1H), 7.46 (dd, J = 9.2, 2.8 Hz, 1H), 7.23-7.07 (m, 1H), 6.52 (t, J = 7.6 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.45-5.33 (m, 1H), 3.52 (s, 3H), 3.45-3.35 (m, 4H), 2.35-2.18 (s, 4H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.17 (2F), −115.75 (1F).
15		496.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.69-8.64 (m, 1H), 7.67-7.39 (m, 2H), 7.25 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 5.50-5.19 (m, 1H), 3.51 (s, 3H), 3.45-3.34 (m, 4H), 2.24-2.17 (m, 4H), 1.60 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.24 (2F), −115.62 (1F).
17		443.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.59-8.35 (m, 1H), 8.06 (m, 4H), 7.81 (dd, J = 8.0, 1.6 Hz, 1H), 7.67 (dd, J = 8.0, 3.2 Hz, 1H), 7.54 (dd, J = 8.8, 3.2 Hz, 1H), 7.29-7.07 (m, 1H), 6.57 (t, J = 7.2 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 5.22-5.01 (m, 1H), 2.08 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.01 (1F).
20		508.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.97 (brs, 1H), 8.58-8.33 (m, 1H), 7.80-7.64 (m, 1H), 7.54-7.36 (m, 2H), 7.36-7.21 (m, 2H), 7.20-7.10 (m, 1H), 7.09-7.00 (m, 1H), 5.53-5.28 (m, 1H), 5.20-4.88 (m, 4H), 3.60 (s, 3H), 2.31 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.74 (1F).

obtained from intermediate 20-1.

TABLE 2-continued

Characterization of exemplary compounds.

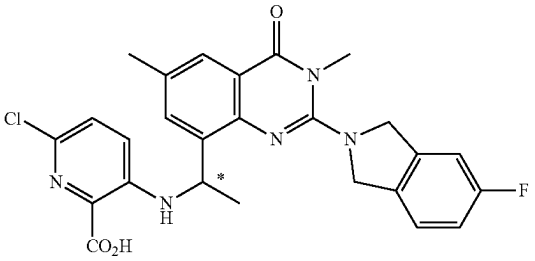
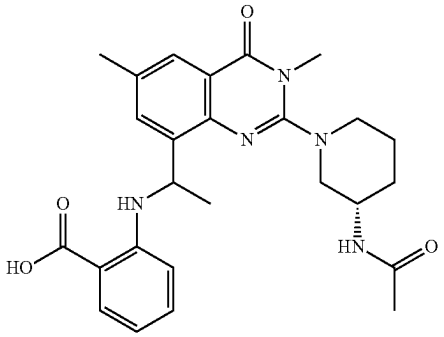
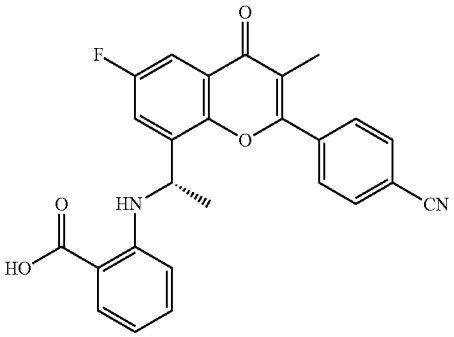
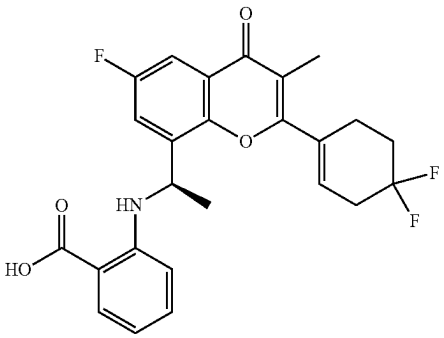
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
21	 obtained from intermediate 20-2.	508.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (brs, 1H), 8.58-8.33 (m, 1H), 7.80-7.64 (m, 1H), 7.54-7.36 (m, 2H), 7.36-7.21 (m, 2H), 7.20-7.10 (m, 1H), 7.09-7.00 (m, 1H), 5.53-5.28 (m, 1H), 5.21-4.84 (m, 4H), 3.60 (s, 3H), 2.32 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.74 (1F).
22		478.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.69 (brs, 1H), 8.63-8.27 (m, 1H), 7.96-7.87 (m, 1H), 7.82-7.64 (m, 2H), 7.50-7.42 (m, 1H), 7.23-7.10 (m, 1H), 6.55-6.35 (m, 2H), 5.50-5.35 (m, 1H), 4.00-3.82 (m, 1H), 3.59-3.45 (m, 4H), 3.44-3.34 (m, 1H), 3.00-2.71 (m, 2H), 2.32 (s, 3H), 1.94-1.63 (m, 6H), 1.60-1.37 (m, 4H).
23		443.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.62-8.43 (m, 1H), 8.06 (m, 4H), 7.82 (dd, J = 8.0, 1.2 Hz, 1H), 7.67 (dd, J = 8.0, 3.2 Hz, 1H), 7.54 (dd, J = 8.8, 3.2 Hz, 1H), 7.29-7.07 (m, 1H), 6.56 (t, J = 7.2 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 5.22-5.01 (m, 1H), 2.08 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.01 (1F).
24		458.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.54 (s, 1H), 7.93 (d, J = 6.8 Hz, 1H), 7.59 (dd, J = 8.2, 3.2 Hz, 1H), 7.43-7.30 (m, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 5.35-5.16 (m, 5H), 2.36 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −94.57 (2 F), −115.49 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

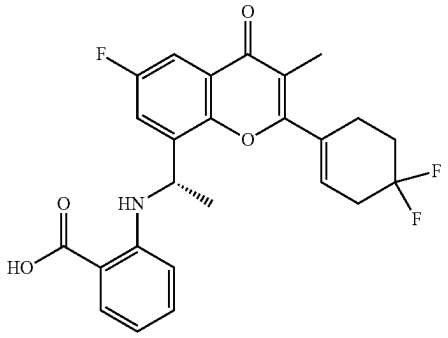
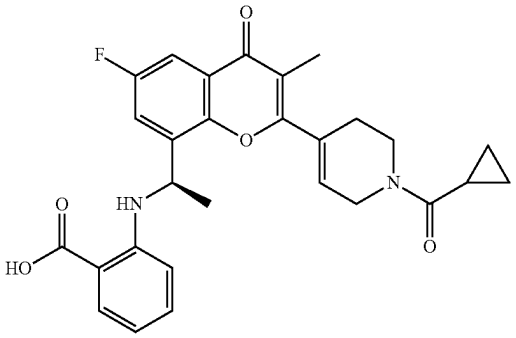
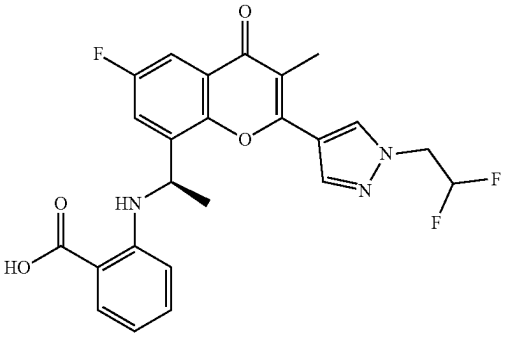
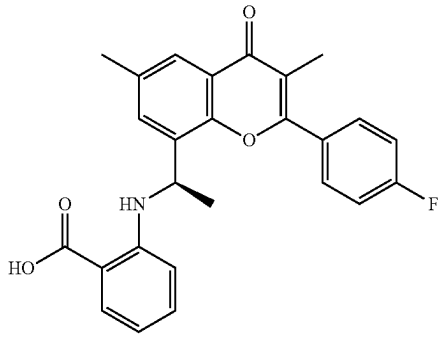
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
25		458.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.55 (s, 1H), 7.92-7.75 (m, 1H), 7.65-7.45 (m, 2H), 7.28-7.11 (m, 1H), 6.63-6.51 (m, 1H), 6.48-6.33 (m, 1H), 6.25-6.14 (m, 1H), 5.23-4.92 (m, 1H), 2.97-2.80 (m, 2H), 2.76-2.65 (m, 2H), 2.31-2.14 (m, 2H), 2.05 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −94.57 (2F), −115.48 (1F).
26		491.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.03-8.66 (m, 1H), 7.87-7.76 (m, 1H), 7.65-7.53 (m, 1H), 7.53-7.45 (m, 1H), 7.22-7.04 (m, 1H), 6.60-6.46 (m, 1H), 6.45-6.29 (m, 2H), 5.21-5.07 (m, 1H), 4.57-4.43 (m, 1H), 4.28-4.15 (m, 1H), 4.07-3.64 (m, 3H), 2.69-2.61 (m, 1H), 2.09 (s, 3H), 2.04-1.93 (m, 1H), 1.59 (d, J = 6.4 Hz, 3H), 0.88-0.67 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.54 (1F).
28		472.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm) δ: 8.46 (s, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.66-7.62 (m, 1H), 7.48-7.44 (m, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.59-6.55 (m, 1H), 6.43-6.13 (m, 2H), 5.34-5.29 (m, 1H), 4.75-4.67 (m, 2H), 2.30 (s, 3H), 1.71 (d, J = 8.0 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −117.25 (1F), −124.91 (2F).
31		432.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.38 (s, 1H), 7.90-7.88 (m, 2H), 7.87-7.77 (m, 2H), 7.53 (s, 1H), 7.46 (t, J = 8.8 Hz, 2H), 7.22-7.18 (m, 1H), 6.56 (t, J = 7.6 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 5.13-5.10 (m, 1H), 2.90-2.83 (m, 2H), 2.69 (s, 2H), 2.36 (s, 3H), 2.07 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −109.68 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

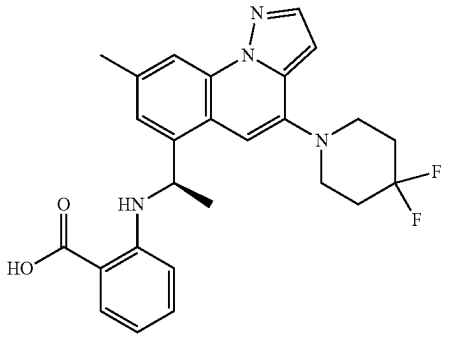
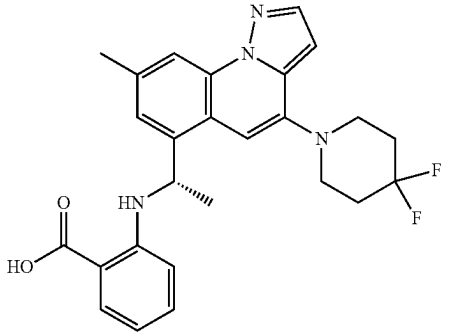
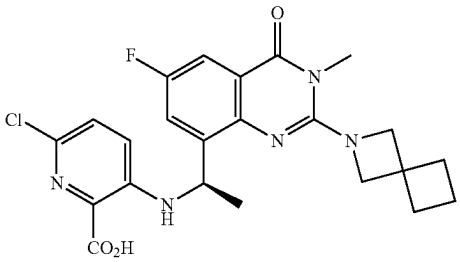
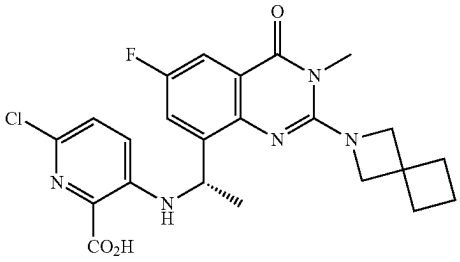
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
32		465.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ: 8.18 (s, 1H), 8.09 (s, 1H), 7.83-7.80 (m, 1H), 7.27 (s, 1H), 7.26-7.17 (m, 2H), 6.84 (d, J = 2.0 Hz, 1H), 6.56 (t, J = 8.0 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 5.41-5.36 (m, 1H), 3.40-3.29 (m, 4H), 2.43 (s, 3H), 2.27-2.08 (m, 4H), 1.62 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.65 (2F).
33		465.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.18 (s, 1H), 8.09 (s, 1H), 7.82-7.80 (m, 1H), 7.27 (s, 1H), 7.26-7.17 (m, 2H), 6.84 (d, J = 2.0 Hz, 1H), 6.55 (t, J = 8.0 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 5.41-5.36 (m, 1H), 3.39-3.30 (m, 4H), 2.43 (s, 3H), 2.27-2.08 (m, 4H), 1.61 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.64 (2F).
34		472.2	1 TFA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.98 (s, 1H), 8.45 (s, 1H), 7.53-7.50 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 5.32-5.29 (m, 1H), 4.28-4.22 (m, 4H), 3.37 (s, 3H), 2.33-2.18 (m, 4H), 1.85-1.78 (m, 2H), 1.64 (d, J = 8.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −118.44 (1F).
35		472.2	1 TFA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (s, 1H), 8.44 (s, 1H), 7.53-7.50 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 5.32-5.29 (m, 1H), 4.28-4.22 (m, 4H), 3.37 (s, 3H), 2.33-2.18 (m, 4H), 1.85-1.78 (m, 2H), 1.64 (d, J = 8.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −118.44 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

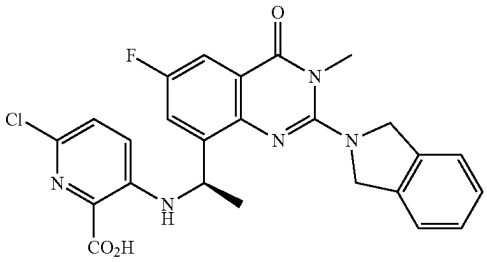
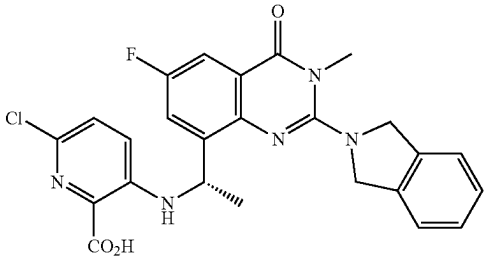
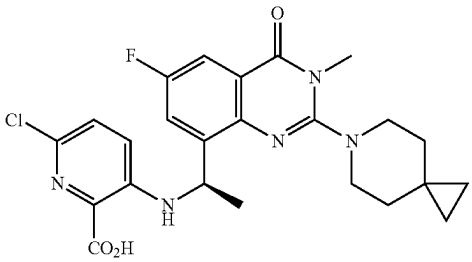
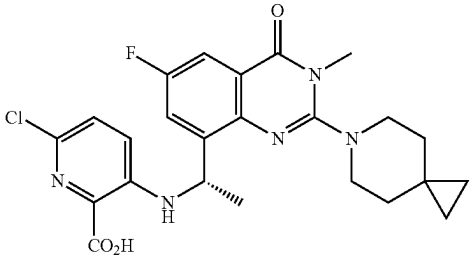
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
36		494.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.95 (d, J = 7.2 Hz, 1H), 7.56-7.53 (m, 1H), 7.42-7.31 (m, 5H), 6.99 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.36-5.33 (m, 1H), 5.15-5.01 (m, 4H), 3.63 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −117.77 (1F).
37		494.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.96 (d, J = 7.2 Hz, 1H), 7.55-7.52 (m, 1H), 7.42-7.31 (m, 5H), 6.98 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.36-5.33 (m, 1H), 5.15-5.01 (m, 5H), 3.63 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −117.77 (1F).
38		486.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.80-9.65 (m, 1H), 7.58-7.51 (m, 1H), 7.40-7.30 (m, 1H), 7.10-7.05 (m, 1H), 6.80-6.70 (m, 1H), 5.35-5.30 (m, 1H), 3.50 (s, 3H), 3.30-3.20 (m, 4H), 1.60-1.50 (m, 7H), 0.41-0.32 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −116.12 (1F).
39		486.3	1 TFA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.0-12.95 (m, 1H), 8.42-8.38 (m, 1H), 7.60-7.50 (m, 2H), 7.40-7.30 (m, 1H), 7.10-7.00 (m, 1H), 5.40-5.34 (m, 1H), 3.50 (s, 3H), 3.30-3.20 (m, 4H), 1.65-1.60 (m, 3H), 1.58-1.48 (m, 4H), 0.41-0.35 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −116.06 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

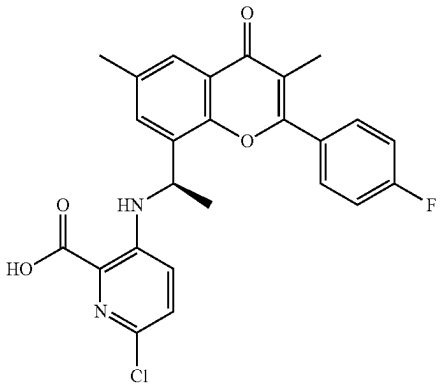
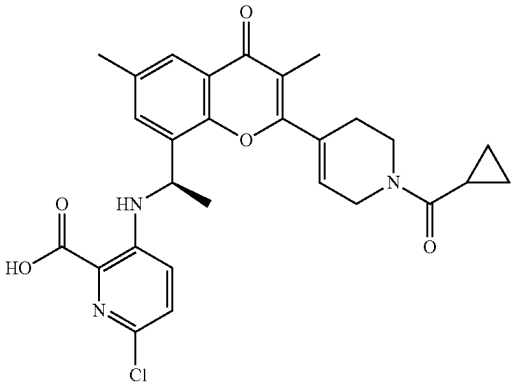
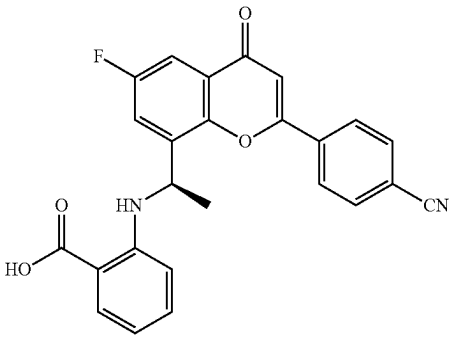
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
40		467.2	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.35-8.29 (m, 1H), 7.92-7.82 (m, 2H), 7.81-7.76 (m, 1H), 7.55-7.50 (m, 1H), 7.48-7.37 (m, 2H), 7.33-7.26 (m, 1H), 7.10-7.03 (m, 1H), 5.20-5.09 (m, 1H), 2.37 (s, 3H), 2.06 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −109.70 (1F).
41		522.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.39-8.33 (m, 1H), 7.76-7.71 (m, 1H), 7.55-7.50 (m, 1H), 7.37-7.30 (m, 1H), 7.07-7.01 (m, 1H), 6.37-6.33 (m, 1H), 5.20-5.12 (m, 1H), 4.51-4.47 (m, 1H), 4.23-4.18 (m, 1H), 3.95-3.87 (m, 1H), 3.81-3.60 (m, 2H), 2.65-2.60 (m, 1H), 2.35 (s, 3H), 2.15-1.91 (m, 4H), 1.61 (d, J = 6.4 Hz, 3H), 0.81-0.73 (m, 4H).
42		429.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm) δ: 8.26 (d, J = 8.4 Hz, 2H), 7.96-7.92 (m, 3H), 7.71-7.68 (m, 1H), 7.56-7.55 (m, 1H), 7.23-7.18 (m, 1H), 7.10 (s, 1H), 6.62-6.57 (m, 1H), 6.49-6.47 (m, 1H), 5.41-5.36 (m, 1H), 1.77 (d, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −115.88 (1F)

TABLE 2-continued

Characterization of exemplary compounds.

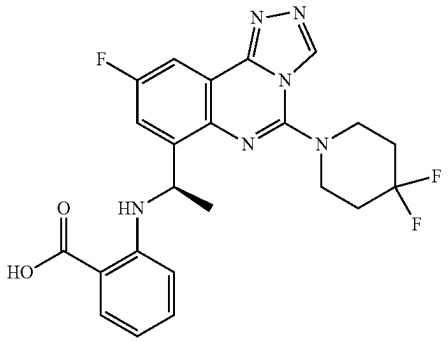
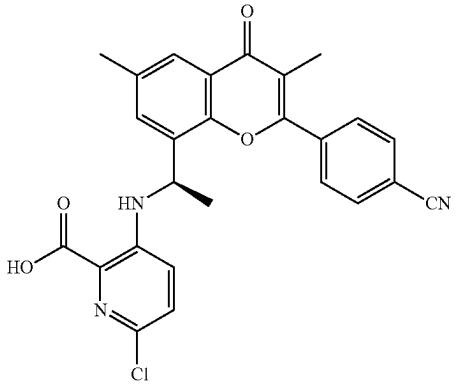
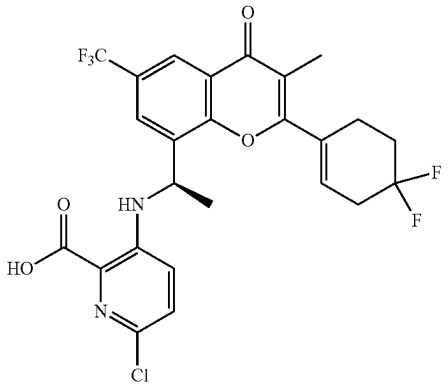
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
44		471.4	1 TFA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.76 (brs, 1H), 9.58 (s, 1H), 8.46 (d, J = 6.0 Hz, 1H), 8.02-7.95 (m, 1H), 7.83-7.79 (m, 1H), 7.48-7.43 (m, 1H), 7.20-6.95 (m, 1H), 6.57-6.50 (m, 1H), 6.43 (d, J = 8.8 Hz, 1H), 5.59-5.46 (m, 1H), 3.76-3.68 (m, 4H), 2.39-2.23 (m, 4H), 1.64 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.03 (1F), −113.39 (2F).
45		474.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.28 (s, 1H), 8.08 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.56 (s, 1H), 7.31-7.29 (m, 1H), 7.10-7.08 (m, 1H), 5.15-5.14 (m, 1H), 2.38 (s, 3H), 2.05 (m, 3H), 1.61 (d, J = 6.4 Hz, 3H).
46		543.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.29-8.21 (m, 1H), 8.04-7.98 (m, 1H), 7.43-7.32 (m, 1H), 7.25-7.15 (m, 1H), 6.23-6.13 (m, 1H), 5.72-5.62 (m, 1H), 2.93-2.80 (m, 2H), 2.71-2.65 (m, 2H), 2.32-2.17 (m, 2H), 2.06 (s, 3H), 1.67 (d, J = 6.6 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −60.87 (3F), −94.56 (2F).

TABLE 2-continued

Characterization of exemplary compounds.

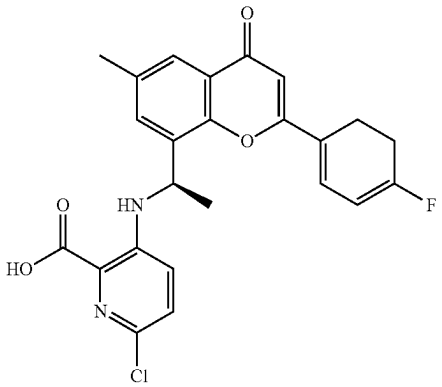
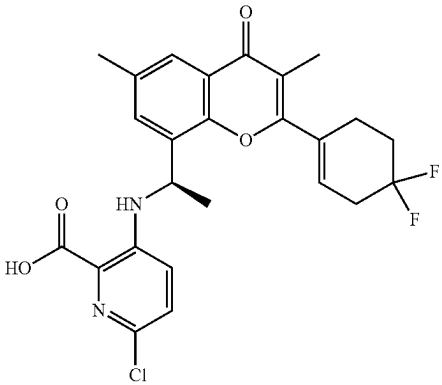
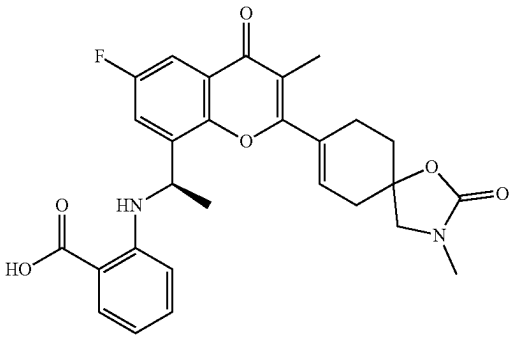
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
47		455.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.10 (s, 1H), 8.43 (s, 1H), 7.69 (s, 1H), 7.50 (s, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.10 (t, J = 6.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.44 (s, 1H), 5.88-5.83 (m, 1H), 5.26-5.22 (m, 1H), 2.85-2.80 (m, 2H), 2.68-2.63 (m, 2H), 2.33 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −92.55 (1F).
48		489.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.33 (s, 1H), 8.16 (s, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.14 (s, 1H), 5.13-5.11 (m, 1H), 2.86-2.82 (m, 2H), 2.66-2.64 (m, 2H), 2.36 (s, 3H), 2.24-2.19 (m, 2H), 2.03 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −94.49 (2F).
49		507.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.79 (brs, 1H), 8.37 (s, 1H), 7.82 (d, J = 6.8 Hz, 1H), 7.61-7.52 (m, 2H), 7.26-7.22 (m, 1H), 6.59-6.55 (t, J = 7.6 Hz, 1H), 6.45-6.42 (m, 1H), 6.21 (s, 1H), 5.14-5.13 (m, 1H), 3.47-3.37 (m, 2H), 2.79 (s, 3H), 2.67-2.55 (m, 4H), 2.06 (s, 3H), 197-1.90 (m, 2H), 1.63 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.53 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

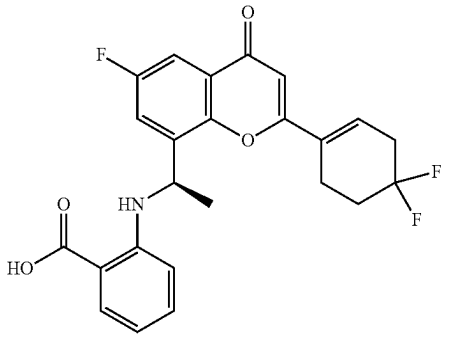
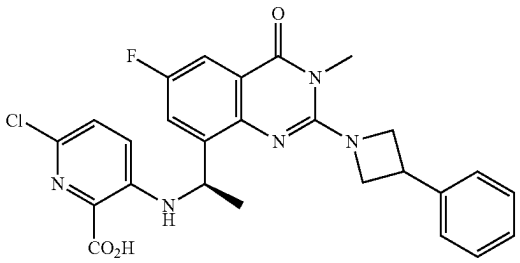
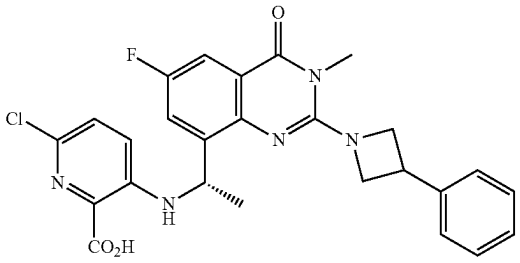
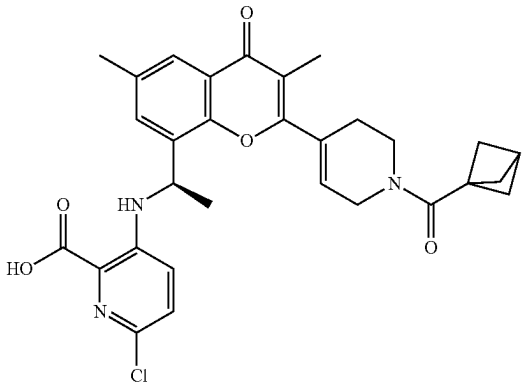
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
50		444.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm) δ: 7.94 (d, J = 6.8 Hz, 1H), 7.64-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.22-7.18 (m, 1H), 6.93 (s, 1H), 6.60 (t, J = 7.6 Hz, 1H), 6.47 (s, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.29-5.24 (m, 1H), 2.88-2.82 (m, 2H), 2.74-2.71 (m, 2H), 2.23-2.19 (s, 2H), 1.71 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −98.62 (2F), −116.60 (1F)
51		508.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ: 9.93 (d, J = 7.2 Hz, 1H), 7.53-7.45 (m, 3H), 7.40-7.28 (m, 4H), 7.04 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.30-5.27 (m, 1H), 4.69-4.64 (m, 2H), 4.34-4.30 (m, 2H), 3.98-3.95 (m, 1H), 3.45 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −118.09 (1F)
52		508.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ: 9.93 (d, J = 7.2 Hz, 1H), 7.53-7.45 (m, 3H), 7.40-7.28 (m, 4H), 7.04 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 5.30-5.27 (m, 1H), 4.69-4.64 (m, 2H), 4.34-4.30 (m, 2H), 3.98-3.95 (m, 1H), 3.44 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −118.09 (1F)
53		548.2	^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.30 (s, 1H), 7.91 (s, 1H), 7.39 (s, 1H), 7.18-7.16 (m, 1H), 6.80-6.77 (m, 1H), 6.18 (s, 1H), 5.02-4.96 (m, 1H), 4.42-4.33 (m, 2H), 3.94-3.92 (m, 2H), 2.58-2.55 (m, 3H), 2.50 (s, 3H), 2.25 (s, 5H), 2.16-2.14 (m, 3H), 1.72-1.68 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

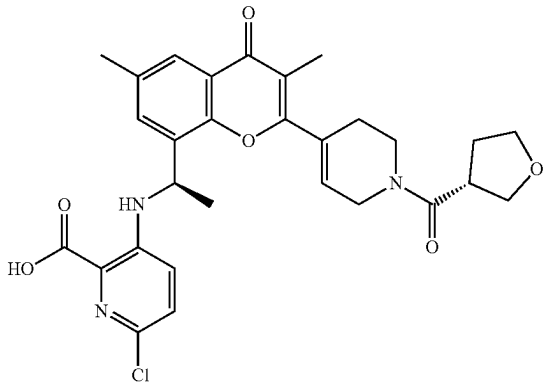
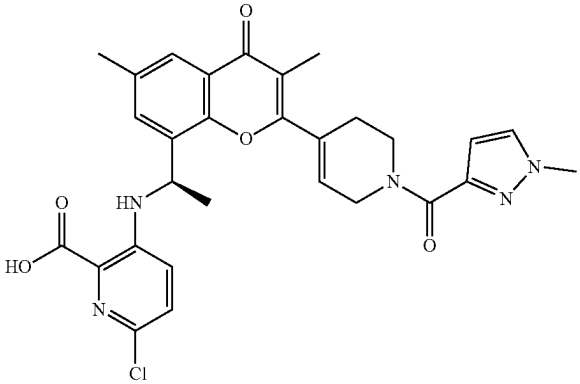
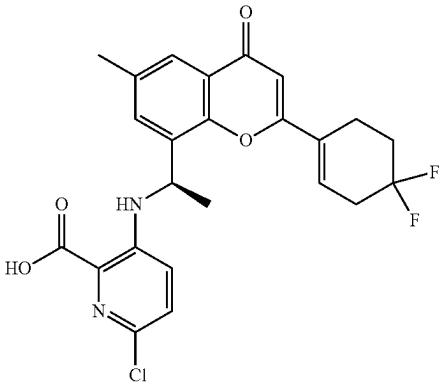
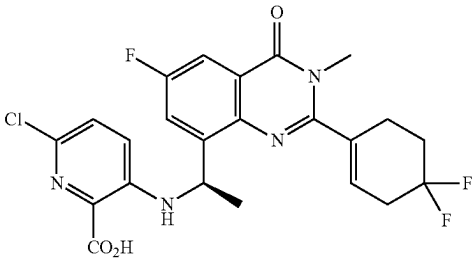
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
54		552.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.48 (s, 1H), 7.72 (s, 1H), 7.52 (s, 1H), 7.32-7.29 (m, 1H), 7.02-7.00 (m, 1H), 6.36-6.31 (m, 1H), 5.14-5.12 (m, 1H), 4.33-4.21 (m, 2H), 3.93-3.91 (m, 1H), 3.78-3.65 (m, 5H), 2.59 (s, 2H), 2.34 (s, 3H), 2.09-2.02 (m, 5H), 1.61 (d, J = 6.4 Hz, 3H).
55		562.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.79 (s, 1H), 7.72 (s, 1H), 7.47 (s, 1H), 7.16-7.14 (m, 1H), 6.87-6.85 (m, 1H), 6.60 (s, 1H), 6.41-6.35 (m, 1H), 5.11-5.08 (m, 1H), 4.75-4.74 (m, 1H), 4.36-4.08 (m, 4H), 3.91 (s, 3H), 2.62-2.60 (m, 2H), 2.32 (s, 3H), 2.08-2.50 (m, 3H), 1.58 (d, J = 6.4 Hz, 3H).
56		475.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.12 (s, 1H), 8.36 (s, 1H), 7.71 (s, 1H), 7.52 (s, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.89 (s, 1H), 6.46 (s, 1H), 5.27-5.23 (m, 1H), 2.92-2.85 (m, 2H), 2.66 (s, 2H), 2.34 (s, 3H), 2.26-2.18 (m, 2H), 1.64 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.07 (2F).
57		493.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.73-7.70 (m, 1H), 7.53-7.50 (m, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 9.2 Hz, 1H), 6.05 (s, 1H), 5.56-5.51 (m, 1H), 3.59 (s, 3H), 2.83-2.76 (m, 4H), 2.32-2.22 (m, 2H), 1.64 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −98.06 (2F), −113.87 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

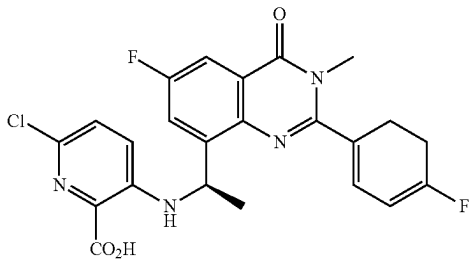
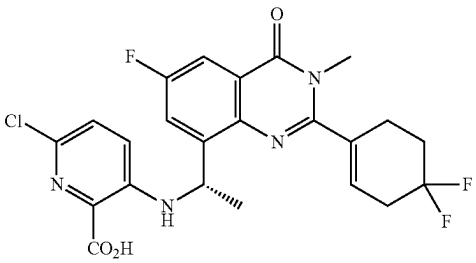
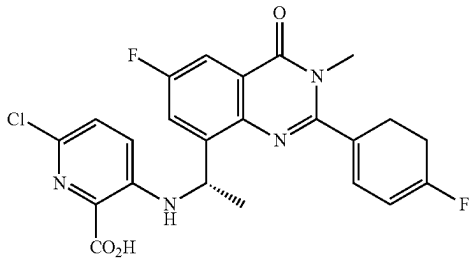
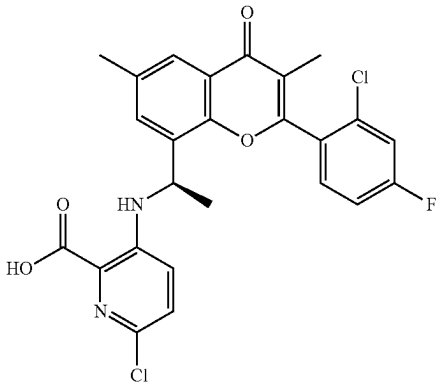
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
58		473.2	2 TFA salt. ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.74-7.71 (m, 1H), 7.53-7.50 (m, 1H), 7.22 (d, J = 9.2 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.42 (t, J = 6.0 Hz, 1H), 5.76-5.71 (m, 1H), 5.56-5.52 (m, 1H), 3.67 (s, 3H), 2.97-2.92 (m, 2H), 2.71-2.66 (m, 2H), 1.68 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d_4, ppm): δ −98.04 (1F), −114.13 (1F).
59		493.2	^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.71-7.69 (m, 1H), 7.50-7.47 (m, 1H), 7.10-7.07 (m, 1H), 6.90-6.88 (m, 1H), 6.06 (s, 1H), 5.57-5.53 (m, 1H), 3.60 (s, 3H), 2.99-2.77 (m, 4H), 2.32-2.21 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d_4, ppm): δ −98.06 (2F), −113.89 (1F).
60		473.2	2 TFA salt. ^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.72-7.71 (m, 1H), 7.56-7.48 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.42 (t, J = 6.0 Hz, 1H), 5.76-5.71 (m, 1H), 5.56-5.52 (m, 1H), 3.66 (s, 3H), 2.98-2.92 (m, 2H), 2.71-2.66 (m, 2H), 1.68 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d_4, ppm): δ −98.03 (1F), −114.11 (1F).
61		501.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 10.01 (d, J = 6.8 Hz, 1H), 7.87-7.74 (m, 3H), 7.49-7.45 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 4.90-4.87 (m, 1H), 2.36 (s, 3H), 1.82 (m, 3H), 1.50 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −107.74 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

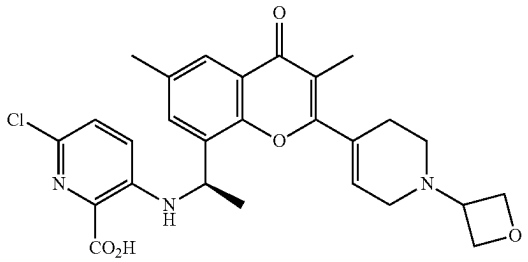
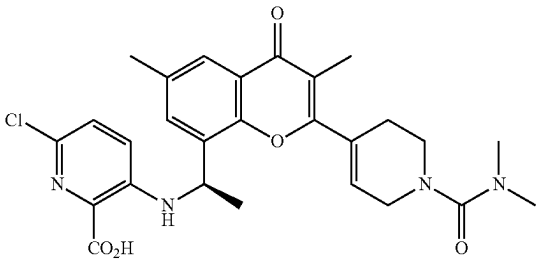
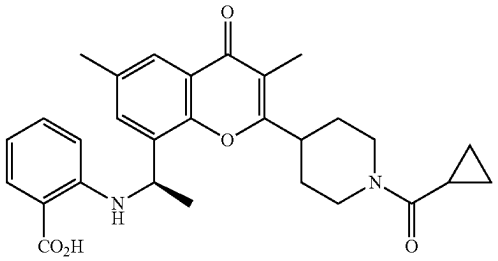
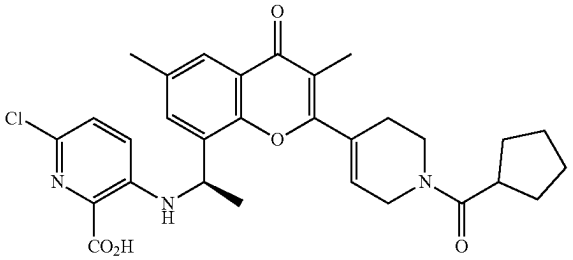
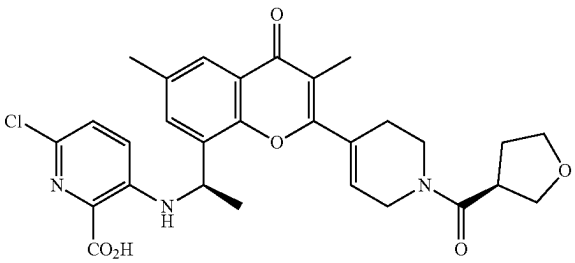
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
63		510.2	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.80 (brs, 1H), 8.37 (s, 1H, FA), 7.69 (s, 1H), 7.42 (s, 1H), 7.05-7.01 (m, 1H), 6.71-6.68 (m, 1H), 6.31 (s, 1H), 5.11-5.01 (m, 1H), 4.61-4.58 (m, 2H), 4.53-4.50 (m, 2H), 3.62-3.55 (m, 1H), 3.09-3.08 (m, 2H), 2.53-2.51 (m, 4H), 2.31 (s, 3H), 2.07 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H).
64		525.2	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.75 (brs, 1H), 8.37 (s, 1H, FA), 7.69 (s, 1H), 7.43 (s, 1H), 7.05-7.01 (m, 1H), 6.71-6.68 (m, 1H), 6.33 (s, 1H), 5.11-5.01 (m, 1H), 3.93-3.92 (m, 2H), 3.53-3.40 (m, 2H), 2.77 (s, 6H), 2.33-2.32 (m, 4H), 2.06-2.00 (m, 4H), 1.53 (d, J = 6.4 Hz, 3H).
65		489.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.56-8.51 (m, 1H), 7.85-7.78 (m, 1H), 7.73-7.68 (m, 1H), 7.48-7.44 (m, 1H), 7.21-7.13 (m, 1H), 6.57-6.49 (m, 1H), 6.37-6.32 (m, 1H), 5.14-5.07 (m, 1H), 4.54-4.32 (m, 2H), 3.25-3.15 (m, 2H), 2.78-2.70 (m, 1H), 2.32 (s, 3H), 2.06 (s, 3H), 2.00-1.71 (m, 5H), 1.57 (d, J = 6.8 Hz, 3H), 0.74-0.67 (m, 4H).
66		550.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.00 (s, 1H), 8.34 (s, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.40-7.30 (m, 1H), 7.13-6.98 (m, 1H), 6.40-6.28 (m, 1H), 5.23-5.06 (m, 1H), 4.35-4.17 (m, 2H), 3.85-3.60 (m, 2H), 3.12-2.96 (m, 1H), 2.64-2.54 (m, 1H), 2.42-2.25 (s, 3H), 2.12-1.97 (s, 3H), 1.87-1.44 (m, 12H).
67		552.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.2-12.8 (m, 1H), 8.5-8.2 (m, 1H), 7.72 (s, 1H), 7.52 (s, 1H), 7.37-7.25 (m, 1H), 7.09-6.97 (m, 1H), 6.38-6.27 (m, 1H), 5.21-5.07 (m, 1H), 4.37-4.13 (m, 2H), 3.96-3.86 (m, 1H), 3.80-3.65 (m, 5H), 2.65-2.53 (m, 1H), 2.36-2.32 (m, 4H), 2.13-1.96 (m, 6H), 1.64-1.56 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

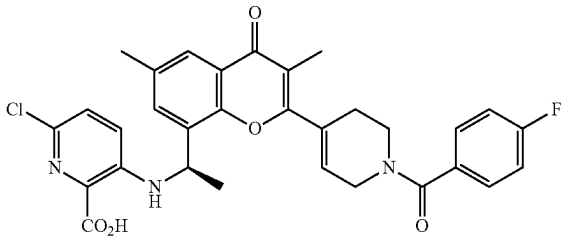
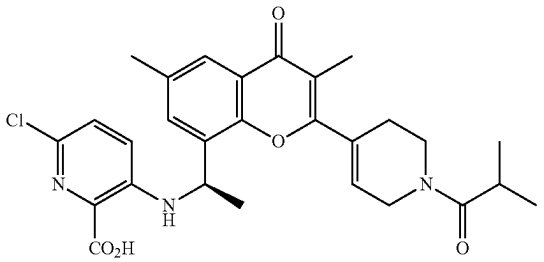
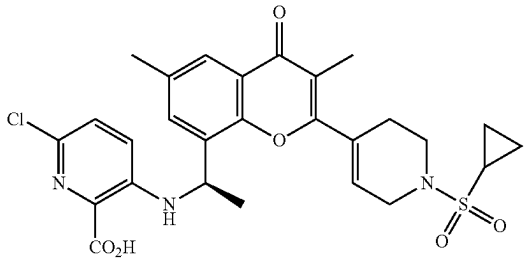
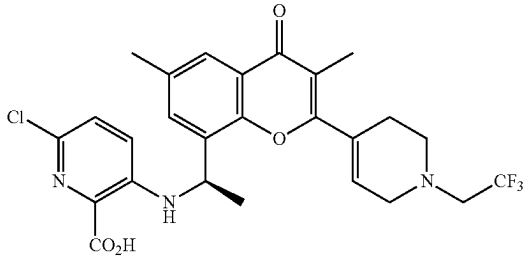
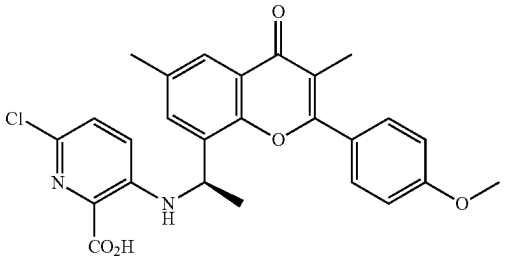
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
68		576.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (s, 1H), 8.35 (s, 1H), 7.73 (s, 1H), 7.62-7.50 (m, 3H), 7.40-7.23 (m, 3H), 7.10-6.97 (m, 1H), 6.50-6.18 (m, 1H), 5.23-5.07 (m, 1H), 4.49-4.03 (m, 2H), 3.96-3.44 (m, 2H), 2.69-2.53 (m, 2H), 2.53 (s, 3H), 2.07 (s, 3H), 1.67-1.53 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −110.91 (1F).
69		524.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.8 (m, 1H), 8.5-8.2 (m, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.35-6.31 (m, 1H), 5.21-5.07 (m, 1H), 4.32-4.13 (m, 2H), 3.72-3.66 (m, 2H), 2.97-2.89 (m, 1H), 2.59-2.57 (m, 1H), 2.35 (s, 3H), 2.06-1.90 (m, 4H), 1.60 (d, J = 8.0 Hz, 3H), 1.04 (d, J = 6.0 Hz, 6H).
70		558.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.7 (m, 1H), 8.5-8.2 (m, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.35-6.31 (m, 1H), 5.21-5.07 (m, 1H), 4.10-4.00 (m, 2H), 3.52-3.46 (m, 2H), 2.73-2.64 (m, 3H), 2.35 (s, 3H), 2.07 (s, 3H), 1.60 (d, J = 4.8 Hz, 3H), 1.20-0.99 (m, 4H).
71		536.2	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.60-9.50 (m, 1H), 8.31 (s, 1H, FA), 7.70 (s, 1H), 7.41 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.75-6.71 (m, 1H), 6.30 (s, 1H), 5.05 (t, J = 6.4 Hz, 1H), 3.45-3.42 (m, 2H), 3.38-3.33 (m, 3H), 2.91-2.88 (m, 2H), 2.61-2.52 (m, 1H), 2.31 (s, 3H), 2.06 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H).
72		479.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.05-9.95 (m, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H), 7.46 (s, 1H), 7.12 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.10-4.95 (m, 1H), 3.85 (s, 3H), 2.34 (s, 3H), 2.09 (s, 3H), 1.55 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

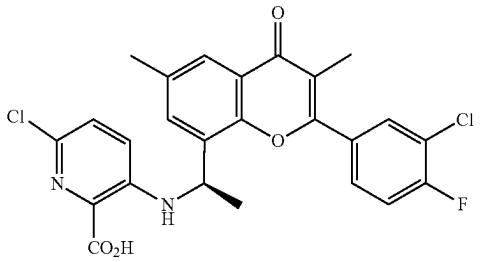
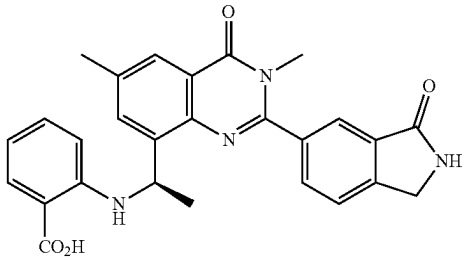
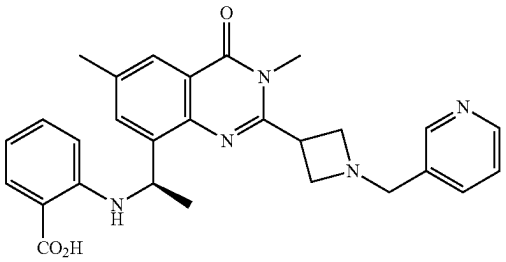
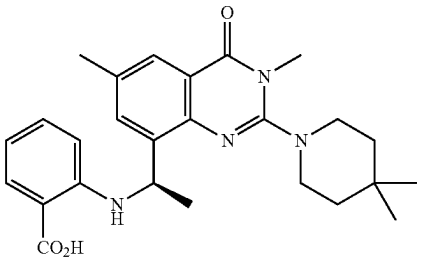
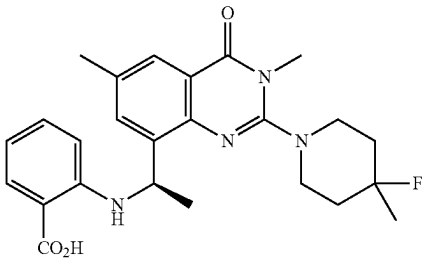
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
73		501.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.85 (brs, 1H), 8.15-8.05 (m, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 7.70-7.60 (m, 1H), 7.47 (s, 1H), 7.09-6.95 (m, 1H), 6.88-6.73 (m, 1H), 5.10-4.95 (m, 1H), 2.35 (s, 3H), 2.06 (s, 3H), 1.60-1.50 (m, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.92 (1F).
74		469.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.77 (s, 1H), 8.05 (s, 1H), 8.03-7.99 (m, 1H), 7.88 (s, 1H), 7.80-7.77 (m, 2H), 7.57 (s, 1H), 7.10 (s, 1H), 6.48-6.34 (m, 2H), 5.46 (s, 1H), 4.50 (s, 2H), 3.42 (s, 3H), 2.33 (s, 3H), 1.53 (d, J = 8.0 Hz, 3H),
76		484.1	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.65-8.39 (m, 3H), 8.15 (s, 1H, FA), 7.83-7.69 (m, 3H), 7.57 (s, 1H), 7.41-7.26 (m, 1H), 7.22-7.09 (m, 1H), 6.58-6.45 (m, 2H), 5.51 (s, 1H), 4.13-4.05 (m, 1H), 3.78-3.60 (m, 6H), 3.39 (s, 3H), 2.37 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).
77		449.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.58 (s, 1H), 8.43 (s, 1H), 7.77 (dd, J = 8.0, 1.6 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.22-7.15 (m, 1H), 6.49 (m, 2H), 5.40 (s, 1H), 3.47 (s, 3H), 3.00 (m, 4H), 2.32 (s, 3H), 1.56 (d, J = 6.8 Hz, 3H), 1.51 (m, 4H), 1.02 (d, J = 9.2 Hz, 6H).
78		453.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.45 (s, 1H), 7.77 (d, J = 6.4 Hz, 1H), 7.71 (s, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.16 (s, 1H), 6.53-6.40 (m, 2H), 5.41 (s, 1H), 3.53-3.40 (m, 5H), 3.15 (m, 2H), 2.32 (s, 3H), 1.90 (m, 4H), 1.55 (d, J = 6.4 Hz, 3H), 1.40 (d, J = 22.0 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

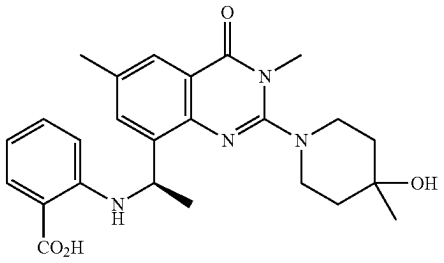
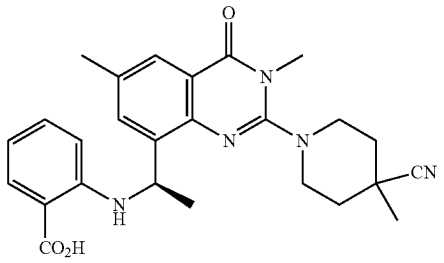
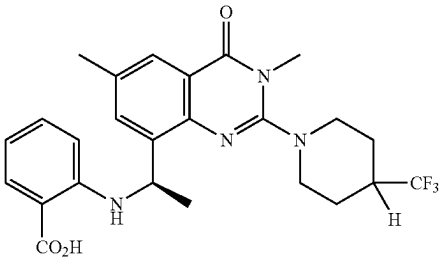
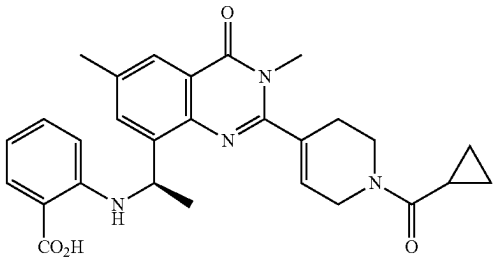
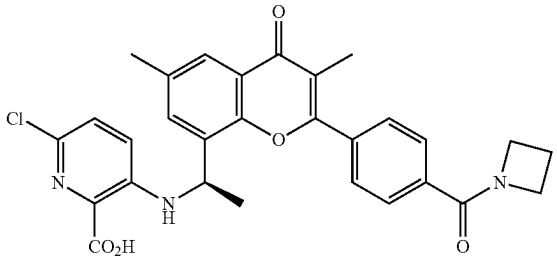
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
79		451.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.63 (s, 1H), 8.43 (s, 1H), 7.78-7.76 (m, 1H), 7.70 (s, 1H), 7.45-7.44 (d, J = 4.0 Hz, 1H), 7.18-7.15 (m, 1H), 6.50-6.44 (m, 2H), 5.43 (s, 1H), 4.38 (s, 1H), 3.47 (s, 3H), 3.25-3.19 (m, 4H), 2.31 (s, 3H), 1.76-1.58 (m, 4H), 1.56-1.54 (d, J = 8.0 Hz, 3H), 1.19 (s, 3H).
80		460.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.43 (s, 1H), 7.79-7.72 (m, 2H), 7.47 (s, 1H), 7.19-7.15 (m, 1H), 8.55-8.46 (m, 2H), 5.42 (s, 1H), 3.64 (d, J = 13.2 Hz, 2H), 3.48 (s, 3H), 3.11-2.98 (m, 2H), 3.32 (s, 3H), 2.07-1.99 (m, 2H), 1.85-1.75 (m, 2H), 1.55 (d, J = 6.8 Hz, 3H), 1.42 (s, 3H).
81		489.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.77 (s, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.25-7.16 (m, 1H), 7.15 (t, J = 7.2 Hz, 1H), 6.50-6.44 (m, 2H), 5.39 (brs, 1H), 3.71 (d, J = 12.4 Hz, 2H), 3.48 (s, 3H), 3.00-2.92 (m, 2H), 2.67-2.61 (m, 1H), 2.32 (s, 3H), 1.93-1.90 (m, 2H), 1.79-1.66 (m, 2H), 1.55 (d, J = 6.8 Hz, 3H).
83		487.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.1 (m, 1H), 8.56-8.37 (m, 1H), 7.82 (s, 1H), 7.80-7.73 (m, 1H), 7.59-7.50 (m, 1H), 7.15 (t, J = 8.4 Hz, 1H), 6.48 (t, J = 7.6 Hz, 1H), 6.45-6.39 (d, J = 8.4 Hz, 1H), 6.26 (s, 1H), 5.47 (s, 1H), 4.46 (s, 1H), 4.18 (s, 1H), 3.95 (s, 1H), 3.75 (s, 1H), 3.53 (s, 3H), 2.70-2.62 (m, 1H), 2.57-2.51 (m, 1H), 2.37 (s, 3H), 2.15-1.95 (m, 1H), 1.65-1.43 (d, J = 13.2 Hz, 3H), 0.85-0.68 (m, 4H).
84		532.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.65-9.35 (br, 1H), 7.93-7.83 (m, 2H), 7.82-7.71 (m, 3H), 7.48 (s, 1H), 7.10-7.00 (m, 1H), 6.87-6.76 (m, 1H), 5.10-5.00 (m, 1H), 4.40-4.30 (m, 2H), 4.10-4.00 (m, 2H), 2.35 (s, 3H), 2.34-2.22 (m, 2H), 2.09 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

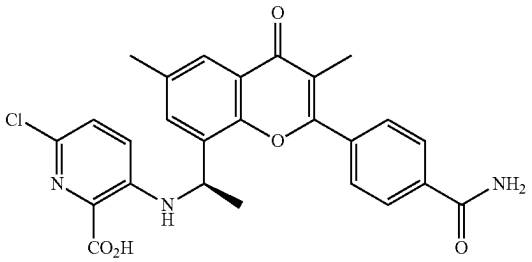
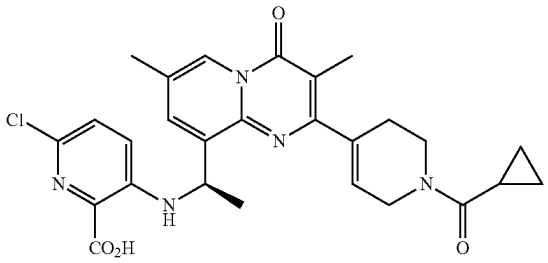
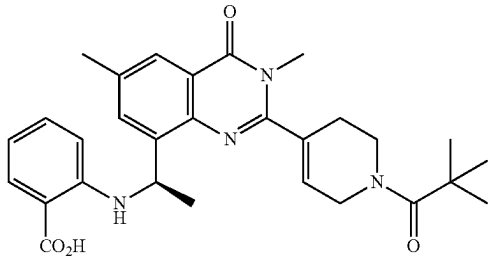
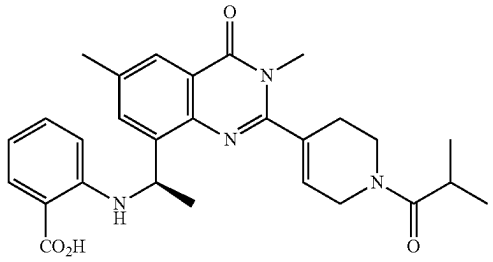
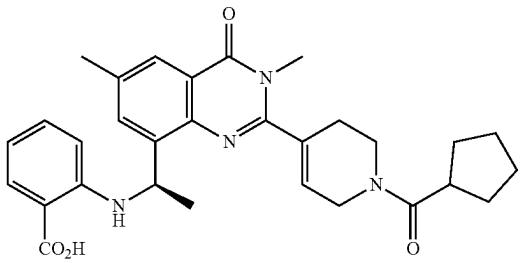
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
85		492.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.93 (brs, 1H), 8.15 (s, 1H), 8.07-7.95 (m, 2H), 7.94-7.84 (m, 2H), 7.78 (s, 1H), 7.60-7.45 (m, 2H), 7.16 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.15-5.05 (m, 1H), 2.36 (s, 3H), 2.08 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
87		522.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.65 (s, 1H), 8.48-8.30 (m, 1H), 7.74-7.64 (m, 1H), 7.36-7.27 (m, 1H), 7.03-6.91 (m, 1H), 6.12-6.02 (m, 1H), 5.42-5.26 (m, 1H), 4.53-4.33 (m, 1H), 4.25-4.11 (m, 1H), 4.03-3.85 (m, 1H), 3.83-3.59 (m, 1H), 2.76-2.53 (m, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 2.13-1.94 (m, 1H), 1.62 (d, J = 6.4 Hz, 3H), 0.82-0.71 (m, 4H).
88		503.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.43 (s, 1H), 8.43 (s, 1H), 7.82-7.76 (m, 2H), 7.55 (s, 1H), 7.16-7.13 (m, 1H), 6.49-6.43 (m, 2H), 6.26 (s, 1H), 5.47 (s, 1H), 4.24 (s, 2H), 3.81-3.80 (m, 2H), 3.51 (s, 3H), 2.51 (s, 2H), 2.37 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.25 (s, 9H).
89		489.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm) δ 7.88-7.85 (m, 2H), 7.60 (s, 1H), 7.10-7.06 (m, 1H), 6.48-6.40 (m, 2H), 6.24-6.21 (m, 1H), 5.56-5.51 (m, 1H), 4.37-4.29 (m, 2H), 3.89-3.87 (m, 2H), 3.61 (s, 3H), 3.23-3.02 (m, 1H), 2.75-2.56 (m, 2H), 2.39 (s, 3H), 1,59 (d, J = 6.8 Hz, 3H), 1.17-1.14 (m, 6H).
90		515.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.58 (s, 1H), 8.50 (s, 1H), 7.78-7.76 (m, 2H), 7.55 (s, 1H), 7.12 (m, 1H), 7.01-6.41 (m, 2H), 6.26 (m, 1H), 5.46 (s, 1H), 4.29 (s, 1H), 4.17 (s, 1H), 3.77 (m, 2H), 3.55 (s, 3H), 3.10-3.04 (m, 2H), 2.51 (s, 1H), 2.33 (s, 3H), 1.66-1.23 (m, 11H).

TABLE 2-continued

Characterization of exemplary compounds.

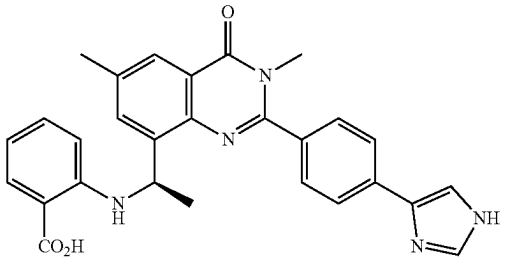
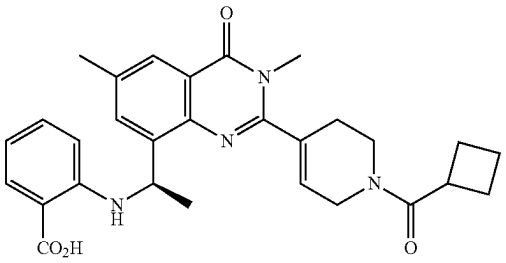
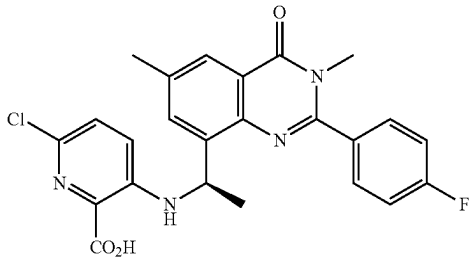
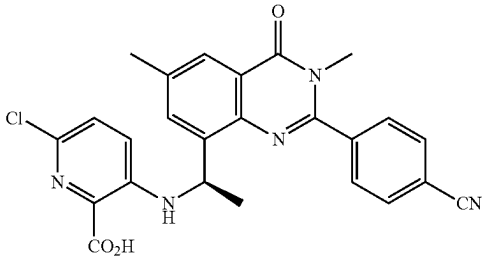
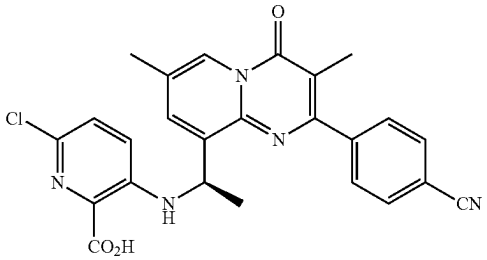
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
91		480.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.70 (s, 1H), 12.28 (s, 1H), 8.45 (s, 1H), 7.09-7.76 (m, 8H), 7.57 (s, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.49 (t, J = 8.0 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 5.50 (m, 1H), 3.48 (s, 3H), 2.33 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).
92		501.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.49 (s, 1H), 7.81-7.76 (m, 2H), 7.54 (s, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.49-6.40 (m, 2H), 6.25-6.20 (m, 1H), 5.46 (s, 1H), 4.16-4.09 (m, 2H), 3.74-3.71 (m, 1H), 3.61-3.55 (m, 1H), 3.53-3.49 (m, 3H), 3.46-3.40 (m, 1H), 2.60-2.50 (m, 2H), 2.36 (s, 3H), 2.20-2.10 (m, 4H), 1.98-1.82 (m, 1H), 1.79-1.69 (m, 1H), 1.53 (d, J = 6.8 Hz, 3H).
93		467.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.3-12.7 (m, 1H), 8.50-8.37 (m, 1H), 7.92-7.89 (m, 1H), 7.88-7.71 (m, 2H), 7.65-7.58 (m, 1H), 7.46-7.38 (m, 2H), 7.33-7.25 (m, 1H), 7.04-6.95 (m, 1H), 5.51-5.39 (m, 1H), 3.41 (s, 3H), 2.41 (s, 3H), 1.61-1.54 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −110.73 (1F).
94		474.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.7 (m, 1H), 8.48-8.32 (m, 1H), 8.09-8.03 (m, 2H), 8.01-7.95 (m, 2H), 7.91 (s, 1H), 7.64 (s, 1H), 7.32-7.26 (m, 1H), 7.05-6.95 (m, 1H), 5.49-5.37 (m, 1H), 3.38 (s, 3H), 2.41 (s, 3H), 1.62-1.52 (m, 3H).
95		474.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.99 (brs, 1H), 8.73 (s, 1H), 8.44-8.30 (m, 1H), 8.05-7.95 (m, 2H), 7.93-7.87 (m, 2H), 7.76-7.12 (m, 1H), 7.31-7.23 (m, 1H), 7.00-6.90 (m, 1H), 5.43-5.30 (m, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

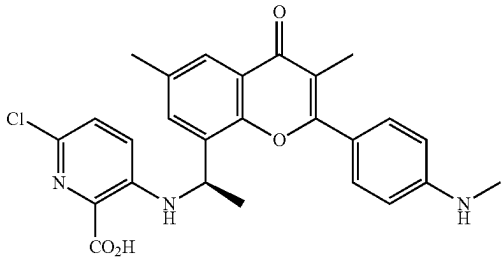
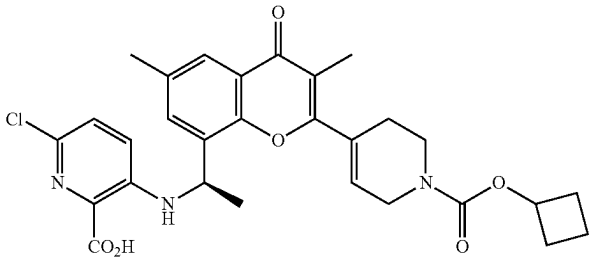
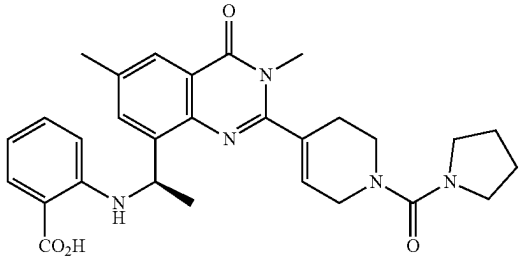
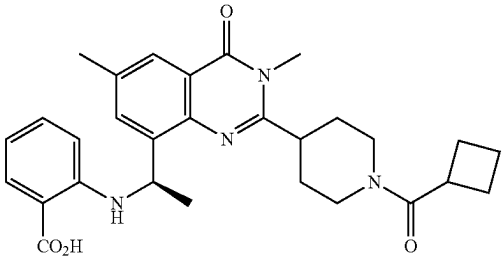
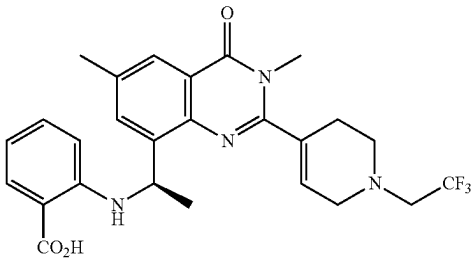
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
96		478.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.04 (brs, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.75 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.48 (s, 1H), 7.32 (d, J = 9.2 Hz, 1H), 7.06 (d, J = 9.2 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.40 (brs, 1H), 5.24-5.12 (m, 1H), 2.76 (s, 3H), 2.36 (s, 3H), 2.13 (s, 3H), 1.62 (d, J = 6.0 Hz, 3H).
97		552.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.5-12.7 (m, 1H), 8.36-8.35 (m, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.33-6.30 (m, 1H), 5.17-5.13 (m, 1H), 4.90-4.86 (m, 1H), 4.25-4.05 (m, 2H), 3.68-3.57 (m, 2H), 2.65-2.55 (m, 2H), 2.35 (s, 3H), 2.31-2.23 (m, 2H), 2.08-1.98 (m, 5H), 1.74-1.71 (m, 1H), 1.69-1.50 (m, 4H).
98		516.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.66 (s, 1H), 8.41 (s, 1H), 7.80-7.76 (m, 2H), 7.54 (s, 1H), 7.18-7.14 (m, 1H), 6.51-6.42 (m, 2H), 6.21 (s, 1H), 5.49-5.46 (m, 1H), 3.95 (s, 2H), 3.51 (s, 3H), 3.47-3.44 (m, 2H), 3.33 (s, 4H), 2.56 (s, 2H), 2.36 (s, 3H), 1.79-1.76 (m, 4H), 1.54 (d, J = 6.4 Hz, 3H).
99		503.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.48 (s, 1H), 7.80-7.78 (m, 2H), 7.54 (s, 1H), 7.13 (t, J = 7.6 Hz, 1H), 8.51-8.44 (m, 2H), 5.53 (s, 1H), 4.49 (d, J = 12.8 Hz, 1H), 3.85 (d, J = 13.2 Hz, 1H), 3.65 (s, 3H), 3.50-3.30 (m, 2H), 3.16 (t, J = 12.0 Hz, 1H), 2.78 (t, J = 12.0 Hz, 1H), 2.36 (s, 3H), 2.25-2.00 (m, 6H), 1.95-1.85 (m, 1H), 1.82-1.65 (m, 3H), 1.56 (d, J = 6.0 Hz, 3H).
100		501.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.55 (s, 1H), 7.88 (t, J = 8.8 Hz, 2H), 7.59 (s, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.54 (t, J = 7.2 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 6.26 (s, 1H), 5.55-5.58 (m, 1H), 4.83-4.85 (m, 2H), 3.86 (s, 2H), 3.64 (s, 3H), 3.46 (s, 2H), 2.85 (s, 2H), 2.39 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

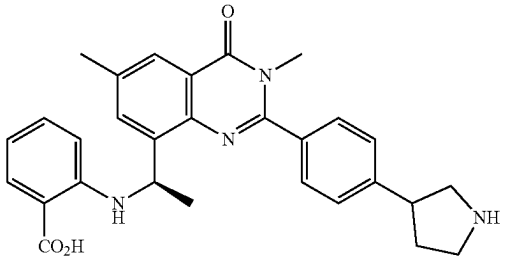
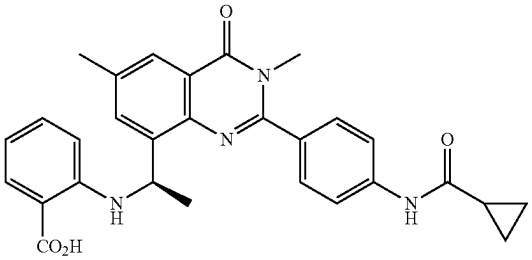
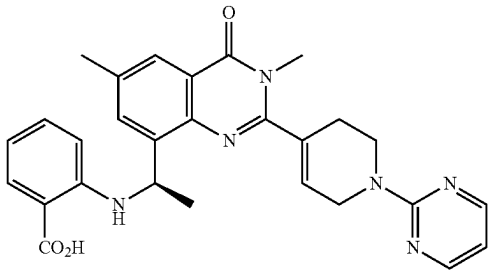
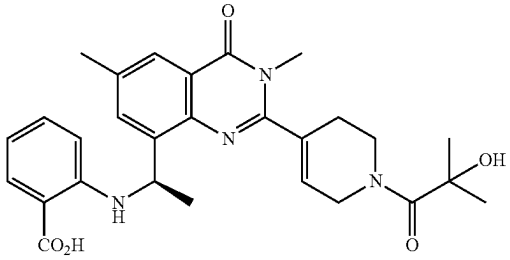
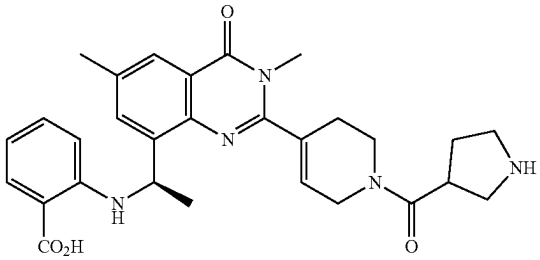
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
101		483.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.49 (s, 1H), 7.91 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 7.2 Hz, 1H), 6.45 (t, J = 7.2 Hz, 1H), 6.33 (d, J = 8.4 Hz, 1H), 5.52-5.57 (m, 1H), 3.75-3.80 (m, 1H), 3.57-3.66 (m, 2H), 3.51 (s, 3H), 3.37-3.43 (m, 1H), 3.26 (s, 1H), 2.52-2.55 (m, 1H), 2.39 (s, 3H), 2.14-2.24 (m, 1H), 1.54 (d, J = 6.8 Hz, 3H).
102		497.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.48 (s, 1H), 8.47 (s, 1H), 7.86 (s, 1H), 7.79-7.72 (m, 5H), 7.56 (d, J = 1.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.49 (s, 1H), 3.45 (s, 3H), 2.38 (s, 3H), 1.85-1.82 (m, 1H), 1.54 (d, J = 6.8 Hz, 3H), 0.85-0.83 (m, 4H).
103		497.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.38 (d, J = 4.8 Hz, 2H), 7.91-7.82 (m, 2H), 7.60 (s, 1H), 7.11-7.04 (m, 1H), 6.64 (t, J = 4.8 Hz, 1H), 6.50-6.45 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.33 (s, 1H), 5.57 (d, J = 6.4 Hz, 1H), 4.46 (d, J = 3.2 Hz, 2H), 4.15 (t, J = 5.6 Hz, 2H), 3.63 (s, 3H), 2.70 (s, 2H), 2.39 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H).
104		505.0	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.84 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.55-6.45 (m, 2H), 6.24 (s, 1H), 5.51 (d, J = 6.4 Hz, 1H), 4.39 (s, 2H), 4.02 (s, 2H), 3.54 (s, 3H), 2.60 (s, 2H), 2.39 (s, 3H), 1.57 (d, J = 6.6 Hz, 3H), 1.41 (s, 6H).
105		516.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.50 (s, 1H), 7.96-7.80 (m, 2H), 7.62 (d, J = 1.6 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.45 (t, J = 7.2 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 6.27-6.12 (m, 1H), 5.58-5.44 (m, 1H), 4.44-4.17 (m, 2H), 4.00-3.79 (m, 2H), 3.79-3.63 (m, 2H), 3.60 (d, J = 4.4 Hz, 3H), 3.47-3.35 (m, 3H), 2.80-2.55 (m, 2H), 2.50-2.40 (m, 1H), 2.38 (s, 3H), 2.22-2.06 (m, 1H), 1.56 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

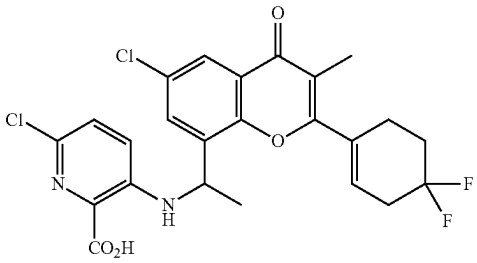
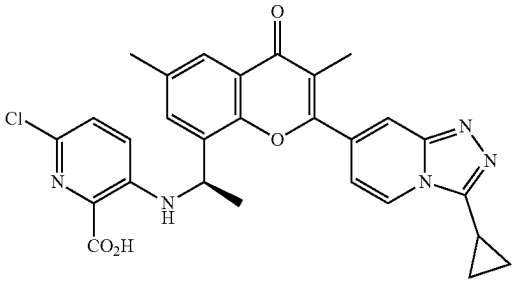
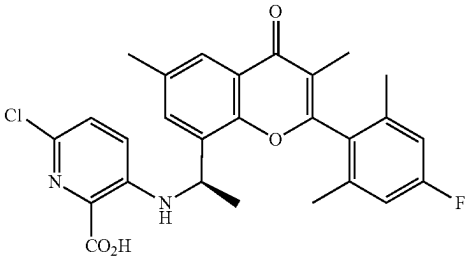
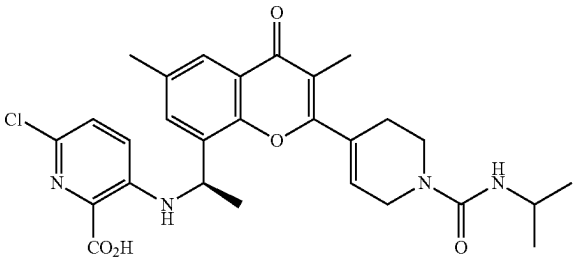
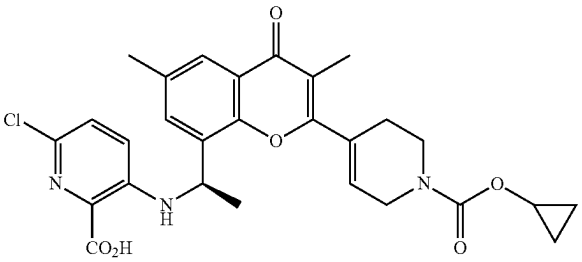
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
106		509.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.35-8.25 (m, 1H), 7.86 (d, J = 2.8 Hz, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.17 (s, 1H), 5.20-5.10 (m, 1H), 3.00-2.80 (m, 2H), 2.75-2.65 (m, 2H), 2.30-2.15 (m, 2H), 2.04 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −94.47 (2F).
107		530.4	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.73 (d, J = 7.2 Hz, 1H), 8.33 (s, 1H, FA), 8.27 (s, 1H), 7.78 (s, 1H), 7.70-7.55 (m, 1H), 7.48 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.90-6.75 (m, 1H), 5.20-5.00 (m, 1H), 2.40-2.30 (m, 4H), 2.15 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.20-1.05 (m, 4H).
108		495.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.94 (br, 1H), 8.32 (brs, 1H), 7.82 (s, 1H), 7.60 (s, 1H), 7.20-6.90 (m, 4H), 5.10-4.95 (m, 1H), 2.40 (s, 3H), 2.15-2.00 (m, 6H), 1.69 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.25 (1F)
109		539.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.07 (brs, 1H), 8.42 (s, 1H), 7.74 (s, 1H), 7.53-7.49 (m, 1H), 7.40-7.33 (m, 1H), 7.04 (s, 1H), 6.34-6.28 (m, 2H), 5.16 (s, 1H), 4.08 (s, 2H), 3.82-3.81 (m, 1H), 3.57-3.50 (m, 2H), 2.53-2.50 (m, 2H), 2.37 (s, 3H), 2.08 (s, 3H), 1.62 (s, 3H), 1.10 (d, J = 6.0 Hz, 6H).
110		538.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.87 (brs, 1H), 8.41 (s, 1H), 7.72 (s, 1H), 7.51 (s, 1H), 7.31 (s, 1H), 7.02 (s, 1H), 6.30 (s, 1H), 5.14 (s, 1H), 4.10-4.04 (m, 3H), 3.56 (s, 2H), 2.53-2.50 (m, 2H), 2.35 (s, 3H), 2.05 (s, 3H), 1.59 (s, 3H), 0.65 (s, 4H).

TABLE 2-continued

Characterization of exemplary compounds.

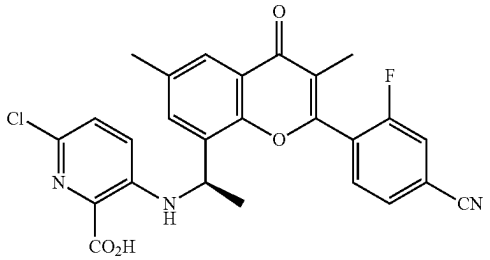
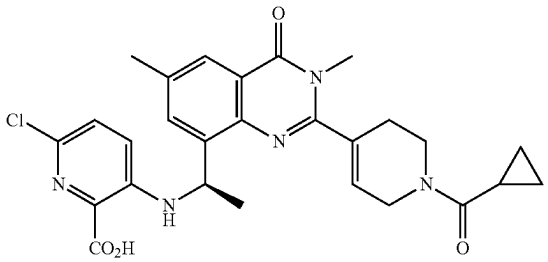
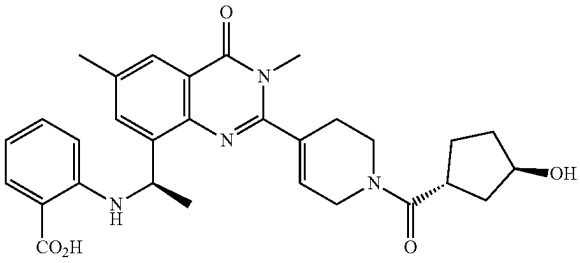
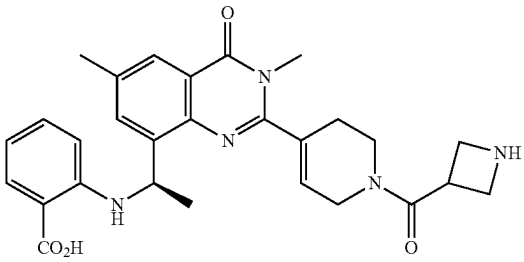
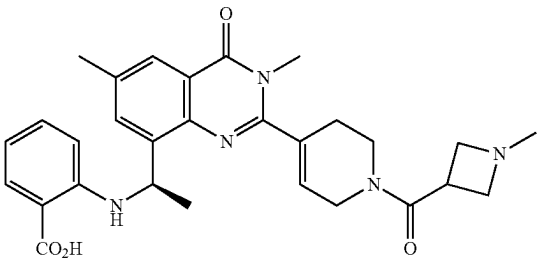
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
111		492.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.7 (m, 1H), 8.28-8.26 (m, 1H), 8.16-8.15 (m, 1H), 8.13-8.12 (m, 1H), 8.01-7.93 (m, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 5.11-5.03 (m, 1H), 2.39 (s, 3H), 1.89 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −110.5 (1F).
112		522.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.92 (brs, 1H), 8.55-8.29 (m, 1H), 7.88-7.65 (m, 1H), 7.64-7.53 (m, 1H), 7.34-7.23 (m, 1H), 7.12-7.01 (m, 1H), 6.32-6.19 (m, 1H), 5.55-5.37 (m, 1H), 4.63-4.26 (m, 1H), 4.25-4.13 (m, 1H), 4.02-3.90 (m, 1H), 3.88-3.67 (m, 1H), 3.52 (s, 3H), 2.73-2.53 (m, 2H), 2.39 (s, 3H), 2.17-1.94 (m, 1H), 1.59 (d, J = 6.8 Hz, 3H), 0.84-0.71 (m, 4H).
115		531.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.89-7.86 (m, 2H), 7.61 (m, 1H), 7.10-7.08 (m, 1H), 6.50 (m, 1H), 6.40 (m, 1H), 6.25-6.22 (m, 1H), 5.55-5.53 (m, 1H), 4.31-4.26 (m, 3H), 3.88 (m, 2H), 3.33 (s, 3H), 3.13 (m, 1H), 2.65-2.63 (m, 2H), 2.39 (s, 3H), 2.23-2.16 (m, 1H), 2.04-1.97 (m, 2H), 1.88-1.84 (m, 2H), 1.76-1.73 (m, 1H), 1.60-1.58 (m, 3H).
116		502.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.88-7.51 (m, 3H), 7.13-6.89 (m, 1H), 6.77-6.59 (m, 1H), 6.44-6.16 (m, 2H), 5.30-5.05 (m, 1H), 4.36-4.11 (m, 3H), 4.10-3.80 (m, 4H), 3.57 (s, 3H), 3.27-3.01 (m, 2H), 2.78-2.57 (m, 1H), 2.42-2.15 (m, 4H), 1.66-1.39 (m, 3H).
117		516.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.20-8.09 (m, 1H), 7.92-7.73 (m, 2H), 7.64-7.54 (m, 1H), 7.21-7.08 (m, 1H), 6.62-6.44 (m, 2H), 6.29-6.15 (m, 1H), 5.56-5.38 (m, 1H), 4.29-3.97 (m, 4H), 3.76-3.36 (m, 8H), 2.65-2.54 (m, 1H), 2.49-2.43 (m, 1H), 2.41-2.35 (m, 3H), 2.27 (s, 3H), 1.57 (d, J = 8.0 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

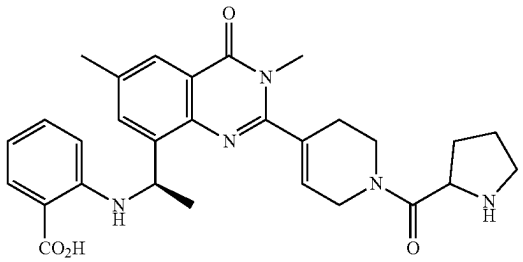
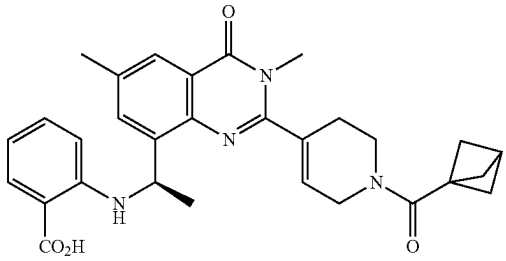
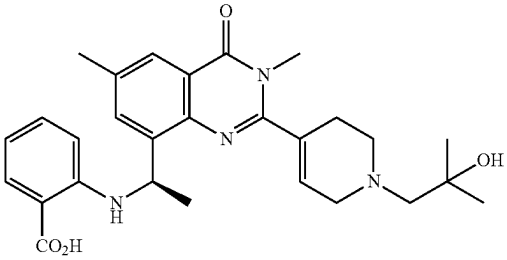
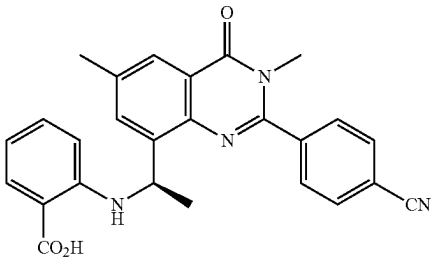
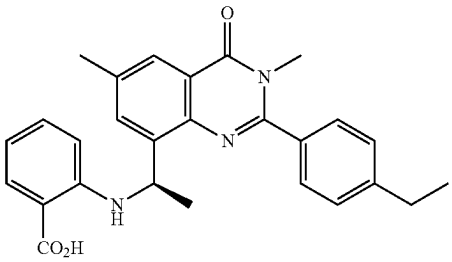
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
118		516.8	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.52 (s, 1H), 7.87-7.81 (m, 2H), 7.66 (s, 1H), 7.03-6.96 (m, 1H), 6.48-6.35 (m, 2H), 6.21-6.17 (m, 1H), 5.38-5.29 (m, 1H), 4.75-4.66 (m, 1H), 4.54-4.52 (m, 1H), 4.39-4.37 (m, 1H), 4.23-4.19 (m, 1H), 3.91-3.88 (m, 1H), 3.81-3.71 (m, 1H), 3.64-3.62 (m, 3H), 3.49-3.38 (m, 1H), 2.86-2.84 (m, 1H), 2.63-2.49 (m, 2H), 2.41 (s, 3H), 2.15-1.90 (m, 3H), 1.60 (d, J = 6.8 Hz, 3H).
119		513.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.88-7.85 (m, 2H), 7.59 (s, 1H), 7.11-7.07 (m, 1H), 6.50-6.39 (m, 2H), 6.23 (s, 1H), 5.53 (q, J = 6.4 Hz, 1H), 4.45 (d, J = 2.8 Hz, 1H), 4.27-4.26 (m, 1H), 4.01-3.97 (m, 1H), 3.87-3.83 (m, 1H), 3.62 (s, 3H), 2.70-2.61 (m, 2H), 2.51 (d, J = 2.4 Hz, 1H), 2.39 (s, 3H), 2.35-2.12 (brs. 6H), 1.58 (d, J = 6.8 Hz, 3H).
120		490.8	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.44 (s, 1H), 7.87-7.72 (m, 2H), 7.59-7.45 (m, 1H), 7.18-7.05 (m, 1H), 6.52-6.39 (m, 2H), 6.16 (s, 1H), 5.49 (s, 1H), 3.51 (s, 3H), 3.37-3.29 (m, 2H), 2.90-2.81 (m, 2H), 2.59-2.52 (m, 2H), 2.40 (s, 2H), 2.36 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.14 (s, 6H).
121		438.8	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.70 (s, 2H), 8.43 (s, 1H), 8.08-8.06 (m, 2H), 8.00-7.98 (m, 2H), 7.89 (m, 1H), 7.79-7.77 (m, 1H), 7.59-7.58 (m, 1H), 7.17-7.13 (m, 1H), 6.51-6.47 (m, 1H), 6.40-6.38 (m, 1H), 5.45-5.42 (m, 1H), 3.56 (s, 3H), 2.40 (s, 3H), 1.53-1.52 (m, 3H).
122		442.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.92 (s, 1H), 7.86 (d, J = 6.4 Hz, 1H), 7.60-7.64 (m, 3H), 7.41 (d, J = 8.4 Hz, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.47 (t, J = 7.6 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.58-5.63 (m, 1H), 3.53 (s, 3H), 2.75-2.77 (m, 2H), 2.40 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.30 (t, J = 7.6 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

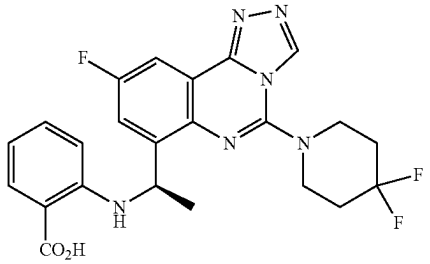
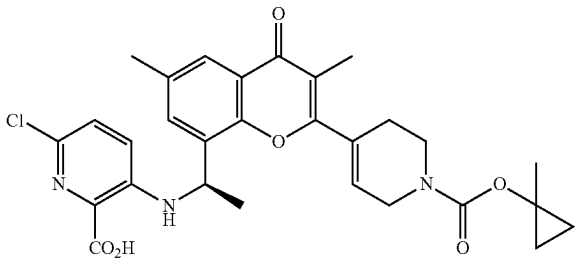
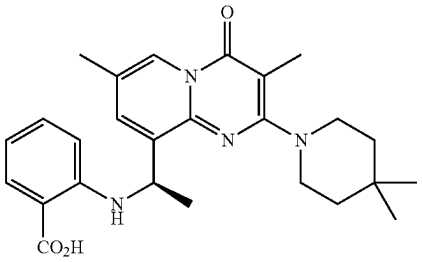
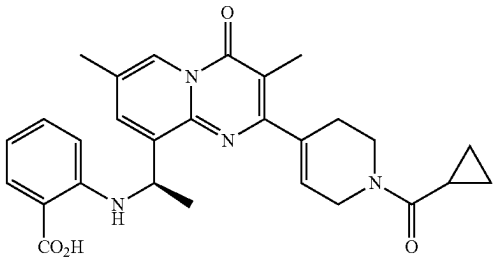
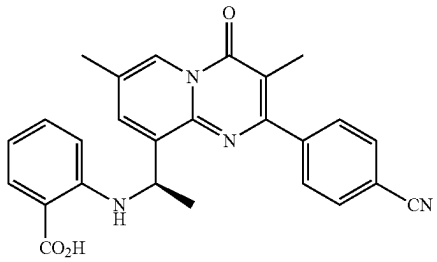
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
123		470.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.42 (s, 1H), 8.17-8.06 (m, 1H), 7.88-7.77 (m, 1H), 7.45-7.35 (m, 1H), 7.25-7.13 (m, 1H), 7.07 (s, 1H), 6.59-6.48 (m, 1H), 6.42-6.32 (m, 1H), 5.54-5.41 (m, 1H), 3.50-3.37 (m, 4H), 2.40-2.20 (m, 4H), 1.60 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.68 (2F), −112.21 (1F).
126		552.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.5-12.7 (m, 1H), 8.43-8.32 (m, 1H), 7.72 (s, 1H), 7.58-7.51 (m, 1H), 7.32-7.29 (m, 1H), 7.02-7.00 (m, 1H), 6.31-6.28 (m, 1H), 5.21-5.03 (m, 1H), 4.20-4.00 (m, 2H), 3.65-3.45 (m, 2H), 2.46-2.40 (m, 2H), 2.35 (s, 3H), 2.05 (s, 3H), 1.65-1.58 (m, 3H), 1.50 (s, 3H), 0.98-0.88 (m, 2H), 0.85-0.70 (m, 2H).
127		449.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.70 (brs, 1H), 8.56 (s, 1H), 8.50-8.33 (m, 1H), 7.86-7.73 (m, 1H), 7.60-7.53 (m, 1H), 7.27-7.15 (m, 1H), 6.60-6.49 (m, 1H), 6.43-6.30 (m, 1H), 5.36-5.21 (m, 1H), 3.47-3.39 (m, 4H), 2.26 (s, 3H), 2.07 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H), 1.52-1.38 (m, 4H), 0.985 (s, 6H).
128		487.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.70 (brs, 1H), 8.65 (s, 1H), 8.50-8.30 (m, 1H), 7.85-7.75 (m, 1H), 7.69-7.57 (m, 1H), 7.25-7.14 (m, 1H), 6.59-6.47 (m, 1H), 6.42-6.28 (m, 1H), 6.14-6.03 (m, 1H), 5.43-5.26 (m, 1H), 4.55-3.58 (m, 4H), 2.76-2.52 (m, 2H), 2.31 (s, 3H), 2.25 (s, 3H), 2.13-1.94 (m, 1H), 1.59 (d, J = 6.4 Hz, 3H), 0.82-0.68 (m, 4H).
129		439.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.80 (brs, 1H), 8.72 (s, 1H), 8.58-8.31 (m, 1H), 8.07-7.99 (m, 2H), 7.97-7.89 (m, 2H), 7.85-7.76 (m, 1H), 7.74-7.65 (m, 1H), 7.23-7.11 (m, 1H), 6.59-6.47 (m, 1H), 6.41-6.27 (m, 1H), 5.45-5.29 (m, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

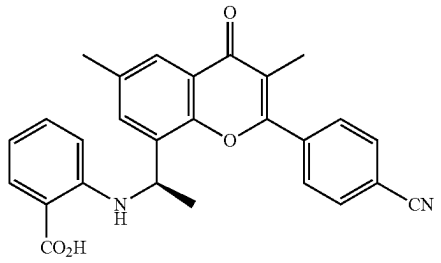
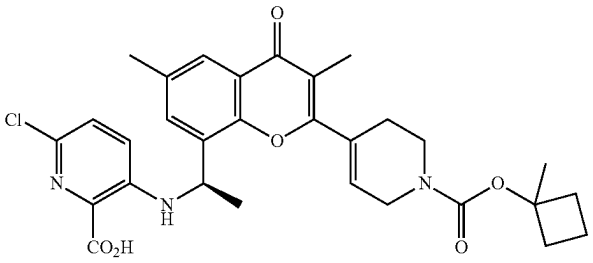
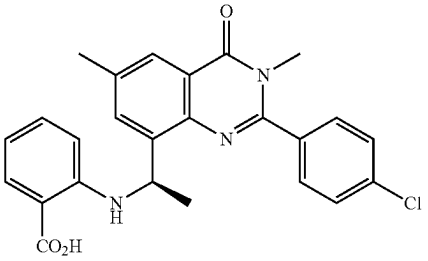
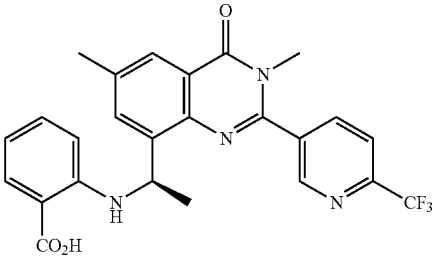
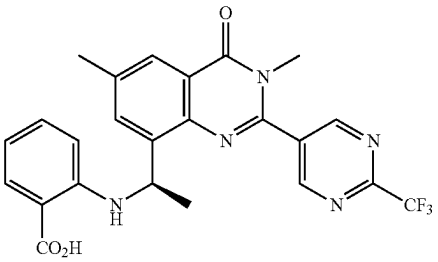
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
130		439.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.81 (s, 1H), 8.04 (d, J = 8.4 Hz, 4H), 7.87-7.72 (m, 2H), 7.54 (s, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.50 (t, J = 7.6 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 5.07 (s, 1H), 2.36 (s, 3H), 2.07 (s, 3H), 1.56 (d, J = 6.8 Hz, 3H).
131		566.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.02 (brs, 1H), 8.47 (s, 1H), 7.73 (s, 1H), 7.51 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.31 (s, 1H), 5.15-5.12 (m, 1H), 4.10 (s, 2H), 3.61-3.57 (m, 2H), 2.53-2.50 (m, 2H), 2.35 (s, 3H), 2.30-2.22 (m, 2H), 2.09-2.04 (m, 5H), 1.76-1.69 (m, 2H), 1.65 (d, J = 6.4 Hz, 3H), 1.59 (s, 3H).
132		448.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.70 (s, 1H), 8.42 (s, 1H), 7.88 (s, 1H), 7.81-7.77 (m, 3H), 7.66-7.64 (m, 2H), 7.57 (m, 1H), 7.17-7.14 (m, 1H), 6.51-6.47 (m, 1H), 6.41-6.39 (m, 1H), 5.45 (m, 1H), 3.50 (s, 3H), 2.32 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H).
133		483.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.61 (s, 1H), 9.21 (s, 1H), 8.55 (dd, J = 8.0, 1.6 Hz, 1H), 8.46 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.78 (dd, J = 8.0, 1.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.20-7.10 (m, 1H), 6.50 (t, J = 7.2 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.51-5.37 (m, 1H), 3.45 (s, 3H), 2.41 (s, 3H), 1.55 (d, J = 6.8 Hz, 3H).
134		484.0	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 9.40 (s, 2H), 7.97 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.41-6.49 (m, 2H), 5.51-5.53 (m, 1H), 3.60 (s, 3H), 2.43 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

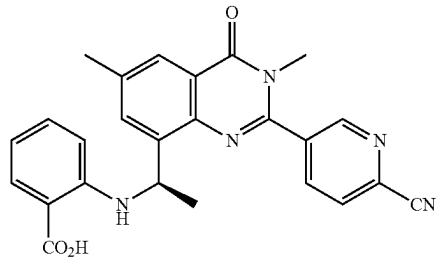
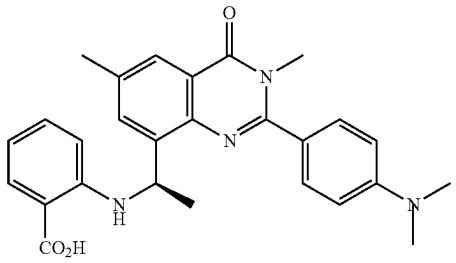
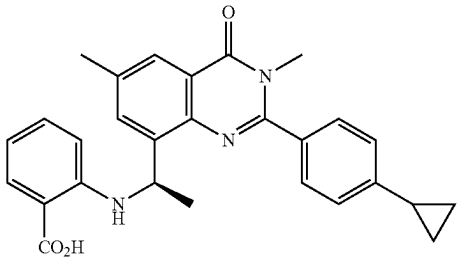
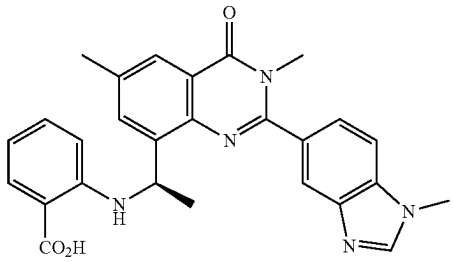
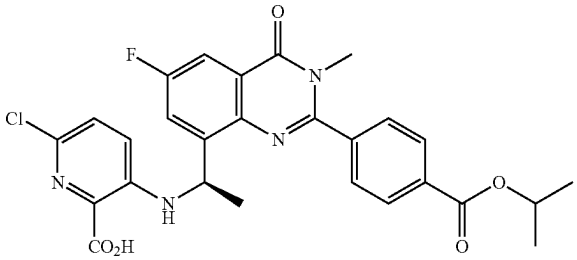
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
135		440.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.69 (s, 1H), 9.18-9.17 (m, 1H), 8.52-8.50 (m, 1H), 8.49-8.45 (m, 1H), 8.29-8.27 (m, 1H), 7.90 (s, 1H), 7.79-7.76 (m, 1H), 7.62-7.61 (m, 1H), 7.17-7.14 (m, 1H), 6.51-6.47 (m, 1H), 6.43-6.41 (m, 1H), 5.45-5.41 (m, 1H), 3.43 (s, 3H), 2.41 (s, 3H), 1.55-1.53 (m, 3H).
136		457.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.43 (s, 1H), 7.83-7.78 (m, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 7.16 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.49-6.42 (m, 2H), 5.51 (s, 1H), 3.51 (s, 3H), 3.01 (s, 6H), 2.33 (s, 3H), 1.54 (d, J = 5.6 Hz, 3H).
137		454.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.43 (s, 1H), 7.86 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.48 (s, 1H), 3.43 (s, 3H), 2.38 (s, 3H), 2.04 (d, J = 5.2 Hz, 1H), 1.53 (d, J = 6.4 Hz, 3H), 1.08-1.06 (m, 2H), 0.81-0.77 (m, 2H).
138		468.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.73 (s, 1H), 8.45 (m, 1H), 8.35 (s, 1H), 8.09 (s, 1H), 7.88 (s, 1H), 7.79-7.75 (m, 2H), 7.70-7.68 (m, 1H), 7.56 (m, 1H), 7.18-7.14 (m, 1H), 6.51-6.47 (m, 1H), 6.43-6.41 (m, 1H), 5.51 (m, 1H), 3.92 (s, 3H), 3.46 (s, 3H), 2.33 (s, 3H), 1.55-1.53 (m, 3H).
139		539.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.99 (brs, 1H), 8.44-8.32 (m, 1H), 8.16-8.09 (m, 2H), 7.94-7.85 (m, 2H), 7.82-7.76 (m, 1H), 7.75-7.67 (m, 1H), 7.33-7.26 (m, 1H), 7.07-6.99 (m, 1H), 5.49-5.37 (m, 1H), 5.27-5.12 (m, 1H), 3.39 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H), 1.36 (d, J = 6.0 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.75 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

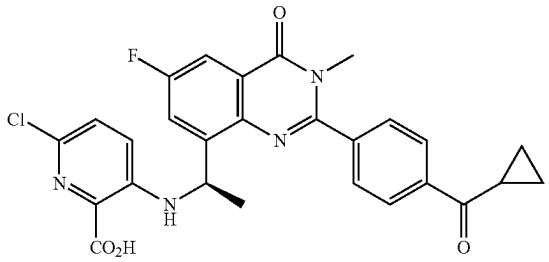
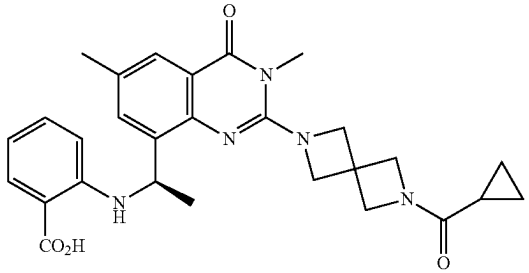
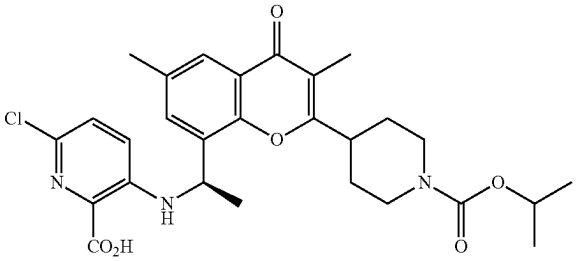
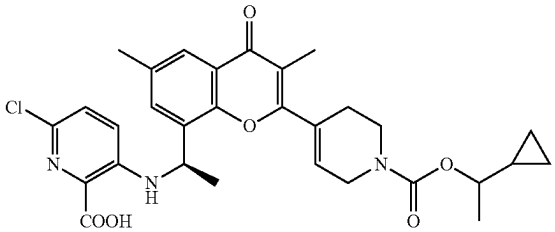
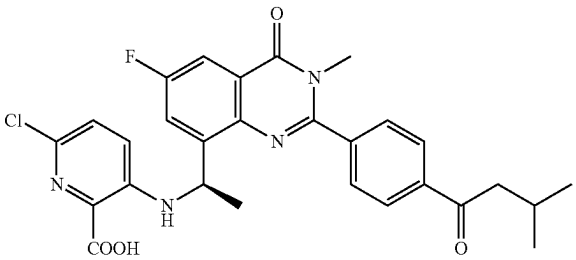
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
141		521.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.46-8.31 (m, 1H), 8.26-8.15 (m, 2H), 7.95-7.89 (m, 2H), 7.82-7.76 (m, 1H), 7.73-7.67 (m, 1H), 7.33-7.25 (m, 1H), 7.05-6.97 (m, 1H), 5.55-5.37 (m, 1H), 3.42 (s, 3H), 3.06-2.94 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H), 1.20-1.00 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.74 (1F).
142		502.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.61 (brs, 1H), 8.67-8.18 (m, 1H), 7.81-7.73 (m, 1H), 7.68-7.63 (m, 1H), 7.44-7.38 (m, 1H), 7.23-7.16 (m, 1H), 6.52-6.31 (m, 2H), 5.40-5.26 (m, 1H), 4.52-4.37 (m, 6H), 4.11-4.00 (m, 2H), 3.39 (s, 3H), 2.29 (s, 3H), 1.60-1.48 (m, 4H), 0.74-0.64 (m, 4H).
143		542.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.58 (s, 1H), 7.69 (s, 1H), 7.40 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.13-4.92 (m, 1H), 4.78 (dt, J = 12.5, 6.0 Hz, 1H), 4.20-3.92 (m, 2H), 3.19-3.09 (m, 1 H), 3.03-2.87 (m, 2H), 2.28 (s, 3H), 2.04 (s, 3H), 1.88-1.67 (m, 4H), 1.53 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 3.6 Hz, 6H).
144		566.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.5-12.7 (m, 1H), 8.43-8.32 (m, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.31-6.28 (m, 1H), 5.21-5.03 (m, 1H), 4.26-4.22 (m, 1H), 4.18-4.05 (m, 2H), 3.65-3.45 (m, 2H), 2.46-2.40 (m, 2H), 2.35 (s, 3H), 2.05 (s, 3H), 1.65-1.58 (m, 3H), 1.27 (s, 3H), 1.05-1.00 (m, 1H), 0.50-0.44 (m, 2H), 0.36-0.33 (m, 1H), 0.30-0.26 (m, 1H).
145		537.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.7 (m, 1H), 8.48-8.26 (m, 1H), 8.14 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H), 7.80-7.77 (m, 1H), 7.71-7.68 (m, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.46-5.42 (m, 1H), 3.40 (s, 3H), 2.98 (d, J = 6.4 Hz, 2H), 2.24-2.17 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.7 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

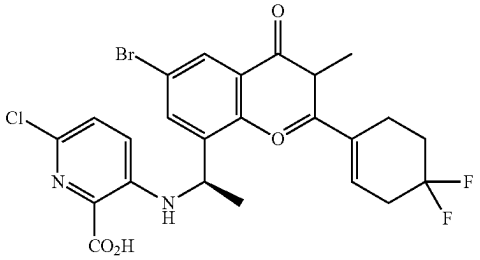
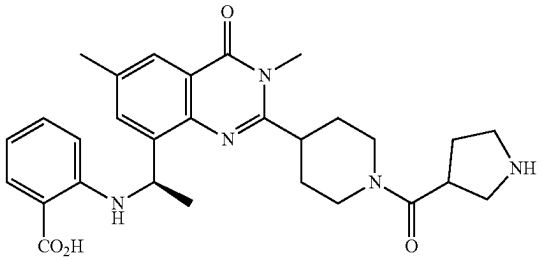
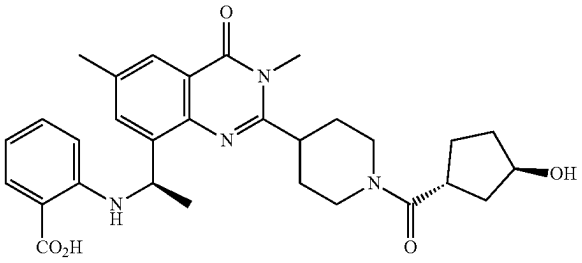
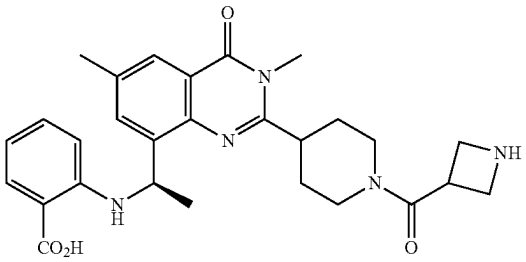
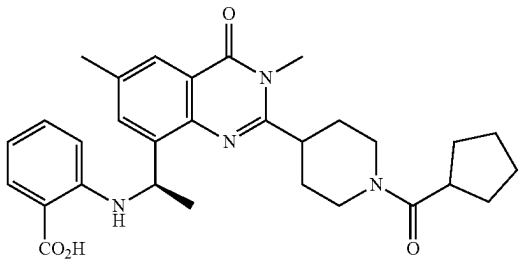
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
146		553.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 13.07 (brs, 1H), 8.31 (d, J = 6.8 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.18 (s, 1H), 5.20-5.10 (m, 1H), 2.93-2.80 (m, 2H), 2.68 (s, 2H), 2.30-2.10 (m, 2H), 2.04 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm) δ −94.45 (1F), −94.58 (1F).
147		518.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.53 (s, 1H), 7.85-7.82 (m, 2H), 7.63 (s, 1H), 7.00-6.99 (m, 1H), 6.44-6.37 (m, 2H), 5.52-5.44 (m, 1H), 4.66-4.63 (m, 1H), 4.20-4.17 (m, 1H), 3.72-3.61 (m, 5H), 3.35-3.31 (m, 5H), 2.98-2.91 (m, 1H), 2.38-2.31 (m, 4H), 2.12-2.07 (m, 4H), 1.89-1.83 (m, 1H), 1.61-1.59 (m, 3H).
148		533.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.42 (s, 1H), 7.79-7.76 (m, 2H), 7.53 (m, 1H), 7.15-7.10 (m, 1H), 6.50-6.43 (m, 2H), 5.51 (m, 1H), 4.60-4.50 (m, 2H), 4.10-4.04 (m, 2H), 3.64 (s, 3H), 3.40-3.26 (m, 1H), 3.10-3.01 (m, 1H), 2.81-2.75 (m, 1H), 2.35 (s, 3H), 2.07-2.00 (m, 3H), 1.82-1.46 (m, 11H).
149		504.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.52 (s, 1H), 7.96-7.70 (m, 2H), 7.62 (s, 1H), 7.07-6.90 (m, 1H), 6.53-6.28 (m, 2H), 5.49-5.34 (m, 1H), 4.69-4.55 (m, 1H), 4.49-3.96 (m, 5H), 3.84-3.55 (m, 4H), 3.40-3.31 (m, 1H), 3.28-3.14 (m, 1H), 3.00-2.85 (m, 1H), 2.37 (s, 3H), 2.16-1.77 (m, 4H), 1.67-1.32 (m, 3H).
150		517.3	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.86 (s, 2H), 7.57 (s, 1H), 7.06-7.11 (m, 1H), 6.42-6.48 (m, 2H), 5.49-5.60 (m, 1H), 4.65-4.68 (m, 1H), 4.26 (d, J = 13.6 Hz, 1H), 3.72 (s, 3H), 3.34-3.39 (m, 2H), 3.10-3.14 (m, 1H), 2.85-2.91 (m, 1H), 2.37-2.38 (m, 3H), 2.04-2.11 (m, 3H), 1.86-1.92 (m, 3H), 1.66-1.81 (m, 4H), 1.57-1.62 (m, 5H).

TABLE 2-continued

Characterization of exemplary compounds.

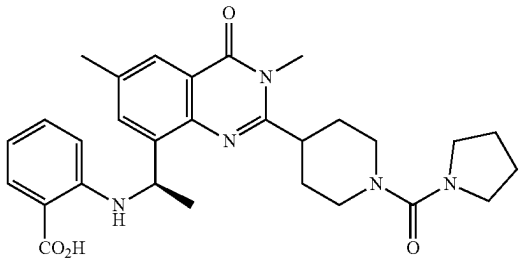
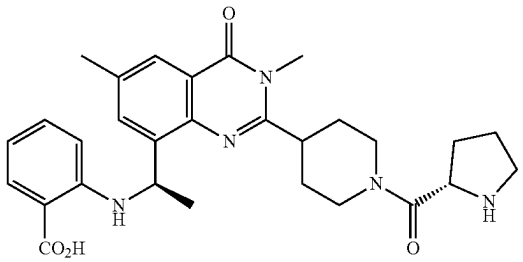
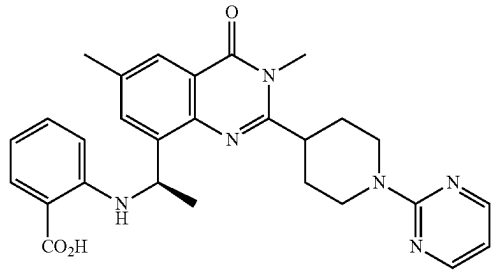
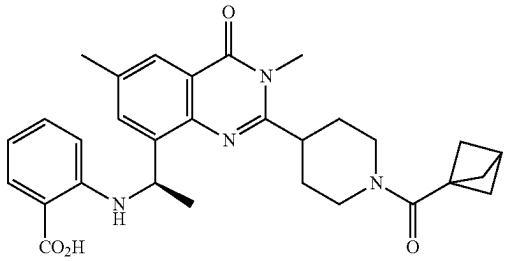
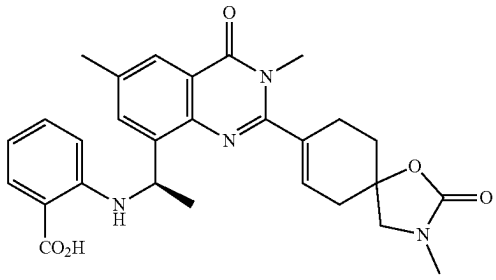
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
151		518.1	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.57 (s, 1H), 7.78-7.76 (m, 2H), 7.55 (s, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.47 (t, J = 7.6 Hz, 2H), 5.51 (s, 1H), 3.81-3.78 (m, 2H), 3.63 (s, 3H), 3.26-3.15 (m, 5H), 2.90 (m, 2H), 2.35 (s, 3H), 1.98-1.80 (m, 5H), 1.92-1.62 (m, 3H), 1.55 (d, J = 6.8 Hz, 3H).
152		518.3	^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 8.40 (s, 1H), 7.85-7.78 (m, 2H), 7.64-7.62 (m, 1H), 7.09-7.02 (m, 1H), 6.46-6.39 (m, 2H), 5.48-5.46 (m, 0.38 H), 5.09-5.05 (m, 0.78 H), 4.67-4.61 (m, 2H), 4.05-4.01 (m, 1H), 3.60-3.59 (m, 3H), 3.43-3.40 (m, 3H), 3.09-2.93 (m, 1H), 2.62-2.39 (m, 5H), 2.23-1.72 (m, 7H), 1.69-1.65 (m, 3H).
153		499.1	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.57 (s, 1H), 8.37 (t, J = 8.4 Hz, 3H), 7.83-7.70 (m, 2H), 7.52 (d, J = 1.6 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.59 (t, J = 4.8 Hz, 1H), 6.44 (dd, J = 12.4, 8.0 Hz, 2H), 5.50 (s, 1H), 4.81 (d, J = 10.8 Hz, 2H), 3.68 (s, 3H), 3.40 (d, J = 11.6 Hz, 1H), 3.10 (t, J = 11.6 Hz, 2H), 2.35 (s, 3H), 2.08 (s, 2H), 1.86-1.78 (m, 2H), 1.51 (d, J = 6.4 Hz, 3H).
154		515.3	^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.91-7.81 (m, 2H), 7.63-7.56 (m, 1H), 7.13-7.03 (m, 1H), 6.52-6.39 (m, 2H), 5.63-5.45 (m, 1H), 4.63-4.53 (m, 1H), 4.44 (d, J = 13.2 Hz, 1H), 3.72 (d, J = 2.8 Hz, 3H), 3.44-3.32 (m, 2H), 2.96-2.86 (m, 1H), 2.48 (d, J = 1.6 Hz, 1H), 2.38 (d, J = 4.8 Hz, 3H), 2.25-2.15 (m, 6H), 2.14-1.98 (m, 3H), 1.91-1.83 (m, 1H), 1.67-1.55 (m, 3H).
155		503.4	^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.91-7.82 (m, 2H), 7.59 (s, 1H), 7.12-7.03 (m, 1H), 6.47 (t, J = 7.6 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.07 (s, 1H), 5.59-5.50 (m, 1H), 3.60 (s, 3H), 3.57-3.50 (m, 2H), 2.90 (s, 3H), 2.81-2.72 (m, 1H), 2.69-2.55 (m, 3H), 2.38 (s, 3H), 2.24-2.17 (m, 1H), 2.08-2.00 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

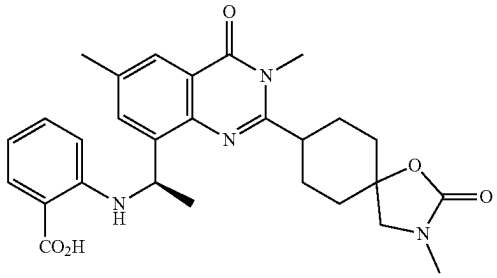
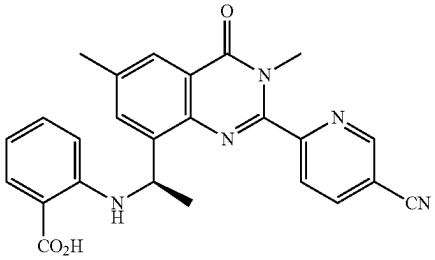
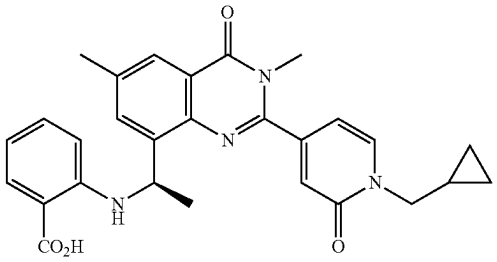
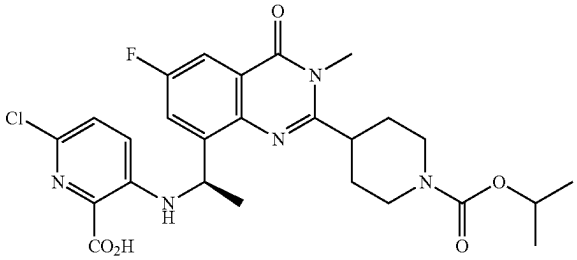
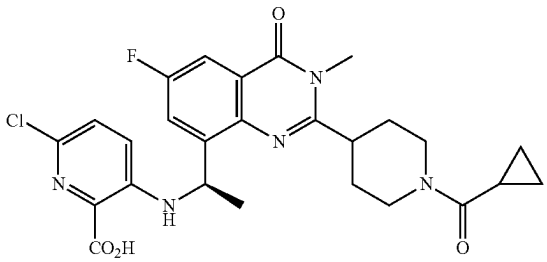
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
156		505.3	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.86-7.84 (m, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.14-7.01 (m, 1H), 6.53-6.34 (m, 2H), 5.68-5.49 (m, 1H), 3.70 (s, 3H), 3.59-3.46 (m, 1H), 3.40 (s, 1H), 3.19-3.09 (m, 1H), 2.87-2.85 (m, 3H), 2.37 (d, J = 6.8 Hz, 3H), 2.27-1.95 (m, 7H), 1.89-1.78 (m, 1H), 1.67-1.55 (m, 3H).
160		440.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 9.06 (s, 1H), 8.43-8.40 (m, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.87-7.85 (m, 1H), 7.66 (s, 1H), 7.11-7.07 (m, 1H), 6.48 (t, J = 7.4 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.57-5.52 (m, 1H), 3.63 (s, 3H), 2.43 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).
161		485.3	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.94 (s, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.63 (s, 1H), 7.07-7.11 (m, 1H), 6.89 (s, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.48 (t, J = 7.2 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.52-5.57 (m, 1H), 3.94 (d, J = 7.2 Hz, 2H), 3.56 (s, 3H), 2.41 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H), 1.34-1.39 (m, 1H), 0.60-0.65 (m, 2H), 0.46-0.50 (m, 2H).
162		546.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.11-12.74 (m, 1H), 8.55-8.45 (m, 1H), 7.69-7.66 (m, 1H), 7.63-7.61 (m, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.51-5.47 (m, 1H), 4.82-4.75 (m, 1H), 4.12-4.09 (m, 2H), 3.64 (s, 3H), 3.22-3.15 (m, 1H), 3.12-2.85 (m, 2H), 2.00-1.97 (m, 2H), 1.78-1.68 (m, 2H), 1.61 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.4 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.9 (1F).
163		528.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.18-12.70 (m, 1H), 8.55-8.45 (m, 1H), 7.70-7.67 (m, 1H), 7.63-7.61 (m, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.51-5.47 (m, 1H), 4.52-4.39 (m, 2H), 3.66 (s, 3H), 3.42-3.31 (m, 2H), 2.83-2.76 (m, 1H), 2.07-1.97 (m, 3H), 1.89-1.79 (m, 1H), 1.78-1.61 (m, 4H), 0.74-0.70 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.9 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

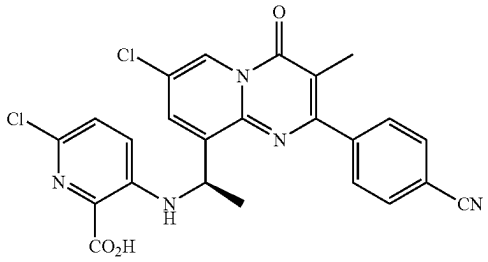
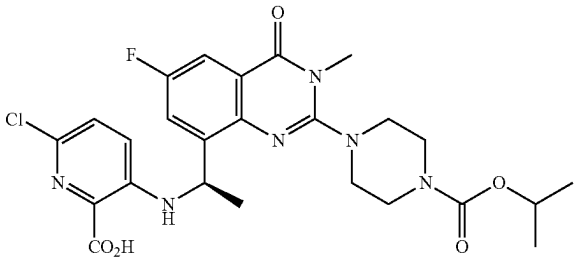
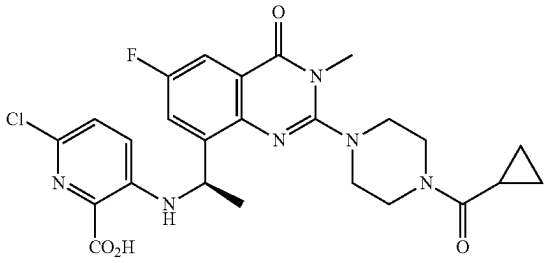
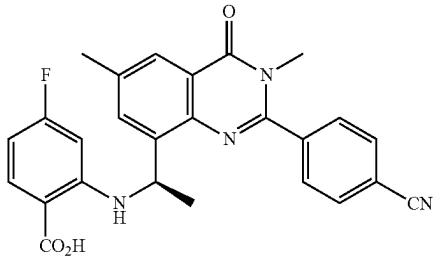
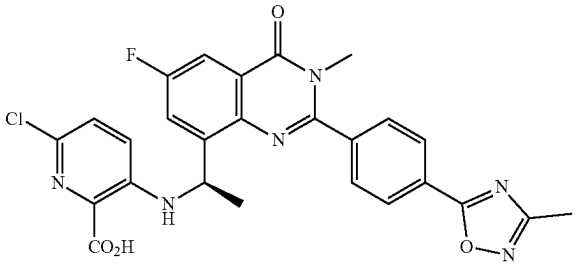
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
164		494.0	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.68 (brs, 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.25 (s, 1H, FA), 8.03-7.92 (m, 4H), 7.62 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.73-6.71 (m, 1H), 5.26-5.23 (m, 1H), 2.23 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
165		547.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.32 (s, 1H), 7.59-7.56 (m, 1H), 7.44-7.42 (m, 1H), 7.11-7.09 (m, 1H), 6.81 (s, 1H), 5.35-5.32 (m, 1H), 4.84-4.78 (m, 1H), 3.61-3.57 (m, 4H), 3.50 (s, 3H), 3.26-3.24 (m, 4H), 1.56 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.0 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.70 (1F).
166		529.2	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.67 (s, 1H), 8.33 (s, 1H, FA), 7.59-7.56 (m, 1H), 7.39-7.36 (m, 1H), 7.03-7.01 (m, 1H), 6.70-6.68 (m, 1H), 5.35-5.31 (m, 1H), 3.90-3.86 (m, 2H), 3.70-3.68 (m, 2H), 3.53 (s, 3H), 3.28-3.25 (m, 4H), 2.06-2.03 (m, 1H), 1.54 (d, J = 6.4 Hz, 3H), 0.78-0.73 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.72 (1F).
167		457.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.09 (s, 1H), 8.08-8.06 (m, 2H), 8.00-7.98 (m, 2H), 7.91 (s, 1H), 7.86-7.82 (m, 1H), 7.62 (s, 1H), 6.27-6.22 (m, 1H), 6.14-6.10 (m, 1H), 5.39-5.36 (m, 1H), 3.55 (s, 3H), 2.41 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −106.10 (1F).
168		535.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.99 (brs, 1H), 8.46-8.33 (m, 1H), 8.32-8.23 (m, 2H), 8.06-7.97 (m, 2H), 7.82-7.75 (m, 1H), 7.83-7.66 (m, 1H), 7.33-7.26 (m, 1H), 7.05-6.97 (m, 1H), 5.52-5.38 (m, 1H), 3.42 (s, 3H), 2.47 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.66 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

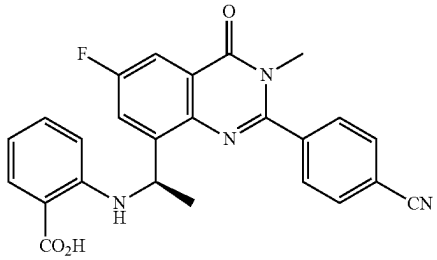
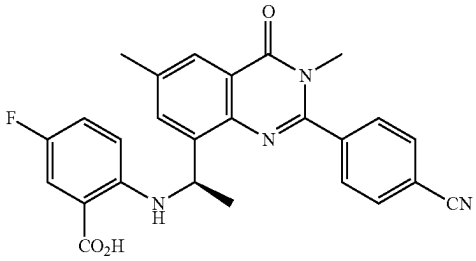
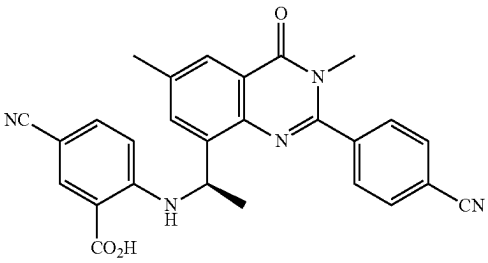
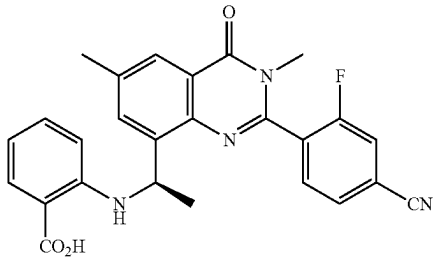
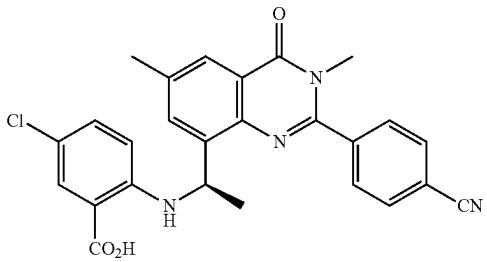
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
169		443.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.7 (brs, 1H), 8.47-8.30 (m, 1H), 8.12-8.03 (m, 2H), 8.02-7.96 (m, 2H), 7.83-7.73 (m, 2H), 7.60-7.53 (m, 1H), 7.22-7.10 (m, 1H), 6.57-6.48 (m, 1H), 6.41-6.30 (m, 1H), 5.49-5.39 (m, 1H), 3.39 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H). ^{19}F-NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.72 (1F).
170		457.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.02 (brs, 1H), 8.44-8.13 (m, 1H), 8.10-8.03 (m, 2H), 8.01-7.96 (m, 2H), 7.92-7.86 (m, 1H), 7.62-7.54 (m, 1H), 7.52-7.46 (m, 1H), 7.13-7.03 (m, 1H), 6.43-6.33 (m, 1H), 5.46-5.34 (m, 1H), 3.38 (s, 3H), 2.40 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −130.12 (1F).
171		464.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.33 (brs, 1H), 9.16-8.90 (m, 1H), 8.13-8.03 (m, 3H), 8.02-7.95 (m, 2H), 7.95-7.89 (m, 1H), 7.67-7.59 (m, 1H), 7.58-7.49 (m, 1H), 6.67-6.52 (m, 1H), 5.59-5.41 (m, 1H), 3.38 (s, 3H), 2.42 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).
172		457.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.90 (s, 1H), 8.17 (d, J = 9.6 Hz, 1H), 8.09-7.91 (m, 2H), 7.90 (s, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.61 (s, 1H), 7.05 (s, 1H), 6.45 (t, J = 7.2 Hz, 1H), 6.37-6.25 (m, 1H), 5.38 (s, 1H), 3.35 (s, 3H), 2.40 (s, 3H), 1.50 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.81 (1F).
173		473.4	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.74 (s, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 7.89 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.57 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.37 (d, J = 9.2 Hz, 1H), 5.41 (s, 1H), 3.39 (s, 3H), 2.40 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

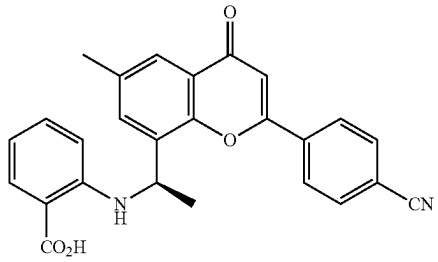
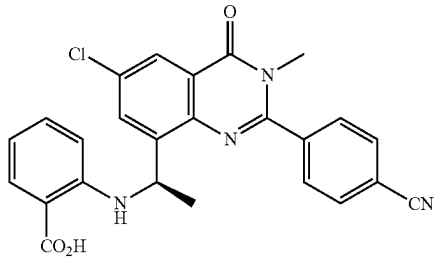
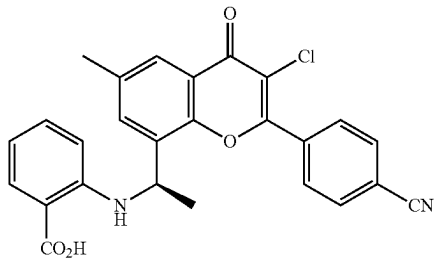
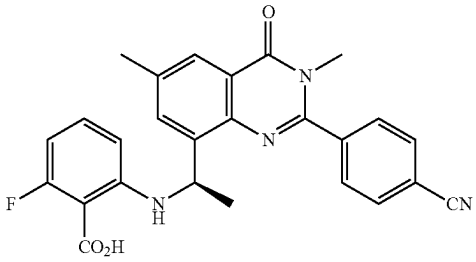
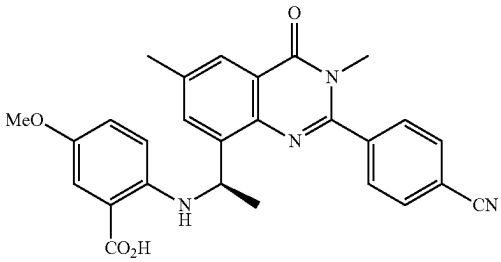
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
174		425.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.49-8.43 (m, 1H), 8.36-8.29 (m, 2H), 8.09-8.02 (m, 2H), 7.85-7.79 (m, 1H), 7.79-7.74 (m, 1H), 7.61-7.56 (m, 1H), 7.28-7.18 (m, 2H), 6.60-6.49 (m, 2H), 5.38-5.29 (m, 1H), 2.37 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).
175		459.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.61 (s, 1H), 8.11-8.06 (m, 2H), 8.04 (d, J = 2.4 Hz, 1H), 8.02-7.97 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.53 (t, J = 7.6 Hz, 1H), 6.33 (d, J = 8.0 Hz, 1H), 5.45-5.36 (m, 1H), 3.54 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).
176		459.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.06-12.59 (m, 1H), 8.58-8.45 (m, 1H), 8.18 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 7.84-7.80 (m, 2H), 7.61 (s, 1H), 7.19-7.14 (m, 1H), 6.56-6.52 (m, 1H), 6.46-6.44 (m, 1H), 5.15-5.05 (m, 1H), 3.34 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).
177		457.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.4-12.5 (m, 1H), 8.17-8.15 (m, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 7.91 (s, 1H), 7.60 (s, 1H), 7.15-7.08 (m, 1H), 6.32-6.27 (m, 1H), 6.25-6.23 (m, 1H), 5.42-5.39 (m, 1H), 3.39 (s, 3H), 2.42 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −105.8 (1F).
178		469.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.57-8.09 (m, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.58 (s, 1H), 7.32 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 9.2 Hz, 1H), 6.35 (d, J = 9.2 Hz, 1H), 5.42-5.39 (m, 1H), 3.62 (s, 3H), 3.39 (s, 3H), 2.40 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

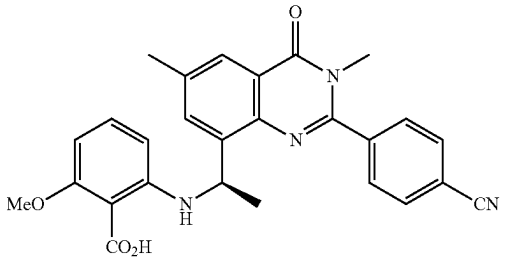
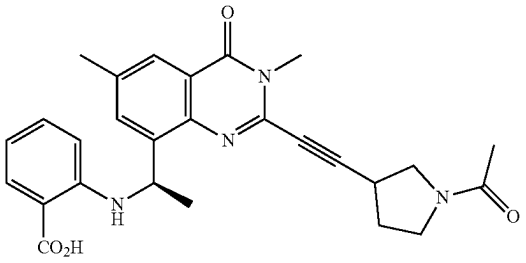
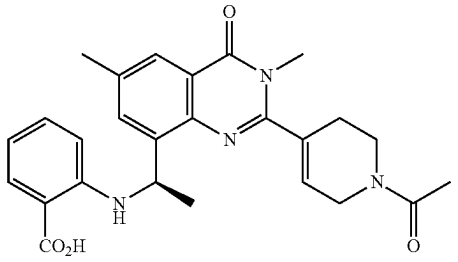
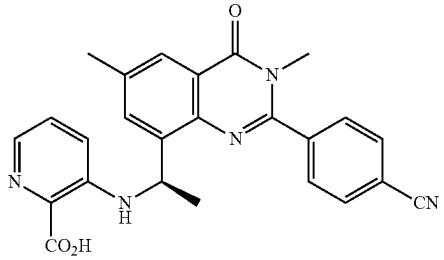
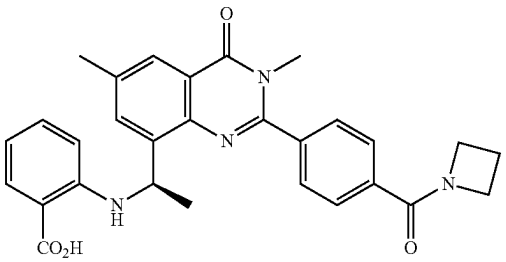
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
179		469.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.08-8.06 (m, 2H), 8.00-7.98 (m, 2H), 7.89 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.21 (s, 1H), 6.99-6.95 (m, 1H), 6.22 (d, J = 8.4 Hz, 1H), 6.01 (d, J = 8.4 Hz, 1H), 5.37-5.35 (m, 1H), 3.72 (s, 3H), 3.39 (s, 3H), 2.40 (s, 3H), 1.47 (d, J = 6.8 Hz, 3H).
180		473.2	^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.92-7.85 (m, 2H), 7.64-7.59 (m, 1H), 7.09-7.02 (m, 1H), 6.53-6.45 (m, 1H), 6.36-6.28 (m, 1H), 5.61-5.53 (m, 1H), 3.97-3.50 (m, 8H), 2.49-2.19 (m, 5H), 2.12-2.08 (m, 3H), 1.61-1.49 (m, 3H).
181		461.4	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.9-12.3 (m, 1H), 8.60-8.28 (m, 1H), 7.82 (s, 1H), 7.80-7.73 (m, 1H), 7.58-7.51 (m, 1H), 7.21-7.07 (m, 1H), 6.48 (t, J = 7.6 Hz, 1H), 6.45-6.40 (d, J = 8.8 Hz, 1H), 6.28-6.19 (m, 1H), 5.52-5.40 (m, 1H), 4.25-4.11 (m, 2H), 3.76-3.65 (m, 2H), 3.52 (s, 3H), 2.66-2.59 (m, 1H), 2.55-2.52 (m, 1H), 2.37 (s, 3H), 2.13-2.05 (m, 3H), 1.57-1.51 (d, J = 6.8 Hz, 3H).
182		440.4	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.98-8.52 (m, 1H), 8.11-8.04 (m, 2H), 8.03-7.97 (m, 2H), 7.93-7.89 (m, 1H), 7.88-7.71 (m, 1H), 7.62 (s, 1H), 7.37-7.17 (m, 1H), 7.10-6.88 (m, 1H), 5.54-5.35 (m, 1H), 3.38 (s, 3H), 2.40 (s, 3H), 1.63-1.48 (m, 3H).
183		497.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.92-11.34 (m, 1H), 8.48 (s, 1H), 7.93-7.83 (m, 3H), 7.83-7.75 (m, 3H), 7.63-7.55 (m, 1H), 7.19-7.11 (m, 1H), 6.49 (t, J = 7.2 Hz, 1H), 6.43-6.36 (d, J = 8.4 Hz, 1H), 5.53-5.40 (m, 1H), 4.49-4.27 (m, 2H), 4.18-3.99 (m, 2H), 3.41 (s, 3H), 2.40 (s, 3H), 2.34-2.23 (m, 2H), 1.61-1.46 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

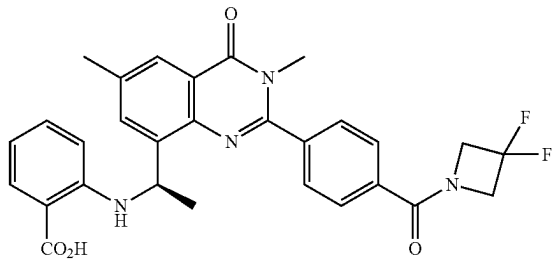
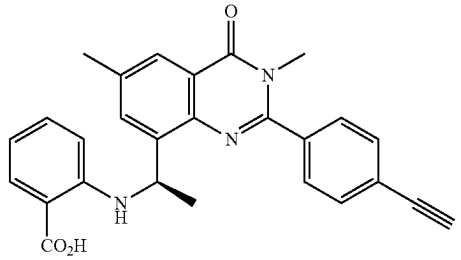
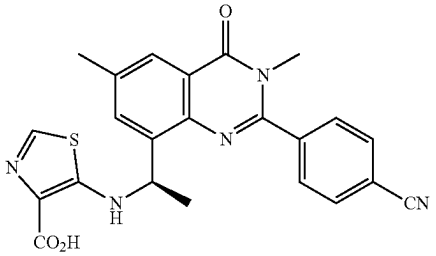
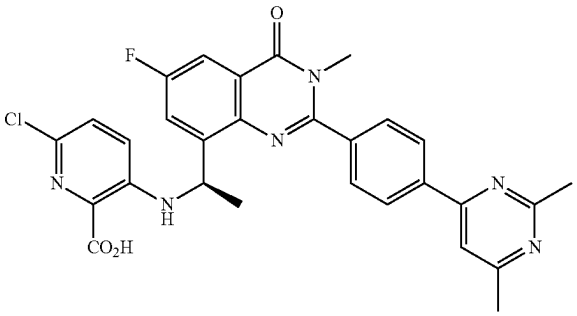
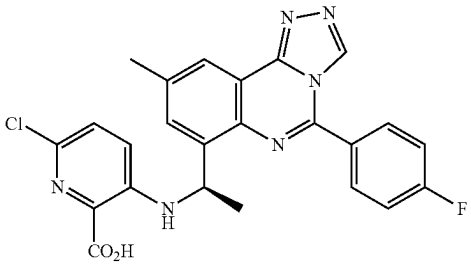
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
184		533.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.20-12.25 (m, 1H), 8.43 (s, 1H), 7.92-7.85 (m, 5H), 7.82-7.74 (m, 1H), 7.61-7.55 (m, 1H), 7.21-7.12 (m, 1H), 6.50 (t, J = 7.2 Hz, 1H), 6.44-6.36 (d, J = 8.4 Hz, 1H), 5.53-5.42 (m, 1H), 5.03-5.36 (m, 4H), 3.41 (s, 3H), 2.40 (s, 3H), 1.61-1.46 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −99.53 (2F).
185		438.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.75 (s, 1H), 7.80-7.64 (m, 4H), 7.58-7.41 (m, 3H), 6.94 (s, 1H), 6.41-6.13 (m, 2H), 5.43-5.23 (m, 1H), 4.27 (s, 1H), 3.32 (s, 3H), 2.26 (s, 3H), 1.39 (d, J = 5.9 Hz, 3H).
186		446.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.27-8.15 (m, 1H), 8.10-8.04 (m, 2H), 8.03-7.97 (m, 2H), 7.96-7.90 (m, 2H), 7.72-7.67 (m, 1H), 5.13-5.05 (m, 1H), 2.52 (s, 3H), 2.44 (s, 3H), 1.69-1.53 (m, 3H).
187		559.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.72 (brs, 1H), 8.35 (d, J = 8.0 Hz, 2H), 7.94-7.89 (m, 3H), 7.79-7.77 (m, 1H), 7.66-7.64 (m, 1H), 7.22 (s, 1H), 6.94 (s, 1H), 5.50-5.40 (m, 1H), 3.45 (s, 3H), 2.67 (s, 3H), 2.53 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.93 (1F).
188		477.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 9.40 (s, 1H), 8.29 (s, 1H), 8.22-8.12 (m, 2H), 7.70 (s, 1H), 7.44 (t, J = 8.8 Hz, 2H), 7.21-7.11 (m, 1H), 7.10-7.00 (m, 1H), 5.80-5.70 (m, 1H), 2.54 (s, 3H), 1.75 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −109.48 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

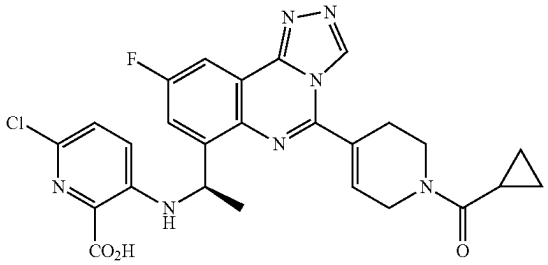
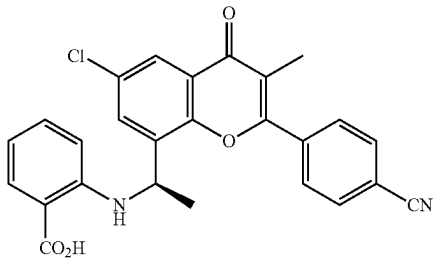
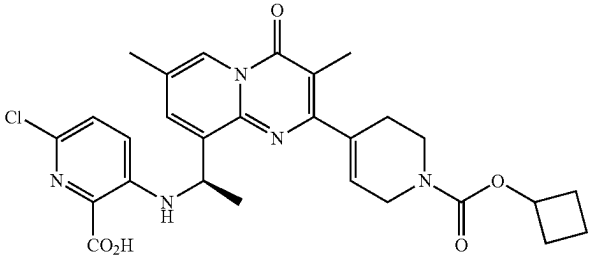
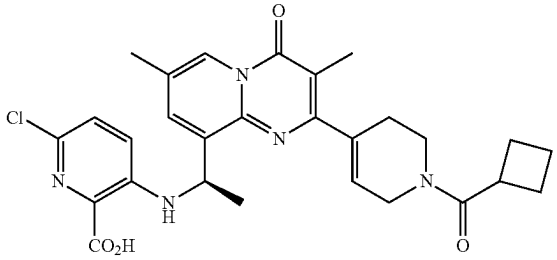
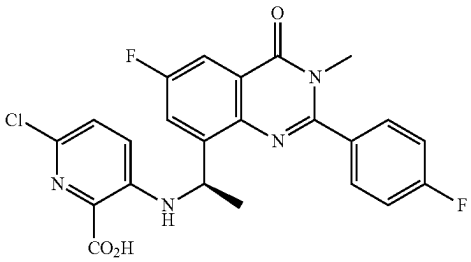
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
189		536.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.83 (s, 1H), 8.14-8.04 (m, 1H), 7.75-7.62 (m, 1H), 7.25-7.13 (m, 1H), 7.06-6.93 (m, 1H), 5.65-5.55 (m, 1H), 5.41-5.24 (m, 1H), 4.46-4.35 (m, 1H), 4.25-3.62 (m, 2H), 3.32-3.21 (m, 2H), 2.35-1.95 (m, 3H), 1.65 (d, J = 6.8 Hz, 3H), 0.90-0.73 (m, 4H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −109.27 (1F).
190		459.4	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.00 (s, 1H), 7.96-7.85 (m, 3H), 7.75-7.60 (m, 1H), 7.50-7.30 (m, 2H), 7.20-7.10 (m, 1H), 6.70-6.40 (m, 2H), 5.20-5.10 (m, 1H), 2.14 (s, 3H), 1.70-1.60 (m, 3H).
191		552.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.65 (s, 1H), 8.54 (s, 1H), 7.68 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 9.2 Hz, 1H), 6.05 (s, 1H), 5.35-5.32 (m, 1H), 4.91-4.87 (m, 1H), 4.11 (s, 2H), 3.62 (s, 2H), 2.61-2.56 (m, 2H), 2.32 (s, 3H), 2.28-2.24 (m, 2H), 2.22 (s, 3H), 2.08-1.98 (m, 2H), 1.77-1.69 (m, 1H), 1.62-1.59 (m, 4H).
192		536.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.29 (s, 1H), 8.63 (s, 1H), 7.57 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.13-6.01 (m, 1H), 5.38-5.18 (m, 1H), 4.21-4.03 (m, 2H), 3.78-3.66 (m, 2H), 3.58-3.43 (m, 2H), 2.25 (s, 3H), 2.21-2.04 (m, 8H), 1.99-1.81 (m, 1H), 1.79-1.69 (m, 1H), 1.56 (d, J = 6.4 Hz, 3H).
193		471.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.97 (s, 1H), 8.69 (s, 1H), 7.85 (dd, J = 8.8, 5.6 Hz, 2H), 7.76 (d, J = 6.4 Hz, 1H), 7.70-7.59 (m, 1H), 7.42 (t, J = 8.8 Hz, 2H), 7.21 (s, 1H), 6.89 (s, 1H), 5.43 (s, 1H), 3.41 (s, 3H), 1.58 (d, J = 6.0 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −110.51 (1F), −112.08 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

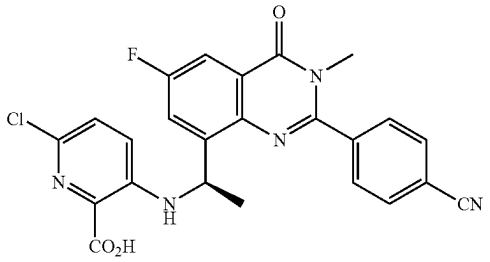
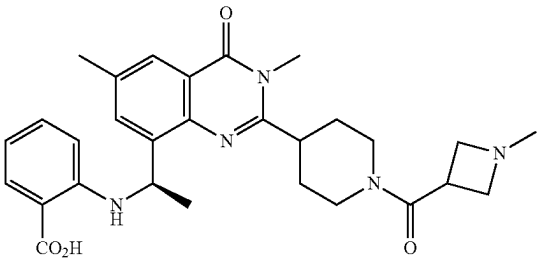
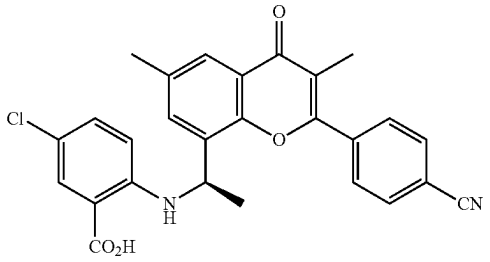
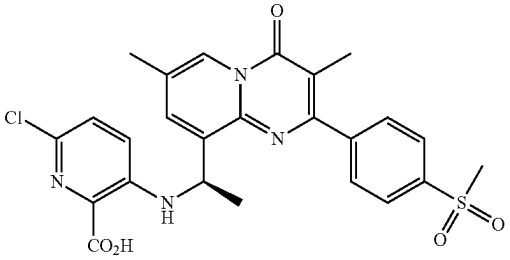
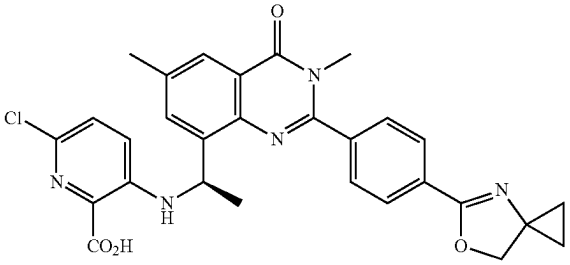
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
194		478.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.01 (s, 1H), 8.55 (s, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 7.78 (dd, J = 8.4, 3.2 Hz, 1H), 7.68 (dd, J = 9.2, 2.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 5.48-5.34 (m, 1H), 3.36 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.52 (1F).
195		518.3	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.87-7.81 (m, 2H), 7.64 (s, 1H), 7.10-6.92 (m, 1H), 6.60-6.35 (m, 2H), 5.45-5.30 (m, 1H), 4.68-4.60 (m, 1H), 4.30-4.10 (m, 1H), 4.06-3.75 (m, 5H), 3.71 (s, 3H), 3.44-3.32 (m, 2H), 3.00-2.83 (m, 1H), 2.68-2.62 (m, 3H), 2.42-2.38 (m, 3H), 2.20-1.80 (m, 4H), 1.65-1.60 (m, 3H).
196		473.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.39 (brs, 1H), 8.08-8.05 (m, 2H), 8.02-7.96 (m, 2H), 7.83-7.78 (m, 1H), 7.74-7.71 (m, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.24-7.18 (m, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.11-5.08 (m, 1H), 2.37 (s, 3H), 2.06 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H).
197		527.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.90 (brs, 1H), 8.72 (s, 1H), 8.10-8.06 (m, 2H), 8.00-7.96 (m, 2H), 7.69 (s, 1H), 7.24-7.14 (m, 1H), 6.87-6.81 (m, 1H), 5.34-5.31 (m, 1H), 3.32 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).
198		544.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.44-12.44 (m, 1H), 8.60-8.46 (m, 1H), 8.04-7.96 (m, 2H), 7.92-7.89 (m, 1H), 7.88-7.82 (m, 2H), 7.65-7.58 (m, 1H), 7.31-7.21 (m, 1H), 7.03-6.94 (m, 1H), 5.50-5.35 (m, 1H), 4.48 (s, 2H), 3.39 (s, 3H), 2.40 (s, 3H), 1.65-1.44 (m, 3H), 1.20-1.05 (m, 2H), 0.96-0.82 (m, 2H).

TABLE 2-continued

Characterization of exemplary compounds.

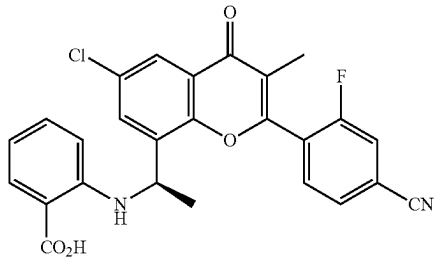
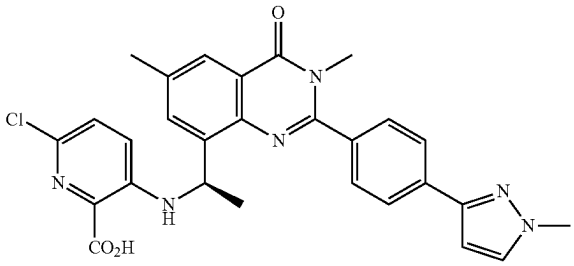
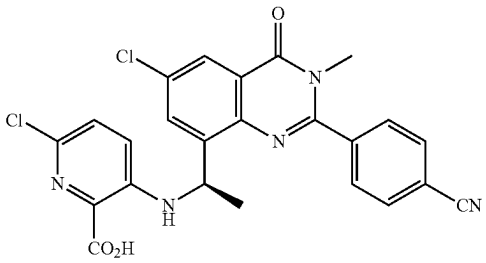
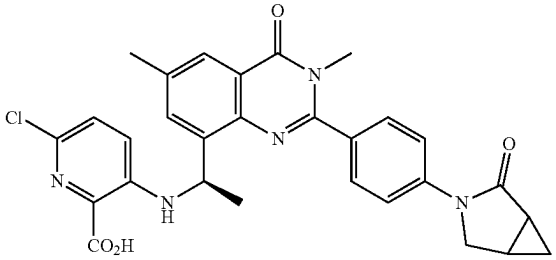
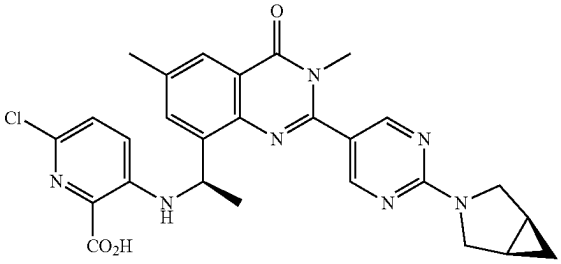
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
199		477.0	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.00 (s, 1H), 7.95-7.75 (m, 4H), 7.71 (s, 1H), 7.12 (t, J = 7.2 Hz, 1H), 6.54 (t, J = 7.2 Hz, 1H), 6.36 (d, J = 8.2 Hz, 1H), 5.10-5.00 (m, 1H), 2.00 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −111.42 (1F).
200		529.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.98-7.90 (m, 3H), 7.80-7.78 (m, 3H), 7.62 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.82 (s, 1H), 5.53-5.42 (m, 1H), 3.92 (s, 3H), 3.46 (s, 3H), 2.41 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H)
201		494.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.94 (s, 1H), 8.10-8.06 (m, 2H), 8.04 (d, J = 2.4 Hz, 1H), 8.02-7.97 (m, 2H), 7.78 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.42-5.32 (m, 1H), 3.38 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H).
202		544.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.81 (s, 1H), 7.87 (s, 1H), 7.77 (s, 4H), 7.59 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.93-6.68 (m, 1H), 5.50-5.36 (m, 1H), 4.14-4.08 (m, 1H), 3.84 (d, J = 10.4 Hz, 1H), 3.45 (s, 3H), 2.39 (s, 3H), 2.16-2.05 (m, 2H), 1.55 (d, J = 6.4 Hz, 3H), 1.24-1.17 (m, 1H), 0.82-0.75 (m, 1H).
203		532.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.89-8.61 (m, 3H), 7.85 (s, 1H), 7.57 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 5.50-5.36 (m, 1H), 3.87 (d, J = 11.2 Hz, 2H), 3.57 (d, J = 11.2 Hz, 2H), 3.54 (s, 3H), 2.38 (s, 3H), 1.73-1.68 (m, 2H), 1.56 (d, J = 6.4 Hz, 3H), 0.82-0.74 (m, 1H), 0.22-0.14 (m, 1H).

TABLE 2-continued

Characterization of exemplary compounds.

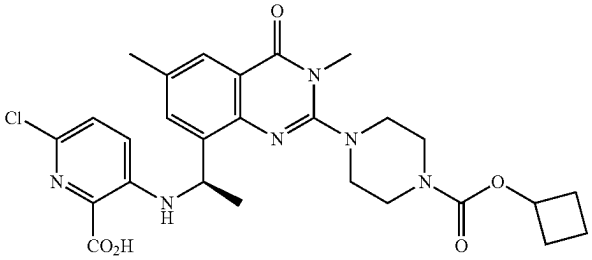
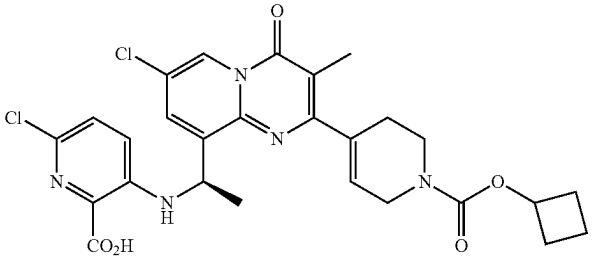
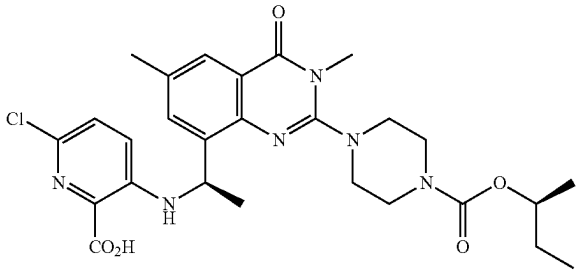
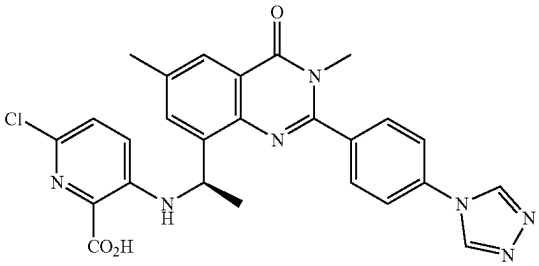
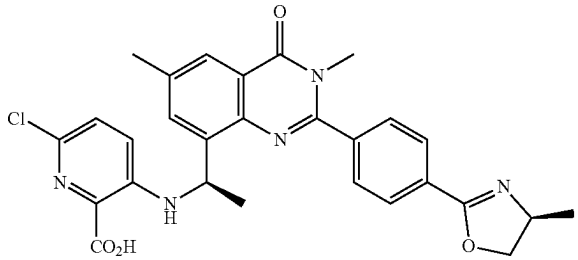
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
204		555.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.80 (s, 1H), 7.74 (s, 1H), 7.50 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.36-5.32 (m, 1H), 4.90-4.83 (m, 1H), 3.57 (s, 4H), 3.50 (s, 3H), 3.23 (s, 4H), 2.34 (s, 3H), 2.30-2.23 (m, 2H), 2.07-1.97 (m, 2H), 1.76-1.71 (m, 1H), 1.63-1.56 (m, 4H).
205		572.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.90-8.80 (m, 2H), 7.73 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.08 (s, 1H), 5.31-5.29 (m, 1H), 4.93-4.85 (m, 1H), 4.12-4.08 (m, 2H), 3.66-3.63 (m, 2H), 2.62-2.54 (m, 2H), 2.31-2.24 (m, 5H), 2.08-1.98 (m, 2H), 1.77-1.69 (m, 1H), 1.63-1.53 (m, 4H).
206		557.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm) δ 7.84 (s, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 5.46-5.44 (m, 1H), 4.79-4.75 (m, 1H), 3.72 (s, 4H), 3.63 (s, 3H), 3.26 (m, 4H), 2.39 (s, 3H), 1.74-1.54 (m, 5H), 1.29 (t, J = 10.4 Hz, 3H), 0.97 (q, J = 7.6 Hz, 3H).
207		516.2	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.35 (brs, 1H), 9.25 (s, 2H), 8.20 (brs, 1H, FA), 8.01-7.99 (m, 2H), 7.93-7.88 (m, 3H), 7.56 (s, 1H), 7.08-7.06 (m, 1H), 6.77-6.75 (m, 1H), 5.42-5.37 (m, 1H), 3.63 (s, 3H), 2.38 (s, 3H), 1.53 (d, J = 6.0 Hz, 3H).
208		532.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.58-12.25 (m, 1H), 9.01-8.38 (m, 1H), 8.07-7.99 (m, 2H), 7.92-7.82 (m, 3H), 7.64-7.58 (m, 1H), 7.27-7.17 (m, 1H), 6.99-6.87 (m, 1H), 5.47-5.35 (m, 1H), 4.62-4.52 (m, 1H), 4.46-4.28 (m, 1H), 3.99 (t, J = 8.0 Hz, 1H), 3.40 (s, 3H), 2.40 (s, 3H), 1.61-1.51 (m, 3H), 1.33-1.22 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

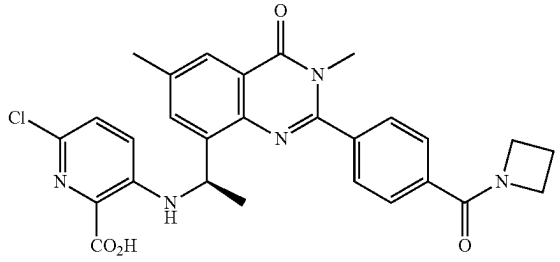
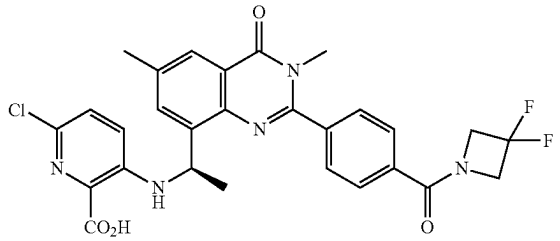
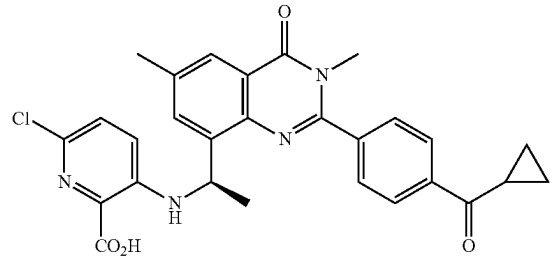
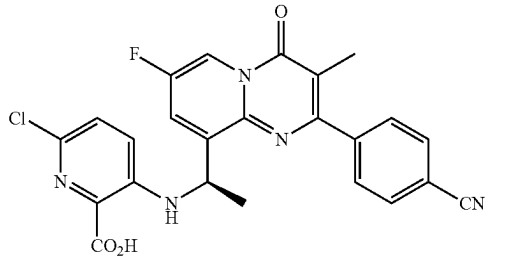
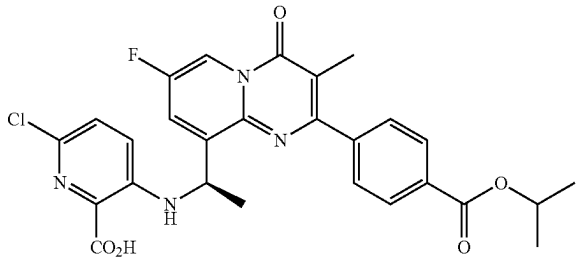
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
209		532.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.74-12.25 (m, 1H), 8.79-8.57 (m, 1H), 7.92-7.87 (m, 1H), 7.86-7.76 (m, 4H), 7.63-7.55 (m, 1H), 7.27-7.17 (m, 1H), 6.97-6.85 (m, 1H), 5.49-5.36 (m, 1H), 4.47-4.30 (m, 2H), 4.19-3.94 (m, 2H), 3.39 (s, 3H), 2.40 (s, 3H), 2.35-2.24 (m, 2H), 1.61-1.46 (m, 3H).
210		568.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.75-12.21 (m, 1H), 8.78-8.56 (m, 1H), 7.92-7.85 (m, 5H), 7.63-7.58 (m, 1H), 7.27-7.17 (m, 1H), 6.98-6.87 (m, 1H), 5.51-5.35 (m, 1H), 5.03-4.71 (m, 2H), 4.69-4.41 (m, 2H), 3.40 (s, 3H), 2.40 (s, 3H), 1.61-1.51 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −99.52 (2F).
211		517.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.82 (brs, 1H), 8.31-8.08 (m, 2H), 8.03-7.84 (m, 3H), 7.68-7.57 (m, 1H), 7.26-7.41 (m, 1H), 6.98-6.82 (m, 1H), 5.60-5.13 (m, 1H), 3.41 (s, 3H), 3.04-2.94 (m, 1H), 2.41 (s, 3H), 1.56 (d, J = 6.8 Hz, 3H), 1.23-0.94 (m, 4H).
213		478.0	^{1}H NMR (400 MHz, MeOD-d$_4$, ppm): δ 8.90-8.80 (m, 1H), 7.95-7.80 (m, 5H), 7.14 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.50-5.40 (m, 1H), 2.29 (m, 3H), 1.70 (d, J = 6.7 Hz, 3H); ^{19}F NMR (376 MHz, MeOD-d$_4$, ppm): δ −134.21 (1F).
214		539.2	^{1}H NMR (400 MHz, MeOD-d$_4$, ppm): δ 8.87 (s, 1H), 8.20-8.00 (m, 2H), 7.90-7.70 (m, 3H), 7.60-7.30 (m, 1H), 7.20-6.90 (m, 1H), 5.60-5.40 (m, 1H), 5.30-5.20 (m, 1H), 2.30 (s, 3H), 1.75-1.65 (m, 3H), 1.45-1.35 (m, 6H); ^{19}F NMR (376 MHz, MeOD-d$_4$, ppm): δ −134.47 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

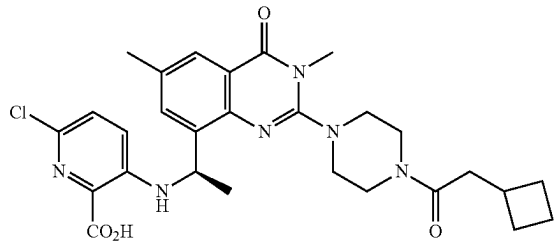
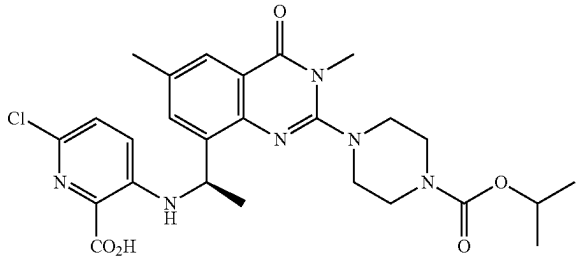
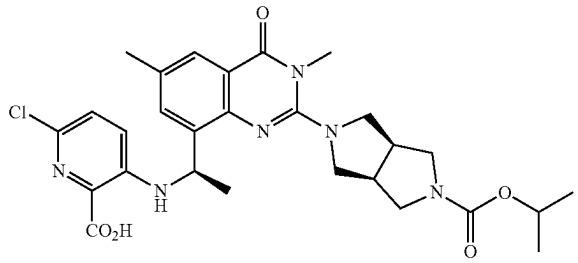
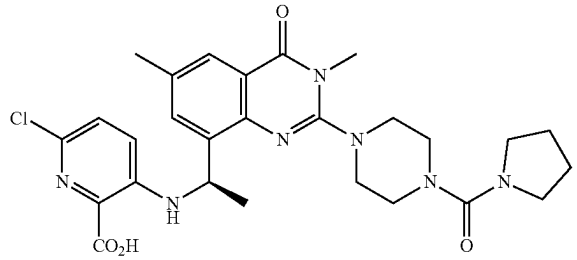
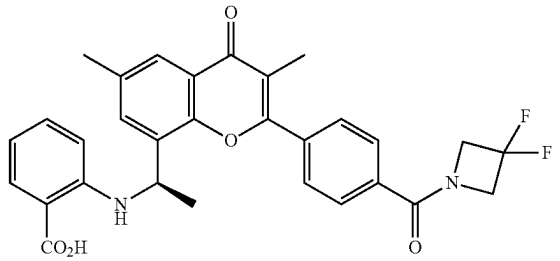
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
215		553.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.85 (s, 1H), 7.56 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 5.46-5.40 (m, 1H), 3.81-3.76 (m, 4H), 3.65 (s, 3H), 3.38 (d, J = 4.8 Hz, 2H), 3.30 (d, J = 4.8 Hz, 2H), 2.75-2.68 (m, 1H), 2.61 (d, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.21-2.15 (m, 2H), 1.98-1.75 (m, 4H), 1.68 (d, J = 6.4 Hz, 3H).
217		543.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.61 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 5.33-5.30 (m, 1H), 4.84-4.78 (m, 1H), 3.68 (s, 4H), 3.57 (s, 3H), 3.24 (s, 4H), 2.42 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H), 1.23-1.21 (m, 6H).
218		569.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.93 (s, 1H), 7.68 (s, 1H), 7.41 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.32-5.29 (m, 1H), 4.78-4.72 (m, 1H), 3.78-3.74 (m, 2H), 3.59-3.50 (m, 4H), 3.46 (s, 3H), 3.28-3.25 (m, 2H), 3.02-2.97 (m, 2H), 2.33 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H), 1.17 (m, 6H).
219		554.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.64 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.71-6.65 (s, 1H), 5.48-5.04 (m, 1H), 3.60-3.45 (m, 7H), 3.35-3.31 (m, 4H), 3.26-3.19 (m, 4H), 2.32 (s, 3H), 1.79-1.70 (m, 4H), 1.51 (d, J = 6.4 Hz, 3H).
220		533.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.80 (s, 1H), 7.97-7.87 (m, 4H), 7.85-7.75 (m, 2H), 7.54 (s, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.50 (t, J = 7.6 Hz, 1H), 6.38 (d, J = 8.4 Hz, 1H), 5.15-5.03 (m, 1H), 4.97-4.82 (m, 2H), 4.63-4.47 (m, 2H), 2.35 (s, 3H), 2.09 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −99.55 (2F).

TABLE 2-continued

Characterization of exemplary compounds.

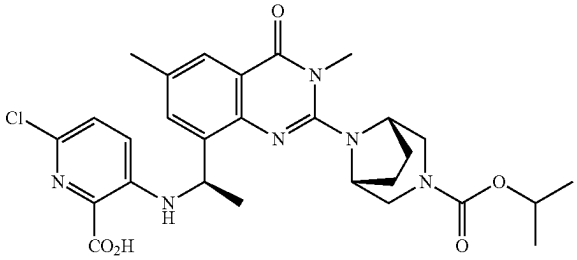
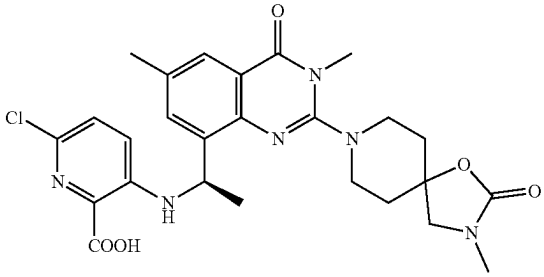
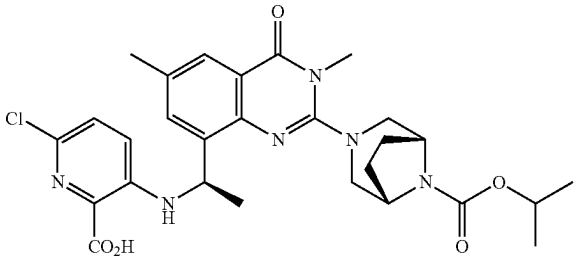
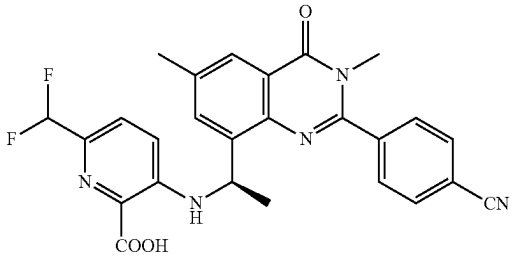
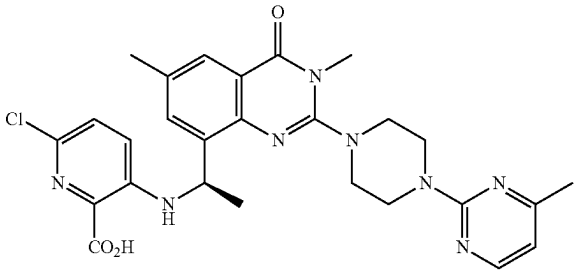
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
221		569.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.02 (br, 1H), 8.46 (br, 1H), 7.73 (s, 1H), 7.47 (s, 1H), 7.28 (d, J = 9.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 5.37 (t, J = 6.4 Hz, 1H), 4.86-4.75 (m, 1H), 4.45-4.19 (m, 2H), 3.89-3.71 (m, 2H), 3.56 (s, 3H), 3.26-3.15 (m, 2H), 2.33 (s, 3H), 2.12-1.91 (m, 2H), 1.68-1.49 (m, 5H), 1.21 (d, J = 5.2 Hz, 6H)
222		541.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.96 (s, 1H), 8.47 (d, J = 6.8 Hz, 1H), 7.75 (s, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 9.2 Hz, 1H), 5.41-5.29 (m, 1H), 3.50 (s, 3H), 3.42 (s, 2H), 3.34-3.24 (m, 4H), 2.79 (s, 3H), 2.34 (s, 3H), 2.06-1.91 (m, 4H), 1.61 (d, J = 6.4 Hz, 3H).
223		569.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.91 (s, 1H), 8.79 (s, 1H), 7.73 (s, 1H), 7.49 (s, 1H), 7.28-7.13 (m, 1H), 6.95 (s, 1H), 5.41-5.22 (m, 1H), 4.93-4.74 (m, 1H), 4.27 (s, 2H), 3.51 (s, 3H), 3.50-3.42 (m, 2H), 3.17-3.04 (m, 2H), 2.33 (s, 3H), 2.08-1.95 (m, 2H), 1.94-1.81 (m, 2H), 1.56 (d, J = 6.4 Hz, 3H), 1.23-1.13 (m, 6H).
224		490.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.48-8.26 (m, 1H), 8.07 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.92 (s, 1H), 7.66 (s, 1H), 7.50-7.47 (m, 1H), 7.04-7.01 (m, 1H), 6.91-6.63 (m, 1H), 5.49-5.45 (m, 1H), 3.39 (s, 3H), 2.41 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.6 (2F).
225		549.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.2-12.7 (m, 1H), 8.68-8.56 (m, 1H), 8.26 (d, J = 4..8 Hz, 1H), 7.75 (s, 1H), 7.52 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 4.8 Hz, 1H), 5.37-5.33 (m, 1H), 3.95-3.89 (m, 4H), 3.55 (s, 3H), 3.45-3.33 (m, 4H), 2.35 (s, 3H), 2.31 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

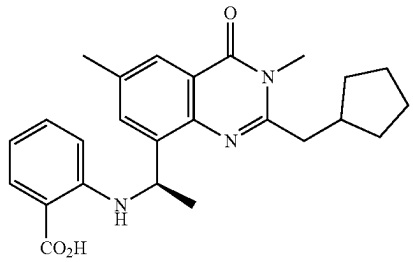
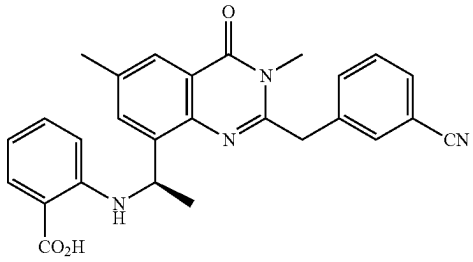
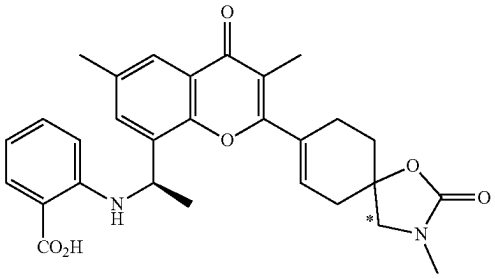
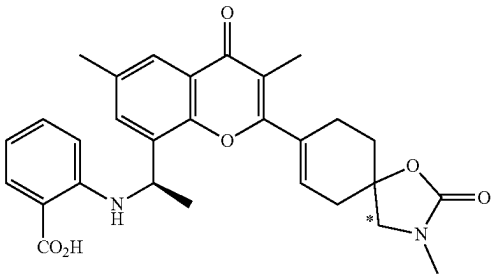
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
228		420.3	^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.97-7.94 (m, 2H), 7.53 (s, 1H), 7.17-7.14 (m, 1H), 6.56-6.53 (m, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.68-5.63 (m, 1H), 3.64 (s, 3H), 2.89-2.87 (m, 2H), 2.63-2.57 (m, 1H), 2.39 (s, 3H), 2.01-1.98 (m, 2H), 1.70-1.69 (m, 2H), 1.62-1.60 (m, 4H), 1.40-1.30 (m, 2 H), 1.25 (s, 1H).
229		453.0	^{1}H NMR (400 MHz, MeOH-d_4, ppm): δ 7.86-7.84 (m, 3H), 7.79-7.65 (m, 2H), 7.56-7.52 (m, 2H), 7.09-7.06 (m, 1H), 6.47-6.45 (m, 1H), 6.22 (d, J = 8.4 Hz, 1H), 5.23 (t, J = 6.8 Hz, 1H), 4.60 (s, 2H), 3.65 (s, 3H), 2.37 (s, 3H), 1.40-1.30 (m, 3H).
231	 isomer 1	503.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.53 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.53 (t, J = 7.6 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.15-5.03 (m, 1H), 3.47-3.40 (m, 2H), 2.79 (s, 3H), 2.68-2.56 (m, 4H), 2.35 (s, 3H), 2.08-2.01 (m, 4H), 1.98-1.90 (m, 1H), 1.59 (d, J = 6.4 Hz, 3H). Chiral purity 100% ee, retention time 2.510 min. Chiral SFC analysis was performed on Waters UPC2 analytical SFC (SFC-H), ChiralCel OD, 150 × 4.6 mm I.D., 3 μm heated to 35° C., eluted with a mobile phase of CO2 and 5-40% EtOH (0.1% DEA), flowing at 2.5 mL/min.
232	 isomer 2	503.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.53 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.53 (t, J = 7.6 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 6.19 (s, 1H), 5.16-5.06 (m, 1H), 3.48-3.43 (m, 2H), 2.79 (s, 3H), 2.68-2.57 (m, 4H), 2.35 (s, 3H), 2.09-2.01 (m, 4H), 1.97-1.88 (m, 1H), 1.59 (d, J = 6.4 Hz, 3H). Chiral purity 99.54% ee, retention time 4.536 min. Chiral SFC analysis was performed on Waters UPC2 analytical SFC (SFC-H), ChiralCel OD, 150 × 4.6 mm I.D., 3 μm heated to 35° C., eluted with a mobile phase of CO2 and 5-40% EtOH (0.1% DEA), flowing at 2.5 mL/min.

TABLE 2-continued

Characterization of exemplary compounds.

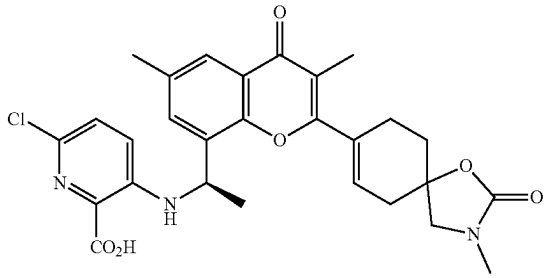
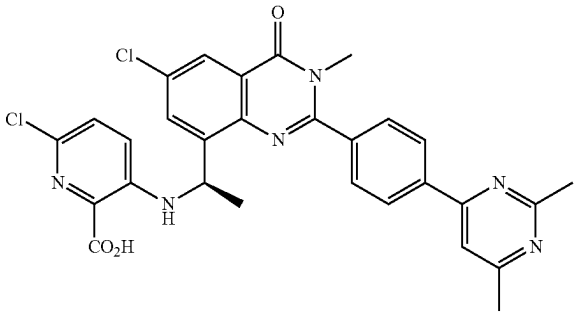
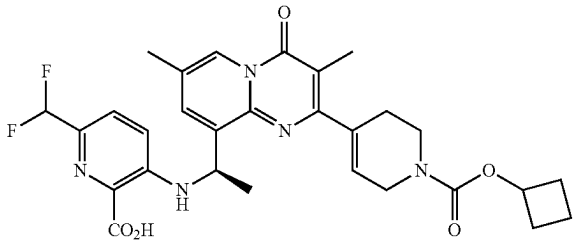
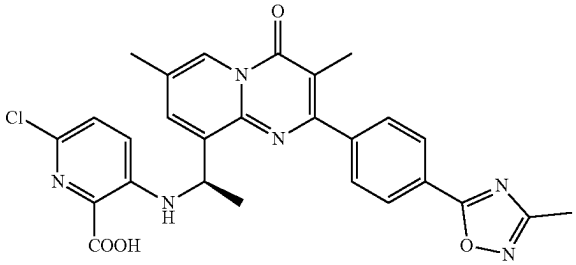
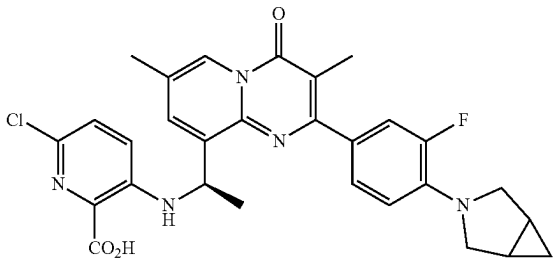
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
233		538.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.94 (s, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 8.8 Hz, 1H), 6.26 (s, 1H), 5.16-5.06 (m, 1H), 3.59-3.48 (m, 2H), 2.88 (s, 3H), 2.78-2.65 (m, 4H), 2.44 (s, 3H), 2.18-2.09 (m, 4H), 2.08-1.95 (m, 1H), 1.68 (d, J = 6.4 Hz, 3H).
234		575.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.67 (s, 1H), 8.36 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.80 (s, 1H), 7.26 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 5.49-5.37 (m, 1H), 3.45 (s, 3H), 2.67 (s, 3H), 2.53 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
235		568.5	1H NMR (400 MHz, DMSO-d6, ppm): δ 13.07-12.85 (m, 1H), 8.82-8.76 (m, 1H), 8.65 (s, 1H), 7.71 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.90-6.62 (m, 1H), 6.09-6.01 (m, 1H), 5.41-5.37 (m, 1H), 4.91-4.87 (m, 1H), 4.20-4.01 (m, 2H), 3.71-3.57 (m, 2H), 2.59-2.52 (m, 2H), 2.32 (s, 3H), 2.30-2.25 (m, 2H), 2.22 (s, 3H), 2.08-1.98 (m, 2H), 1.77-1.68 (m, 1H), 1.64-1.51 (m, 4H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −111.8 (2F).
236		531.4	1 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.88-9.66 (m, 1H), 8.72 (s, 1H), 8.38-8.28 (brs, 1H, FA), 8.24 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.69-6.61 (m, 1H), 5.35-5.24 (m, 1H), 2.46 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
237		548.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.58 (s, 1H), 7.86 (s, 1H), 7.62-7.51 (m, 2H), 7.45 (dd, J = 8.4, 1.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 9.2 Hz, 1H), 6.89-6.79 (m, 1H), 5.50-5.40 (m, 1H), 3.72 (dd, J = 9.6, 2.8 Hz, 2H), 3.49 (s, 3H), 3.40 (s, 2H), 2.39 (s, 3H), 1.75-1.64 (m, 2H), 1.57 (d, J = 6.8 Hz, 3H), 0.74-0.65 (m, 1H), 0.39-0.29 (m, 1H).

TABLE 2-continued

Characterization of exemplary compounds.

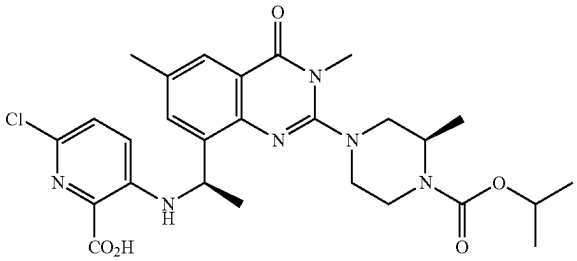
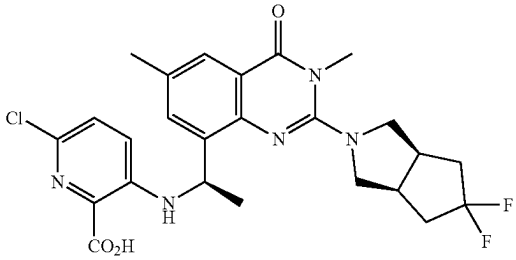
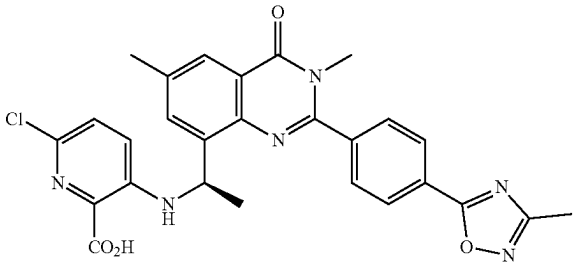
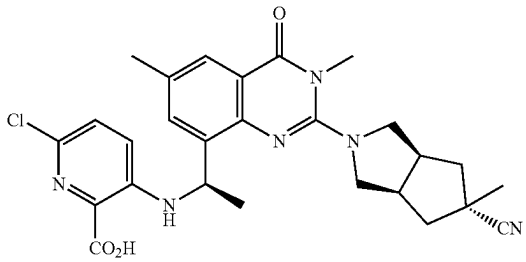
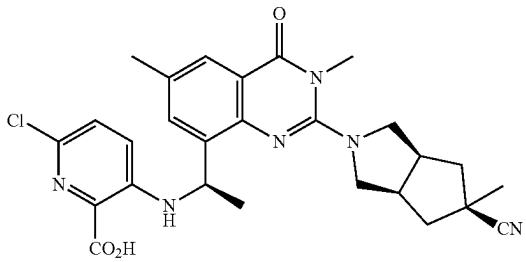
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
238		557.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.49-8.45 (m, 1H), 7.75 (s, 1H), 7.54-7.52 (m, 1H), 7.36-7.33 (m, 1H), 7.14-7.11 (m, 1H), 5.38-5.29 (m, 1H), 4.86-4.75 (m, 1H), 4.35-4.25 (m, 2H), 3.92-3.86 (m, 3H), 3.53 (s, 3H), 3.09-3.02 (m, 1H), 2.86-2.79 (m, 1H), 2.34 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.0 Hz, 6H).
239		518.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.64 (s, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 9.2 Hz, 1H), 5.36-5.33 (m, 1H), 3.60-3.57 (m, 2H), 3.50 (s, 3H), 3.46-3.44 (m, 2H), 2.93-2.89 (m, 2H), 2.45-2.36 (m, 2H), 2.32 (s, 3H), 2.18-2.06 (m, 2H), 1.58 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −92.07 (2F).
240		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.54 (s, 1H), 8.28 (d, J = 7.2 Hz, 2H), 8.03 (d, J = 6.8 Hz, 2H), 7.90 (s, 1H), 7.55 (s, 1H), 7.04 (s, 1H), 6.73 (s, 1H), 5.45-5.35 (m, 1H), 3.44 (s, 3H), 2.47 (s, 3H), 2.39 (s, 3H), 1.52 (s, 3H).
241		521.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.96 (brs, 1H), 8.79-8.38 (m, 1H), 7.74-7.66 (m, 1H), 7.52-7.42 (m, 1H), 7.36-7.23 (m, 1H), 7.07-6.92 (m, 1H), 5.40-5.27 (m, 1H), 3.50 (s, 3H), 3.48-3.36 (m, 4H), 2.98-2.84 (m, 2H), 2.43-2.36 (m, 2H), 2.32 (s, 3H), 1.61-1.49 (m, 5H), 1.44 (s, 3H).
242		521.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (brs, 1H), 8.49-8.38 (m, 1H), 7.76-7.70 (m, 1H), 7.51-7.44 (m, 1H), 7.36-7.28 (m, 1H), 7.09-7.01 (m, 1H), 5.42-5.28 (m, 1H), 3.54-3.38 (m, 7H), 2.97-2.84 (m, 2H), 2.32 (s, 3H), 2.22-2.08 (m, 2H), 2.02-1.91 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.33 (s, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

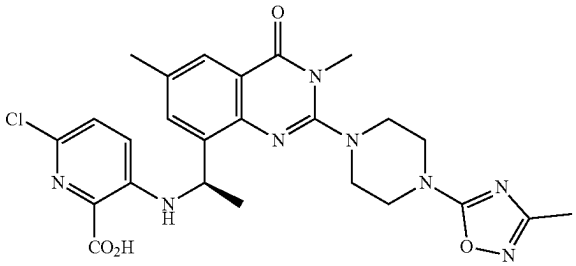
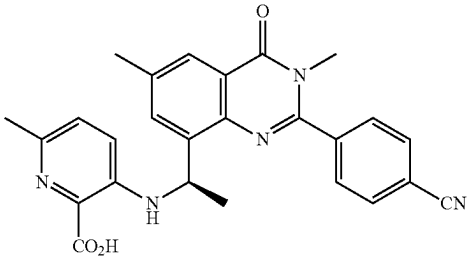
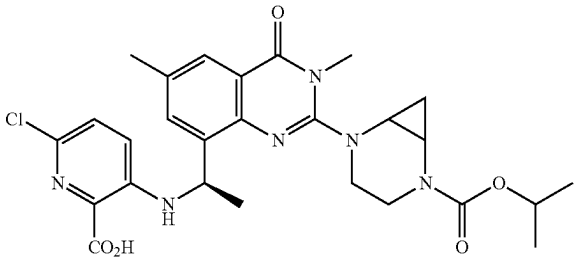
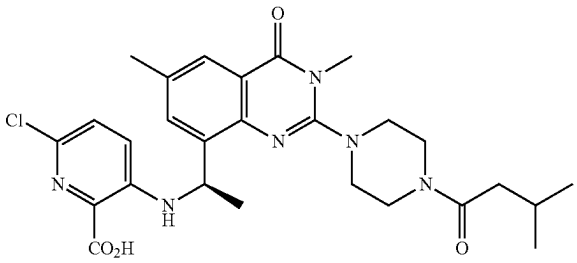
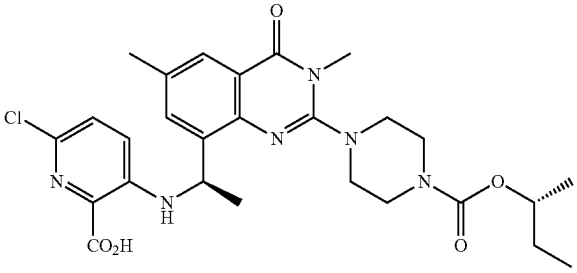
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
243		539.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (brs, 1H), 8.78-8.34 (m, 1H), 7.78-7.73 (m, 1H), 7.56-7.50 (m, 1H), 7.35-7.25 (m, 1H), 7.14-7.01 (m, 1H), 5.42-5.27 (m, 1H), 3.80-3.67 (m, 4H), 3.52 (s, 3H), 3.47-3.37 (m, 4H), 2.34 (s, 3H), 2.14 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).
244		454.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.64 (brs, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.60 (d, J = 1.6 Hz, 1H), 7.11 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.42 (t, J = 6.8 Hz, 1H), 3.38 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H).
245		555.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.03 (s, 1H), 8.67 (s, 1H), 7.69 (s, 1H), 7.54-7.36 (m, 1H), 7.26-7.07 (m, 1H), 7.04-6.88 (m, 1H), 5.41-5.24 (m, 1H), 4.95-4.71 (m, 1H), 4.15-3.91 (m, 1H), 3.76-3.60 (m, 1H), 3.57 (s, 3H), 3.26 (s, 3H), 2.94-2.85 (m, 1H), 2.30 (s, 3H), 1.53 (t, J = 6.8 Hz, 3H), 1.22-1.02 (m, 7H), 0.51-0.42 (s, 1H).
246		541.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.01 (s, 1H), 7.73 (s, 1H), 7.48 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 5.34 (t, J = 6.8 Hz, 1H), 3.67 (s, 4H), 3.51 (s, 3H), 3.28 (s, 2H), 3.21 (s, 2H), 2.32 (s, 3H), 2.25 (d, J = 6.8 Hz, 2H), 2.01 (m, 1H), 1.56 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.4 Hz, 6H).
247		557.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.86-9.55 (m, 1H), 7.70 (s, 1H), 7.44 (s, 1H), 7.35-7.02 (m, 1H), 6.94-6.63 (m, 1H), 5.38-5.28 (m, 1H), 4.65 (d, J = 6.0 Hz, 1H), 3.58 (s, 4H), 3.50 (s, 3H), 3.24 (s, 4H), 2.34-2.29 (m, 3H), 1.60-1.47 (m, 5H), 1.18 (d, J = 6.4 Hz, 3H), 0.90-0.85 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

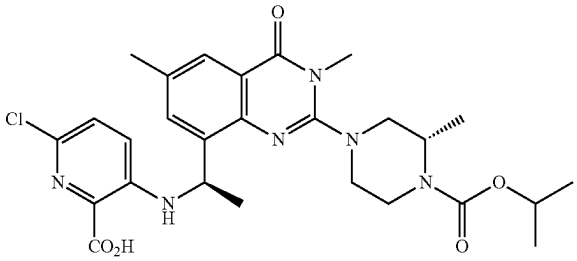
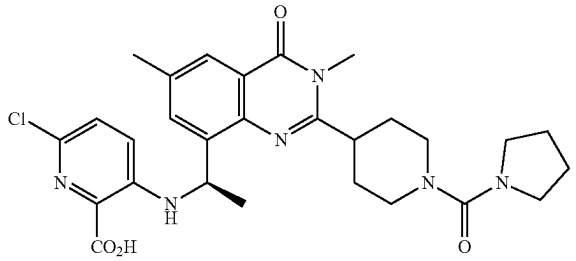
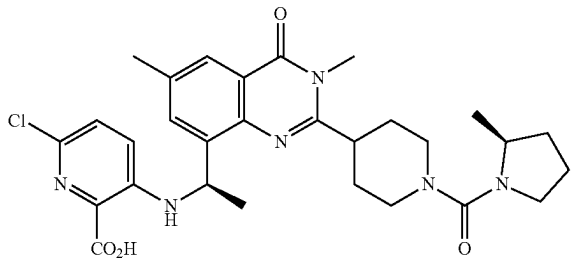
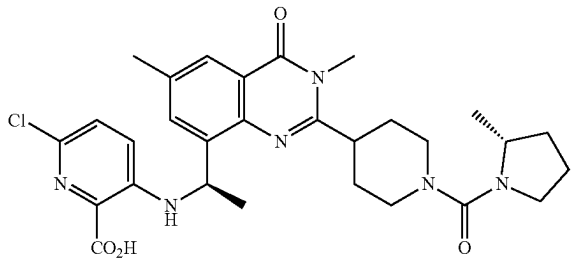
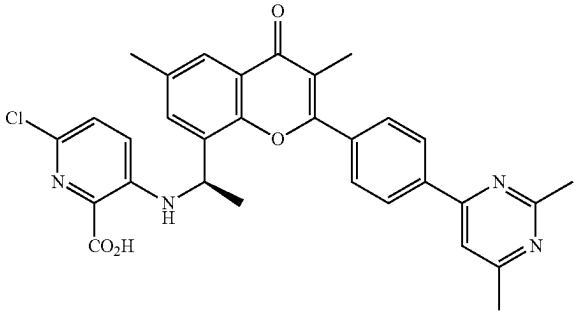
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
248		557.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 12.93 (brs, 1H), 8.70 (brs, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.30-7.20 (m, 1H), 7.10-7.00 (m, 1H), 5.34-5.31 (m, 1H), 4.84-4.78 (m, 1H), 4.35-4.25 (m, 1H), 3.90-3.83 (m, 1H), 3.62-3.48 (m, 6H), 3.05-2.99 (m, 1H), 2.92-2.82 (m, 1H), 2.33 (s, 3H), 1.62-1.57 (m, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.0 Hz, 6H).
249		553.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 13.45-12.33 (brs, 1H), 8.88-8.51 (m, 1H), 8.16 (s, 1H), 7.81 (s, 1H), 7.28-7.14 (m, 1H), 7.09-6.95 (m, 1H), 5.53-5.39 (m, 1H), 3.86-3.74 (m, 2H), 3.31-3.19 (m, 8H), 2.95-2.82 (m, 2H), 2.36 (s, 3H), 2.02-1.90 (m, 2H), 1.88-1.71 (m, 6H), 1.64-1.54 (m, 3H).
250		567.6	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.22-8.88 (m, 1H), 7.79 (s, 1H), 7.54 (s, 1H), 7.21-7.00 (m, 1H), 6.99-6.77 (m, 1H), 5.53-5.36 (m, 1H), 3.94-3.79 (m, 2H), 3.78-3.70 (m, 1H), 3.40-3.30 (m, 6H), 3.01-2.91 (m, 1H), 2.88-2.78 (m, 1H), 2.35 (s, 3H), 2.07-1.86 (m, 4H), 1.84-1.68 (m, 2H), 1.64-1.52 (m, 4H), 1.43-1.29 (m, 1H), 1.12-1.01 (m, 3H).
251		567.6	1H NMR (400 MHz, DMSO-d6, ppm): δ 14.45-12.51 (brs, 1H), 8.61-8.38 (m, 1H), 7.84-7.79 (m, 1H), 7.62-7.56 (m, 1H), 7.34-7.23 (m, 1H), 7.15-7.04 (m, 1H), 5.56-5.35 (m, 1H), 3.93-3.70 (m, 3H), 3.36-3.31 (m, 6H), 2.99-2.78 (m, 2H), 2.37 (s, 3H), 2.07-1.69 (m, 6H), 1.68-1.53 (m, 4H), 1.43-1.29 (m, 1H), 1.10-1.00 (m, 3H).
252		555.2	1 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.57 (brs, 1H), 8.36-8.34 (m, 2H), 8.22 (brs, 1H, FA), 7.99-7.97 (m, 2H), 7.89 (s, 1H), 7.78 (s, 1H), 7.49 (s, 1H), 7.04 (s, 1H), 6.82 (s, 1H), 5.10-5.02 (m, 1H), 2.66 (s, 3H), 2.50 (s, 3H), 2.33 (s, 3H), 2.13 (s, 3H), 1.57 (d, J = 6.0 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

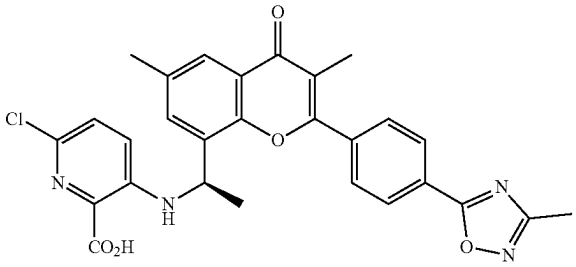
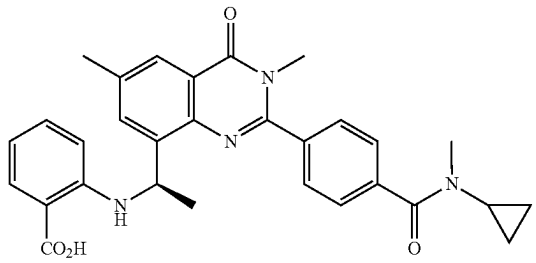
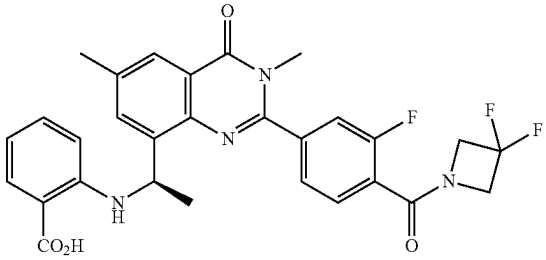
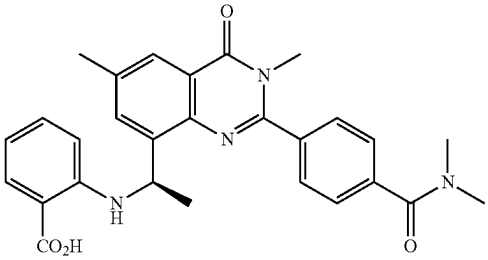
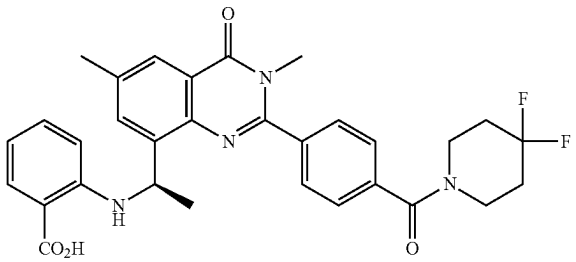
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
253		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.85 (brs, 1H), 8.29-8.26 (m, 2H), 8.06-8.04 (m, 2H), 7.79 (s, 1H), 7.53 (s, 1H), 7.15 (s, 1H), 6.95 (s, 1H), 5.15-5.02 (m, 1H), 2.46 (s, 3H), 2.37 (s, 3H), 2.11 (s, 3H), 1.59 (d, J = 6.0 Hz, 3H).
254		511.2	1 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.41 (br, 1H), 8.14 (brs, 1H, FA), 7.89 (s, 1H), 7.85-7.74 (m, 3H), 7.73-7.61 (m, 2H), 7.58 (s, 1H), 7.25-7.05 (m, 1H), 6.52-6.35 (m, 2H), 5.55-5.40 (m, 1H), 3.42 (s, 3H), 3.05-2.90 (m, 4H), 2.40 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H), 0.67-0.35 (m, 4H).
255		551.4	^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 8.02 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 10.4 Hz, 1H), 7.20-7.10 (m, 1H), 6.58 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.10-5.00 (m, 1H), 4.60-4.45 (m, 4H), 3.55 (s, 3H), 2.44 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H).
256		485.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.73 (br, 1H), 8.40 (brs, 1H), 7.89 (s, 1H), 7.87-7.75 (m, 3H), 7.63-7.50 (m, 3H), 7.22-7.12 (m, 1H), 6.52 (t, J = 7.6 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.54-5.43 (m, 1H), 3.43 (s, 3H), 3.03 (s, 3H), 2.98 (s, 3H), 2.40 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H).
257		561.5	^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 8.02 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.75-7.65 (m, 2H), 7.62-7.52 (m, 3H), 7.20-7.10 (m, 1H), 6.57 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 5.60-5.50 (m, 1H), 4.05-3.60 (m, 4H), 3.56 (s, 3H), 2.44 (s, 3H), 2.20-1.85 (m, 4H), 1.64 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

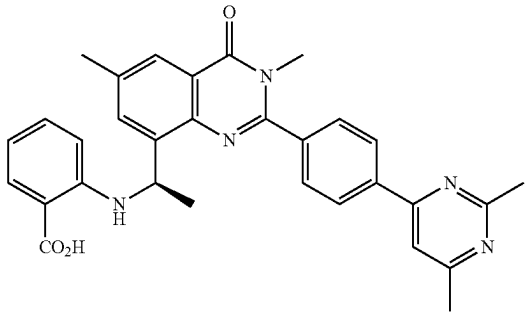
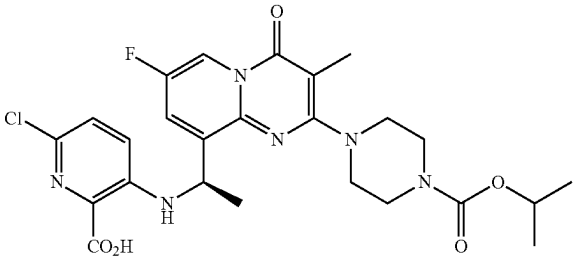
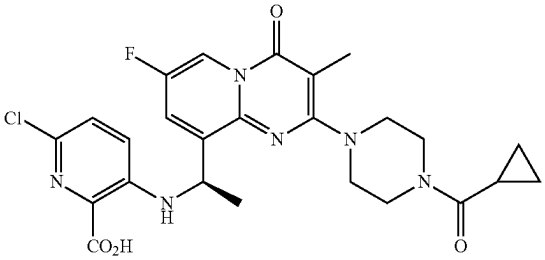
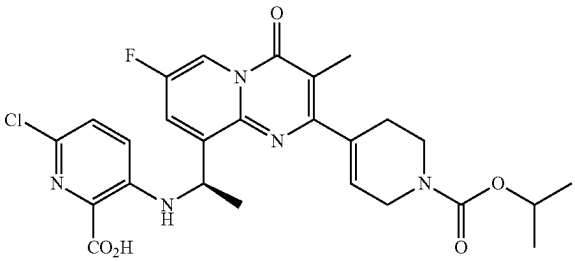
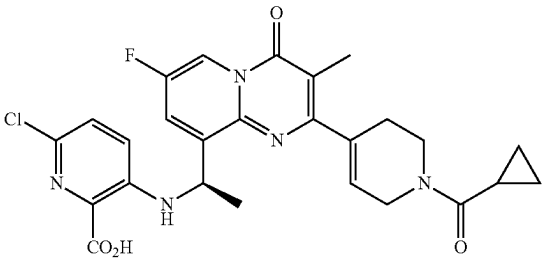
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
258		520.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.40-8.30 (m, 3H), 7.97-7.77 (m, 5H), 7.58 (s, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.43 (t, J = 7.6 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 5.50-5.40 (m, 1H), 3.46 (s, 3H), 2.67 (s, 3H), 2.53 (s, 3H), 2.39 (s, 3H), 1.52 (d, J = 6.4 Hz, 3H).
259		547.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 13.00 (s, 1H), 8.72 (dd, J = 4.8, 2.8 Hz, 1H), 7.89 (dd, J = 8.0, 2.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.33-5.22 (m, 1H), 4.85-4.74 (m, 1H), 3.58-3.47 (m, 4H), 3.45-3.36 (m, 4H), 3.33-3.23 (m, 1H), 2.10 (s, 3H), 1.66 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.4 Hz, 6H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −135.77 (1F).
260		529.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.42 (s, 1H), 8.70 (t, J = 4.0 Hz, 1H), 7.67 (dd, J = 8.0, 2.8 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.29-5.14 (m, 1H), 3.88-3.76 (m, 4H), 3.72-3.55 (m, 4H), 2.12 (s, 3H), 2.11-1.91 (m, 1H), 1.60 (d, J = 6.4 Hz, 3H), 0.81-0.65 (m, 4H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −135.76 (1F).
261		544.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.80-8.70 (m, 1H), 7.95-7.80 (m, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.15-6.00 (m, 1H), 5.40-5.25 (m, 1H), 4.90-4.75 (m, 1H), 4.20-4.05 (m, 2H), 3.70-3.55 (m, 2H), 2.24 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H), 1.30-1.10 (m, 8H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −133.66 (1F).
262		526.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 12.99 (brs, 1H), 8.80-8.70 (m, 1H), 8.40-8.30 (m, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.10 (s, 1H), 5.40-5.30 (m, 1H), 4.50-4.40 (m, 1H), 4.20-4.10 (m, 1H), 4.00-3.85 (m, 1H), 3.80-3.65 (m, 1H), 2.55-2.30 (m, 2H), 2.25 (s, 3H), 2.15-1.95 (m, 1H), 1.66 (d, J = 6.8 Hz, 3H), 0.81-0.70 (m, 4H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −133.67 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

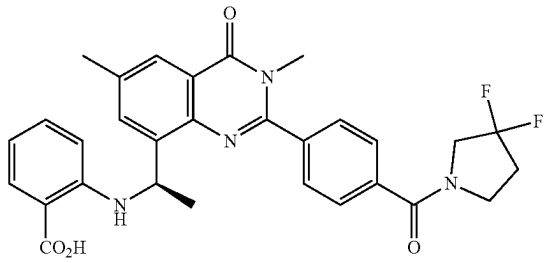
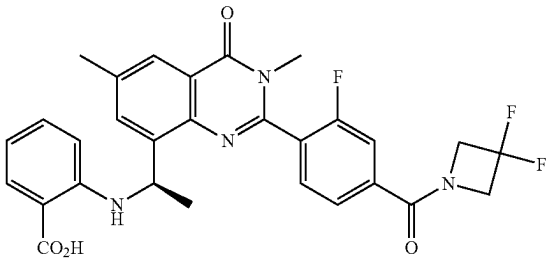
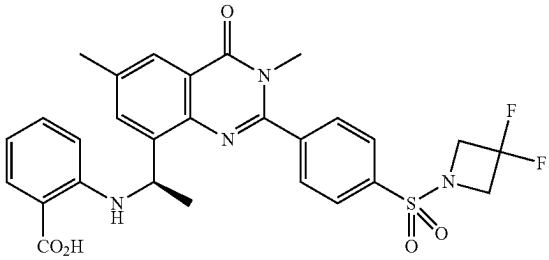
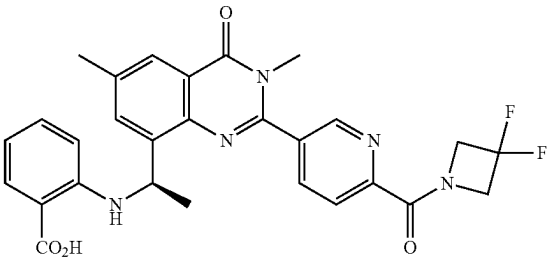
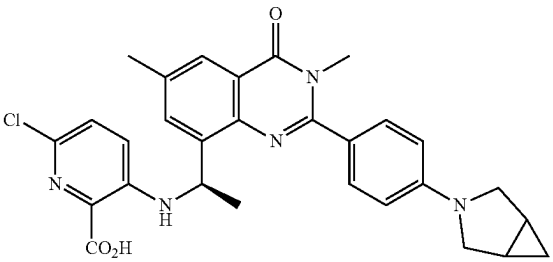
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
263		547.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.66 (brs, 1H), 7.94-7.84 (m, 3H), 7.83-7.70 (m, 3H), 7.58 (s, 1H), 7.17-7.07 (m, 1H), 6.49 (t, J = 7.6 Hz, 1H), 6.38 (d, J = 8.4 Hz, 1H), 5.53-5.43 (m, 1H), 4.05-3.90 (m, 2H), 3.82-3.72 (m, 2H), 3.41 (s, 3H), 2.55-2.40 (m, 2H), 2.39 (s, 3H), 1.53 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −99.99 (1F), −101.41 (1F).
264		551.4	^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 8.04 (s, 1H), 7.96 (d, J = 4.0 Hz, 1H), 7.70-7.60 (m, 1H), 7.62-7.52 (m, 3H), 7.20-7.10 (m, 1H), 6.62-6.52 (m, 1H), 6.44 (d, J = 8.0 Hz, 1H), 5.59-5.48 (m, 1H), 4.70-4.51 (m, 4H), 3.49 (s, 3H), 2.44 (s, 3H), 1.65-1.45 (m, 3H); ^{19}F NMR (376 MHz, CDCl$_3$, ppm): δ −100.28 (2F), −111.43 (1F).
265		569.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 8.49 (brs, 1H), 8.11 (s, 4H), 7.90 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.63 (s, 1H), 7.15 (t, J = 6.8 Hz, 1H), 6.54-6.38 (m, 2H), 5.54-5.39 (m, 1H), 4.39 (t, J = 12.8 Hz, 4H), 3.38 (s, 3H), 2.40 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −98.24 (2F).
266		534.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.67 (brs, 1H), 9.04 (s, 1H), 8.50-8.40 (m, 2H), 8.20 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.85-7.73 (m, 1H), 7.60 (s, 1H), 7.16 (t, J = 7.2 Hz, 1H), 6.50 (t, J = 7.2 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.50-5.40 (m, 1H), 5.15-5.00 (m, 2H), 4.60-4.50 (m, 2H), 3.43 (s, 3H), 2.40 (s, 3H), 1.55 (d, J = 6.6 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −100.26 (2F).
267		530.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.45 (s, 1H), 7.84 (s, 1H), 7.65-7.49 (m, 3H), 7.32-7.19 (m, 1H), 7.05-6.82 (m, 1H), 6.75-6.56 (m, 2H), 5.59-5.36 (m, 1H), 3.61-3.53 (m, 2H), 3.50 (s, 3H), 3.30-3.25 (m, 2H), 2.38 (s, 3H), 1.79-1.67 (m, 2H), 1.57 (d, J = 6.6 Hz, 3H), 0.82-0.67 (m, 1H), 0.30-0.17 (m, 1H).

TABLE 2-continued

Characterization of exemplary compounds.

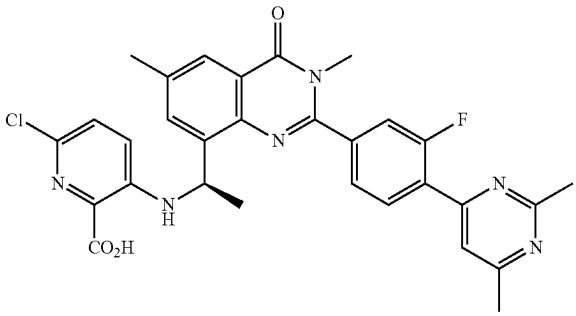
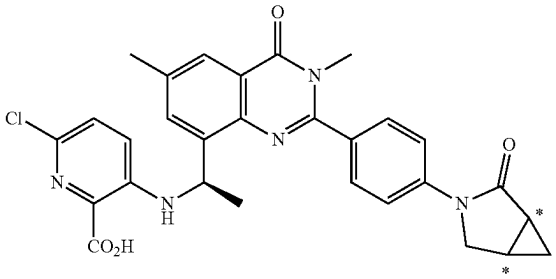
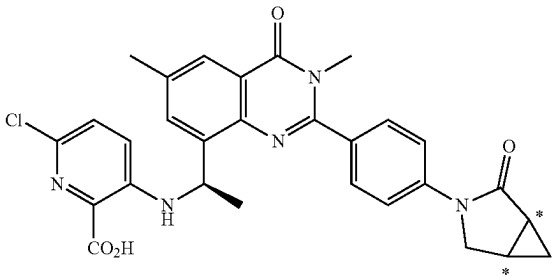
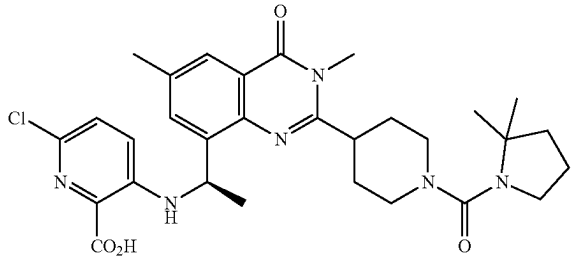
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
268		573.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.23-8.18 (m, 1H), 7.96-7.86 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.63 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.49-5.40 (m, 1H), 3.48 (s, 3H), 2.70 (s, 3H), 2.56 (s, 3H), 2.43 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
269	 isomer 1	544.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.08 (s, 1H), 8.54 (s, 1H), 7.94 (s, 1H), 7.82 (s, 4H), 7.65 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.58-5.42 (m, 1H), 4.22-4.11 (m, 1H), 3.89 (d, J = 10.0 Hz, 1H), 3.50 (s, 3H), 2.45 (s, 3H), 2.22-2.09 (m, 2H), 1.63 (d, J = 5.6 Hz, 3H), 1.32-1.24 (m, 1H), 0.87-0.80 (m, 1H). Chiral purity 100% ee, retention time 2.510 min. Chiral SFC analysis was performed on Waters UPC2 analytical SFC (SFC-H), ChiralCel OD, 150 × 4.6 mm I.D., 3 μm heated to 35° C., eluted with a mobile phase of CO_2 and 5-40% EtOH (0.1% DEA), flowing at 2.5 mL/min.
270	 isomer 2	544.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.93 (s, 1H), 8.43 (s, 1H), 7.89 (s, 1H), 7.77 (s, 4H), 7.61 (s, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 5.54-5.36 (m, 1H), 4.18-4.05 (m, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.45 (s, 3H), 2.40 (s, 3H), 2.18-2.04 (m, 2H), 1.55 (d, J = 4.8 Hz, 3H), 1.28-1.20 (m, 1H), 0.84-0.75 (m, 1H). Chiral purity 100% ee, retention time 5.158 min. Chiral SFC analysis was performed on Waters UPC2 analytical SFC (SFC-H), ChiralCel OD, 150 × 4.6 mm I.D., 3 μm heated to 35° C., eluted with a mobile phase of CO_2 and 5-40% EtOH (0.1% DEA), flowing at 2.5 mL/min.
271		581.5	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 13.24-12.66 (m, 1H), 8.82-8.50 (m, 1H), 7.85-7.77 (m, 1H), 7.62-7.54 (m, 1H), 7.31-7.17 (m, 1H), 7.12-6.96 (m, 1H), 5.52-5.39 (m, 1H), 3.74-3.51 (m, 5H), 3.47-3.39 (m, 2H), 3.24-3.12 (m, 1H), 2.86-2.72 (m, 2H), 2.37 (s, 3H), 2.02-1.65 (m, 8H), 1.63-1.55 (m, 3H), 1.39-1.27 (m, 6H).

TABLE 2-continued

Characterization of exemplary compounds.

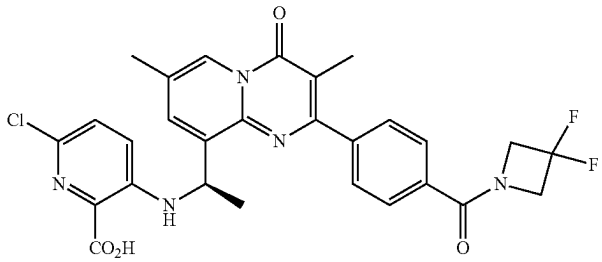
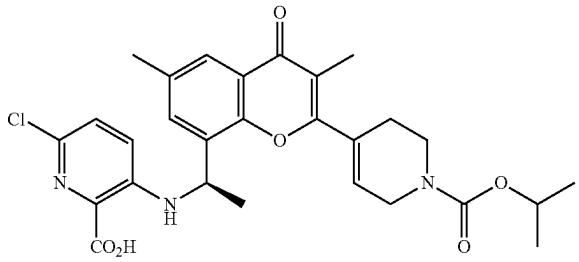
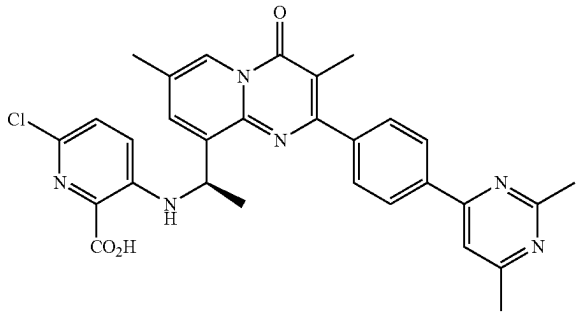
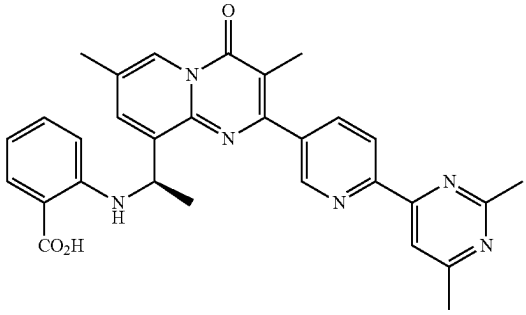
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
272		568.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.80-12.26 (m, 1H), 8.88-8.51 (m, 2H), 7.86-7.81 (m, 4H), 7.71 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 5.40-5.34 (m, 1H), 5.05-4.74 (m, 2H), 4.65-4.34 (m, 2H), 2.35 (s, 3H), 2.24 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −99.5 (2F).
273		540.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.64-8.60 (m, 1H), 7.77-7.72 (m, 1H), 7.55-7.50 (m, 1H), 7.32-7.26 (m, 1H), 7.03-6.96 (m, 1H), 6.37-6.32 (m, 1H), 5.18-5.11 (m, 1H), 4.90-4.80 (m, 1H), 4.17-4.11 (m, 2H), 3.75-3.42 (m, 3H), 2.63-2.53 (m, 1H), 2.37 (s, 3H), 2.08 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 6.4 Hz, 6H).
274		555.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.73 (s, 1H), 8.51-8.69 (brs, 1H), 8.32 (d, J = 8.0 Hz, 2H), 7.90-7.87 (m, 3H), 7.72 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 5.40-5.36 (m, 1H), 3.42 (s, 3H), 2.67 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H).
275		520.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.73 (s, 1H), 8.34-8.32 (m, 2H), 7.95-7.86 (m, 3H), 7.82 (s, 1H), 7.67 (s, 1H), 7.17-7.14 (m, 1H), 6.54-6.50 (m, 1H), 6.36-6.33 (m, 1H), 5.45-5.35 (m, 1H), 2.67 (s, 3H), 2.52 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

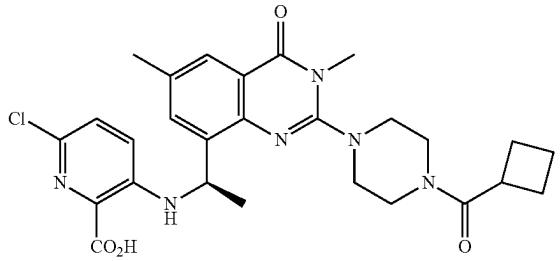
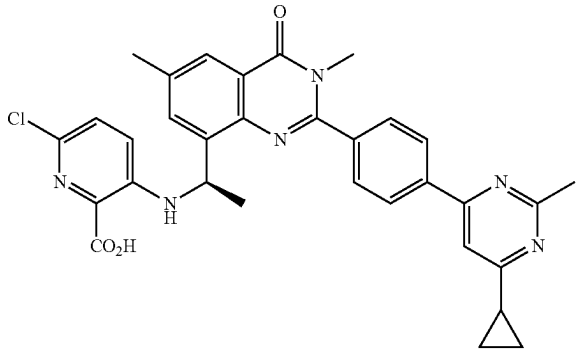
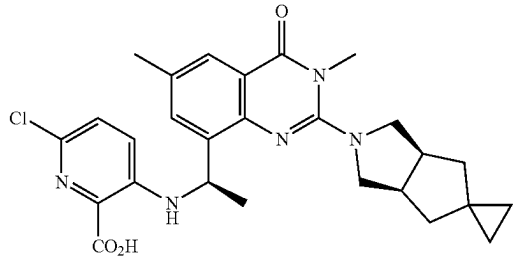
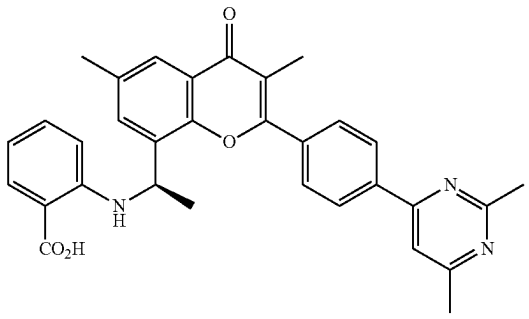
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
276		539.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.63 (s, 1H), 8.37 (s, 1H, FA), 7.70 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.01-6.99 (m, 1H), 6.70-6.68 (m, 1H), 5.32-5.28 (m, 1H), 3.69-3.62 (m, 4H), 3.59 (s, 3H), 3.40-3.18 (m, 4H), 2.30 (s, 3H), 2.18-2.07 (m, 5H), 1.79-1.73 (m, 2H), 1.50 (d, J = 6.4 Hz, 3H).
277		581.4	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.99 (brs, 1H), 8.46-8.39 (m, 1H), 8.38-8.31 (m, 2H), 7.98-7.84 (m, 4H), 7.67-7.60 (m, 1H), 7.34-7.26 (m, 1H), 7.09-7.00 (m, 1H), 5.54-5.40 (m, 1H), 3.45 (s, 3H), 2.62 (s, 3H), 2.42 (s, 3H), 2.32-2.12 (m, 1H), 1.60 (d, J = 6.4 Hz, 3H), 1.17-1.04 (m, 4H).
278		508.4	^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.66 (s, 1H), 7.70 (s, 1H), 7.45 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.36-5.33 (m, 1H), 3.69-3.63 (m, 2H), 3.50 (s, 3H), 3.45-3.40 (m, 2H), 2.86-2.85 (m, 2H), 2.31 (s, 3H), 1.85-1.80 (m, 2H), 1.58 (d, J = 6.4 Hz, 3H), 1.50-1.46 (m, 2H), 0.51-0.48 (m, 2H), 0.40-0.38 (m, 2H).
279		520.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.39-8.37 (m, 2H), 8.31 (s, 1H, FA), 7.99 (d, J = 8.0 Hz, 2H), 7.90 (s, 1H), 7.83 (s, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 7.06 (s, 1H), 6.46 (s, 1H), 6.34 (s, 1H), 5.20-5.05 (m, 1H), 2.67 (s, 3H), 2.50 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H), 1.58-1.56 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

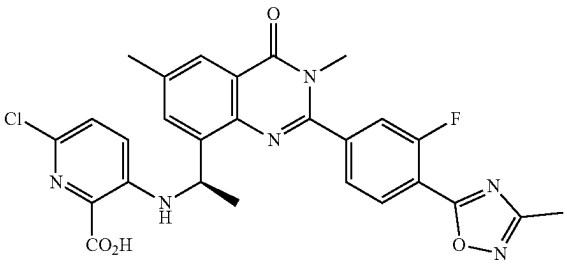
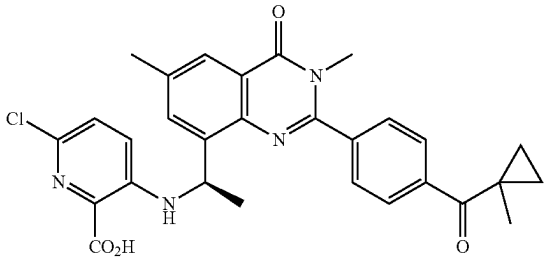
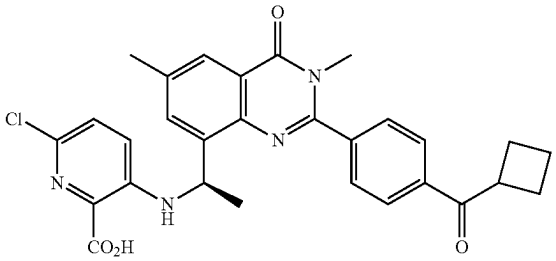
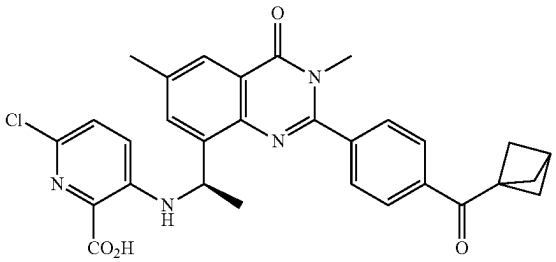
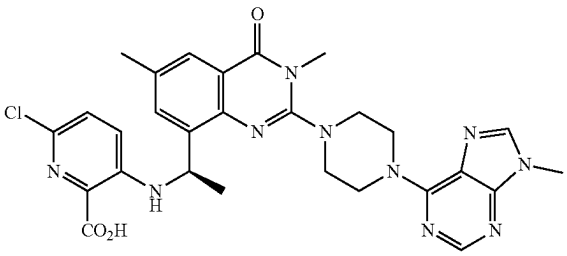
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
280		549.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.01-8.89 (brs, 1H), 8.31 (t, J = 8.0 Hz, 1H), 8.00 (d, J = 11.2 Hz, 1H), 7.91 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.42-5.36 (m, 1H), 3.44 (s, 3H), 2.49 (s, 3H), 2.42 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −108.84 (1H).
281		531.4	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.41 (brs, 1H, FA), 7.95-7.85 (m, 5H), 7.72-7.51 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 6.4 Hz, 1H), 5.53-5.41 (m, 1H), 3.41 (s, 3H), 2.41 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.44 (s, 3H), 1.28-1.17 (m, 2H), 0.95-0.84 (m, 2H).
282		531.4	as 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.18 (s, 1H, FA), 8.06 (d, J = 8.4 Hz, 2H), 7.95-7.85 (m, 3H), 7.56 (s, 1H), 7.16-7.01 (m, 1H), 6.82-6.69 (m, 1H), 5.46-5.31 (m, 1H), 4.30-4.16 (m, 1H), 3.40 (s, 3H), 2.39 (s, 3H), 2.34-2.22 (m, 3H), 2.14-1.95 (m, 2H), 1.88-1.77 (m, 1H), 1.51 (d, J = 6.4 Hz, 3H).
283		589.5	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.75-9.68 (m, 1H), 8.32-8.31 (m, 1H), 8.30 (s, 1H, FA), 8.19 (s, 1H), 7.72 (s, 1H), 7.43 (s, 1H), 6.95-6.85 (m, 1H), 6.67-6.53 (m, 1H), 5.35-5.24 (m, 1H), 4.60-4.45 (m, 4H), 3.75 (s, 3H), 3.55-3.42 (m, 7H), 2.30-2.20 (m, 3H), 1.51 (d, J = 6.4 Hz, 3H).
284		589.5	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.75-9.68 (m, 1H), 8.32-8.31 (m, 1H), 8.30 (s, 1H, FA), 8.19 (s, 1H), 7.72 (s, 1H), 7.43 (s, 1H), 6.95-6.85 (m, 1H), 6.67-6.53 (m, 1H), 5.35-5.24 (m, 1H), 4.60-4.45 (m, 4H), 3.75 (s, 3H), 3.55-3.42 (m, 7H), 2.30-2.20 (m, 3H), 1.51 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

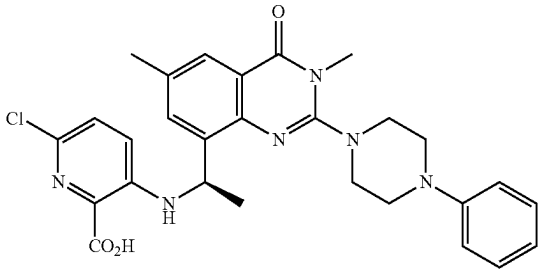
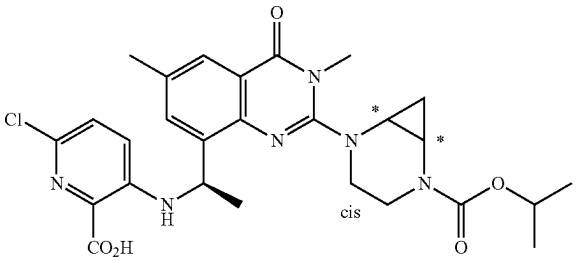
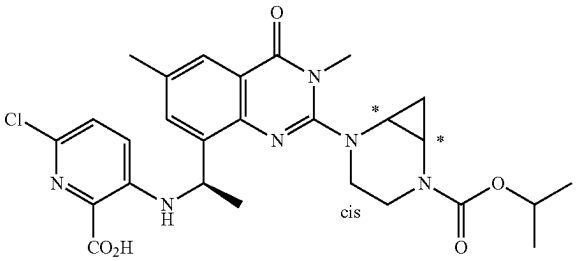
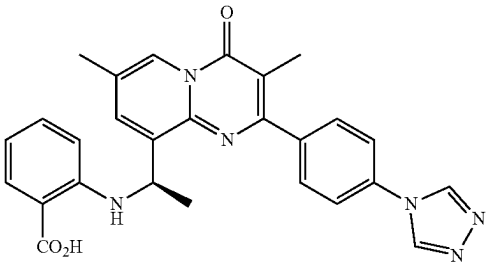
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
285		533.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.74-7.68 (m, 1H), 7.55-7.45 (m, 1H), 7.30-7.23 (m, 3H), 7.05-6.97 (m, 3H), 6.82-6.77 (m, 1H), 5.44-5.12 (m, 1H), 3.50 (s, 3H), 3.47-3.36 (m, 8H), 2.33 (s, 3H), 1.59 (d, J = 5.2 Hz, 3H).
286	 isomer 1	555.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.50 (s, 1H), 7.79-7.67 (m, 1H), 7.55-7.39 (m, 1H), 7.28-7.14 (m, 1H), 7.08-6.92 (m, 1H), 5.42-5.20 (m, 1H), 4.91-4.70 (m, 1H), 4.19-4.01 (m, 1H), 3.83-3.68 (m, 1H), 3.60-3.51 (m, 3H), 3.24-2.81 (m, 4H), 2.36-2.28 (m, 3H), 1.55 (d, J = 6.4 Hz, 3H), 1.25-1.19 (m, 2H), 1.18-1.11 (m, 4H), 1.07-0.99 (m, 1H), 0.54-0.41 (m, 1H). Chiral SFC analysis: 100.0% de. Retention time 3.176 min on Chiralcel OD 150 × 4.6 mm I.D., 3 um; Mobile phase: A for C_2 and B for methanol (0.05% DEA), 100 bar, 2.5 mL/min.
287	 isomer 2	555.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.61-8.36 (m, 1H), 7.80-7.61 (m, 1H), 7.50-7.37 (m, 1H), 7.34-7.22 (m, 1H), 6.91-6.79 (m, 1H), 5.46-5.23 (m, 1H), 4.88-4.68 (m, 1H), 4.10-3.93 (m, 1H), 3.82-3.62 (m, 1H), 3.60-3.54 (m, 3H), 3.24-2.85 (m, 4H), 2.30 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H), 1.27-1.08 (m, 7H), 0.56-0.38 (m, 1H). Chiral SFC analysis: 98.04% de. Retention time 5.776 min on Chiralcel OD 150 × 4.6 mm I.D., 3 um; Mobile phase: A for CO_2 and B for methanol (0.05% DEA), 100 bar, 2.5 mL/min.
288		481.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.23 (s, 2H), 8.72 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.19-7.00 (m, 1H), 6.55-6.51 (m, 1H), 6.34 (d, J = 8.0 Hz, 1H), 5.45-5.36 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

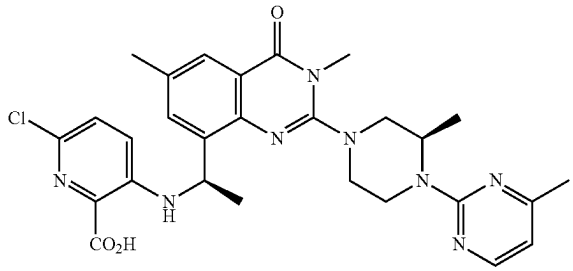
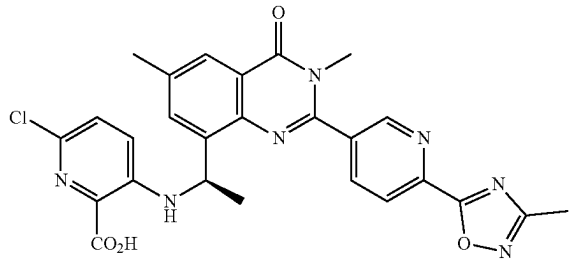
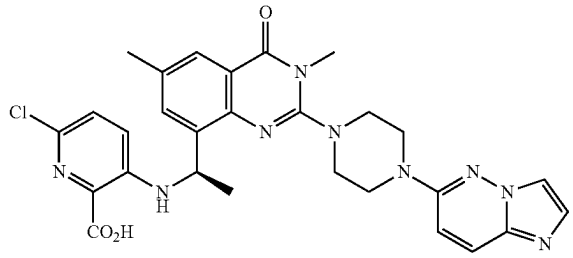
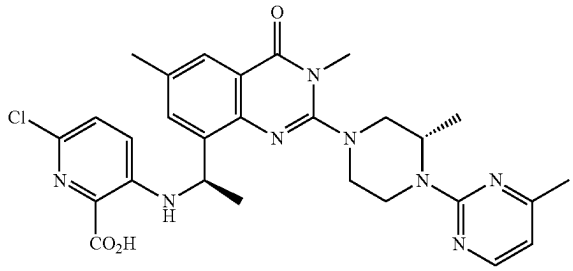
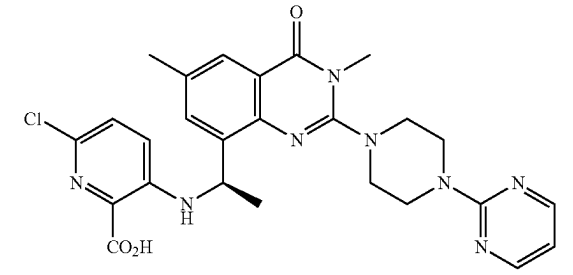
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
289		563.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.88-8.56 (m, 1H), 8.26 (d, J = 4.8 Hz, 1H), 7.74 (s, 1H), 7.51 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.08-6.95 (m, 1H), 6.56 (d, J = 4.8 Hz, 1H), 5.33 (t, J = 6.0 Hz, 1H), 5.05-4.95 (m, 1H), 4.61-4.55 (m, 1H), 3.74-3.69 (m, 1H), 3.59-3.53 (m, 4H), 3.42-3.35 (m, 1H), 3.13-3.07 (m, 1H), 2.96-2.89 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H), 1.29 (d, J = 6.4 Hz, 3H).
291		532.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.28-9.18 (m, 1H), 8.67-8.54 (m, 1H), 8.53-8.48 (m, 1H), 8.44-8.37 (m, 1H), 7.97-7.89 (m, 1H), 7.71-7.60 (m, 1H), 7.34-7.20 (m, 1H), 7.13-6.95 (m, 1H), 5.52-5.37 (m, 1H), 3.47 (s, 3H), 3.40-3.26 (m, 3H), 2.42 (s, 3H), 1.70-1.50 (m, 3H).
292		574.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.29-8.84 (m, 1H), 7.97-7.89 (m, 2H), 7.74 (s, 1H), 7.54-7.44 (m, 2H), 7.32-7.23 (m, 1H), 7.22-7.08 (m, 1H), 6.99-6.83 (m, 1H), 5.47-5.25 (m, 1H), 3.74-3.64 (m, 4H), 3.55 (s, 3H), 3.47-3.40 (m, 4H), 2.32 (s, 3H), 1.61-1.52 (m, 3H).
293		563.5	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.88-8.56 (brs, 1H), 8.25 (d, J = 5.2 Hz, 1H), 7.74 (s, 1H), 7.52 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.55 (d, J = 4.0 Hz, 1H), 5.33 (t, J = 6.0 Hz, 1H), 5.05-4.95 (m, 1H), 4.60-4.55 (m, 1H), 3.72-3.69 (m, 1H), 3.64-3.58 (m, 4H), 3.42-3.35 (m, 1H), 3.12-3.07 (m, 1H), 2.99-2.93 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H), 1.29 (d, J = 6.4 Hz, 3H).
294		535.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.41 (d, J = 4.8 Hz, 2H), 7.73 (s, 1H), 7.49 (s, 1H), 7.21-7.20 (m, 1H), 6.98-6.96 (m, 1H), 6.69-6.66 (m, 1H), 5.35-5.32 (m, 1H), 3.95-3.93 (m, 4H), 3.54 (s, 3H), 3.33-3.25 (m, 4H), 2.32 (s, 3H), 1.58-1.57 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

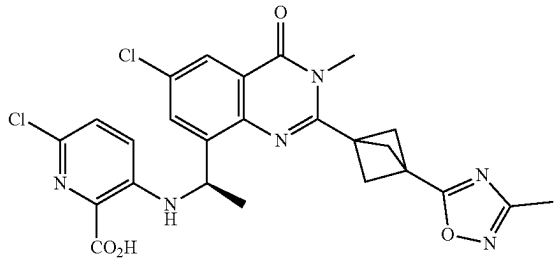
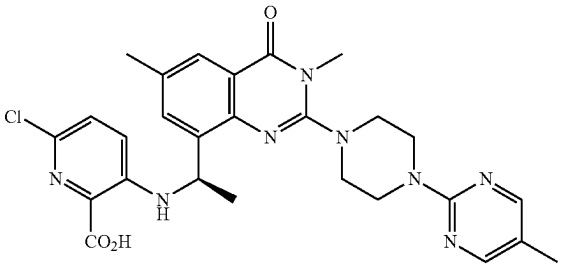
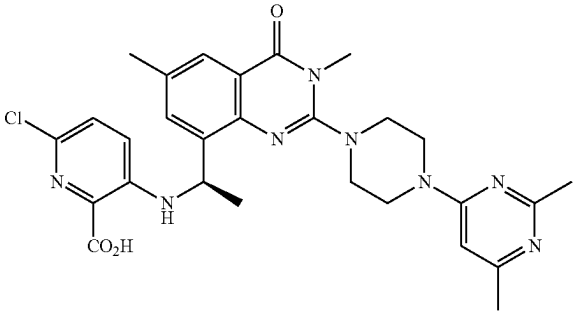
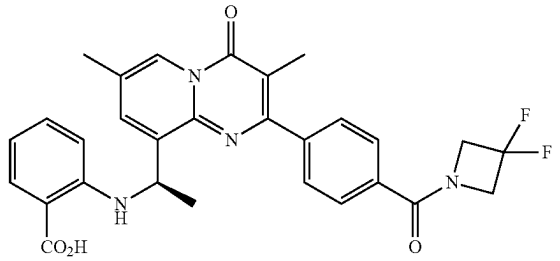
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
295		541.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.86 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.85 (s, 1H), 7.31-7.28 (m, 1H), 7.13-7.11 (m, 1H), 5.39-5.36 (m, 1H), 3.65 (s, 3H), 2.90-2.81 (m, 6H), 2.36 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).
296		549.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.28 (s, 2H), 7.74 (s, 1H), 7.51 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.04 (s, 1H), 5.34 (t, J = 6.8 Hz, 1H), 3.89 (t, J = 5.2 Hz, 4H), 3.54 (s, 3H), 2.51 (s, 3H), 2.34 (s, 4H), 2.10 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
297		563.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.49 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 6.88 (s, 1H), 5.35 (t, J = 6.8 Hz, 1H), 3.95 (s, 4H), 3.55 (s, 3H), 3.39 (d, J = 6.8 Hz, 4H), 2.45 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).
298		533.2	1H NMR (400 MHz, DMSO-d6, ppm) δ 8.72 (s, 1H), 7.86-7.78 (m, 5H), 7.66 (s, 1H), 7.11-7.06 (m, 1H), 6.49 (t, J = 7.2 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 5.37 (s, 1H), 4.87 (s, 2H), 4.53 (s, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −99.53 (2F).

TABLE 2-continued

Characterization of exemplary compounds.

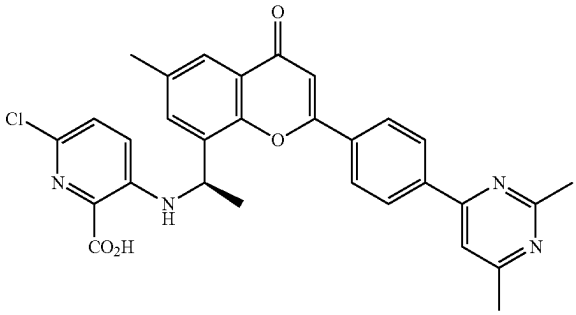
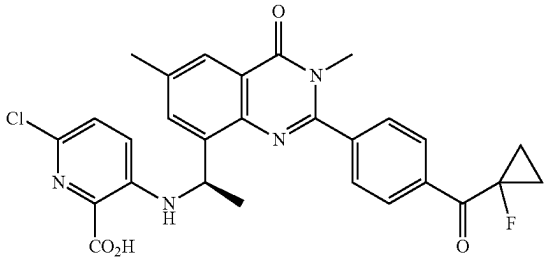
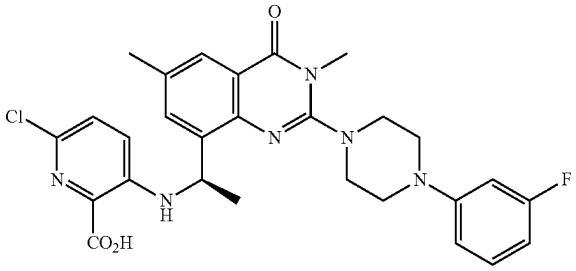
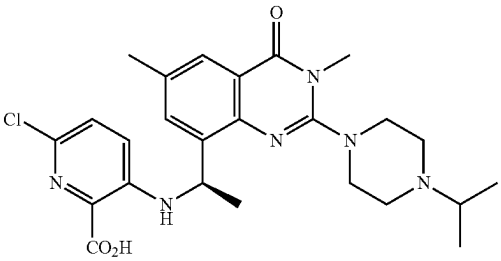
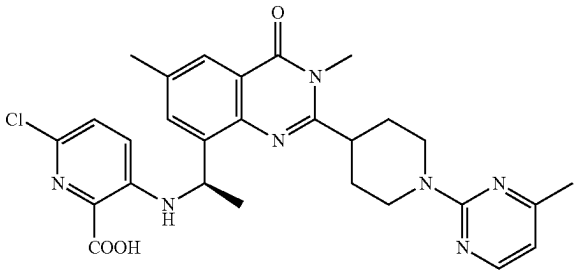
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
299		541.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.50 (brs, 1H), 8.37 (d, J = 8.4 Hz, 2H), 8.29 (d, J = 8.4 Hz, 2H), 7.92 (s, 1H), 7.77 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.21 (s, 1H), 7.15 (d, J = 9.2 Hz, 1H), 5.41-5.38 (m, 1H), 2.68 (s, 3H), 2.51 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
300		535.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 8.70 (s, 1H), 8.09 (d, J = 7.2 Hz, 2H), 8.02-7.86 (m, 3H), 7.62 (s, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 5.43 (s, 1H), 3.42 (s, 3H), 2.41 (s, 3H), 1.71-1.60 (m, 2H), 1.60-1.49 (m, 5H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −190.42 (1F).
301		551.2	^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 8.79 (brs, 1H), 7.77-7.72 (m, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.29-7.21 (m, 2H), 7.04 (s, 1H), 6.88-6.78 (m, 2H), 6.61-6.51 (m, 1H), 5.36 (t, J = 6.8 Hz, 1H), 3.54 (s, 3H), 3.44-3.39 (m, 4H), 3.39-3.38 (m, 4H), 2.34 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d6, ppm): δ −112.26. (1F).
302		499.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.64 (s, 1H), 7.73 (s, 1H), 7.50 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 9.6 Hz, 1H), 5.37-5.25 (m, 1H), 3.48 (s, 3H), 3.35-3.28 (s, 4H), 2.84 (s, 1H), 2.80-2.74 (m, 4H), 2.33 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.4 Hz, 6H).
303		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.27-8.15 (m, 1H), 7.79 (s, 1H), 7.50 (s, 1H), 6.98 (s, 1H), 6.77 (s, 1H), 6.48 (d, J = 4.8 Hz, 1H), 5.49-5.34 (m, 1H), 4.84 (d, J = 13.2 Hz, 2H), 3.67 (s, 3H), 3.05 (t, J = 12.0 Hz, 2H), 2.34 (s, 3H), 2.27 (s, 3H), 2.07 (d, J = 12.0 Hz, 2H), 2.00-1.97 (m, 1H), 1.79-1.75 (m, 2H), 1.50 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

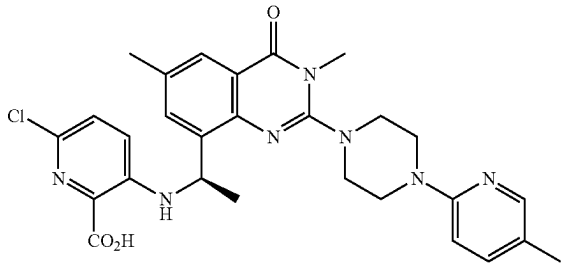
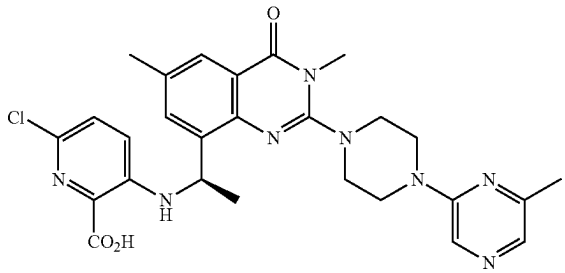
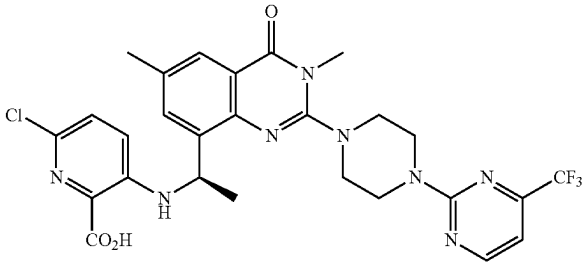
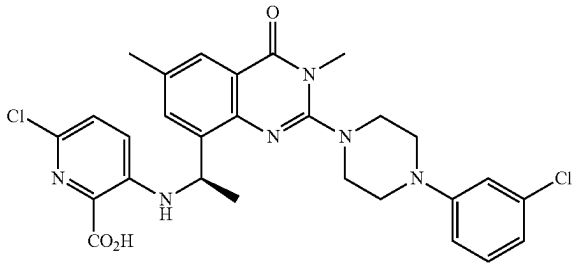
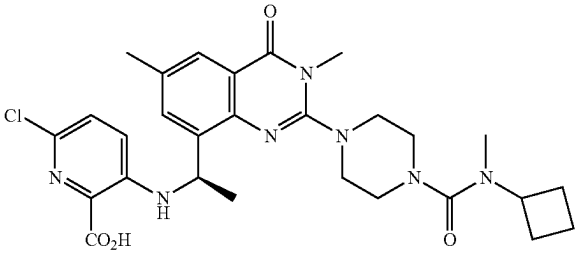
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
304		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.96 (s, 1H), 7.74 (s, 1H), 7.49-7.44 (m, 2H), 7.20-7.18 (m, 1H), 6.98-6.96 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 7.2 Hz, 1H), 5.37-5.34 (m, 1H), 3.69-3.67 (m, 4H), 3.54 (s, 3H), 3.40-3.35 (m, 4H), 2.32 (s, 6H), 1.58 (d, J = 6.4 Hz, 3H).
305		549.5	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.96 (s, 1H), 8.19 (s, 1H), 7.79 (s, 1H), 7.74 (s, 1H), 7.49 (s, 1H), 7.20-7.18 (m, 1H), 6.97-6.95 (m, 1H), 5.36-5.33 (m, 1H), 3.77-3.75 (m, 4H), 3.55 (s, 3H), 3.39-3.35 (m, 4H), 2.33 (s, 6H), 1.58 (d, J = 6.8 Hz, 3H).
306		603.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.74 (s, J = 4.8 Hz, 1H), 7.74 (s, 1H), 7.50 (s, 1H.), 7.23-7.18 (m, 1H,), 7.09-7.02 (m, 2H), 5.35-5.30 (m, 1H), 4.05-3.99 (m, 4H), 3.55 (s, 3H), 3.33-3.30 (m, 4H), 2.33 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d6, ppm): δ −69.46 (3F).
307		567.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.74 (s, 1H), 7.50 (s, 1H), 7.27-7.20 (m, 2H.), 7.02-6.96 (m, 3H,), 6.84-6.81 (m, 1H), 5.38-5.35 (m, 1H), 3.25 (s, 3H), 3.39-3.38 (m, 8H), 2.33 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
308		568.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.63-9.48 (brs, 1H), 8.26 (s, 1H, FA), 7.71-7.62 (m, 1H), 7.46-7.38 (m, 1H), 7.10-7.01 (m, 1H), 6.74-6.68 (m, 1H), 5.51-5.21 (m, 1H), 4.22-4.03 (m, 1H), 3.48 (s, 3H), 3.30-3.21 (m, 8H), 2.73 (s, 3H), 2.30 (s, 3H), 2.15-1.96 (m, 4H), 1.67-1.43 (m, 5H).

TABLE 2-continued

Characterization of exemplary compounds.

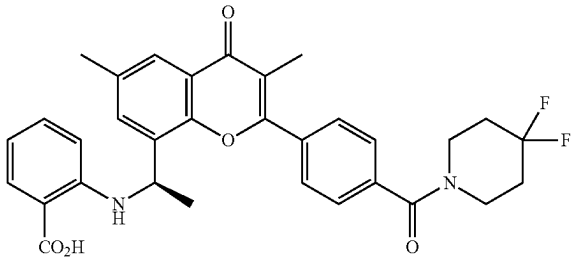
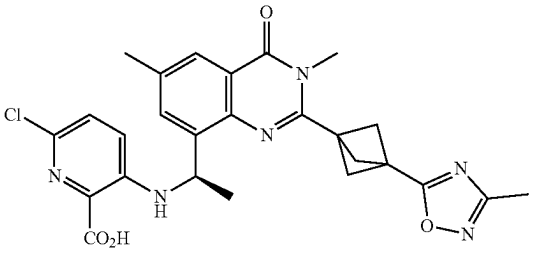
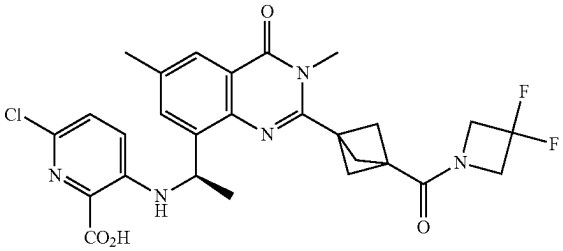
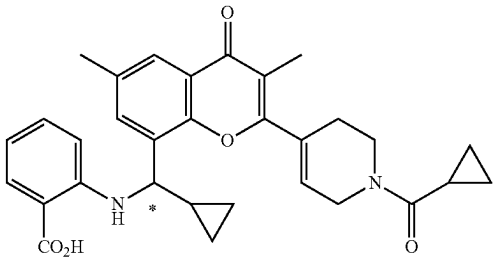
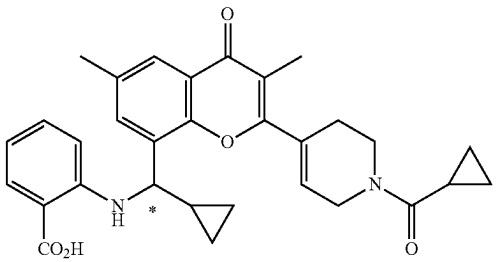
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
310		561.5	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.36 (s, 1H), 7.89-7.87 (m, 2H), 7.82-7.78 (m, 2H), 7.66-7.62 (m, 2H), 7.54 (s, 1H), 7.20-7.18 (m, 1H), 6.50 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 5.15-5.12 (m, 1H), 3.75-3.40 (m, 4H), 2.37 (s, 3H), 2.10 (s, 3H), 2.10-1.90 (m, 4H), 1.59 (d, J = 6.8 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −95.75 (2F).
311		521.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 7.82 (s, 1H), 7.66 (s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 5.45-5.35 (m, 1H), 3.64 (s, 3H), 2.90-2.75 (m, 6H), 2.39 (s, 3H), 2.35 (s, 3H), 1.70-1.60 (m, 3H).
312		558.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 7.80 (s, 1H), 7.63 (s, 1H), 7.36-7.24 (m, 1H), 7.20-7.04 (m, 1H), 5.45-5.30 (m, 1H), 4.81 (t, J = 12.4 Hz, 2H), 4.35 (t, J = 12.4 Hz, 2H), 3.60 (s, 3H), 2.65-2.54 (m, 6H), 2.38 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −99.56 (2F).
313	 obtained from intermediate 313-1.	513.2	As 2.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.46-9.36 (m, 1H), 8.26 (s, 2H, FA), 7.81 (d, J = 7.2 Hz, 1H), 7.71 (s, 1H), 7.56 (s, 1H), 7.02-6.95 (m, 1H), 6.50-6.35 (m, 2H), 6.24 (d, J = 8.0 Hz, 1H), 4.65-4.46 (m, 2H), 4.23-4.19 (m, 1H), 3.99-3.75 (m, 2H), 2.60-2.55 (m, 1H), 2.41-2.30 (m, 4H), 2.20-2.00 (m, 4H), 1.39-1.25 (m, 1H), 0.87-0.69 (m, 4H), 0.65-0.55 (m, 1H), 0.50-0.41 (m, 1H), 0.38-0.29 (m, 2H).
314	 obtained from intermediate 313-2.	513.2	As 1.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.18-9.01 (m, 1H), 8.32 (s, 1H, FA), 7.81-7.75 (m, 1H), 7.72-7.63 (m, 1H), 7.57-7.43 (m, 1H), 7.15-6.91 (m, 1H), 6.51-6.39 (m, 1H), 6.39-6.23 (m, 2H), 4.58-4.48 (m, 2H), 4.24-4.13 (m, 1H), 3.86-3.73 (m, 2H), 2.65-2.58 (m, 1H), 2.36 (s, 3H), 2.12-1.91 (m, 5H), 1.39-1.28 (m, 1H), 0.72-0.62 (m, 4H), 0.59-0.50 (m, 1H), 0.43-0.35 (m, 1H), 0.34-0.25 (m, 2H).

TABLE 2-continued

Characterization of exemplary compounds.

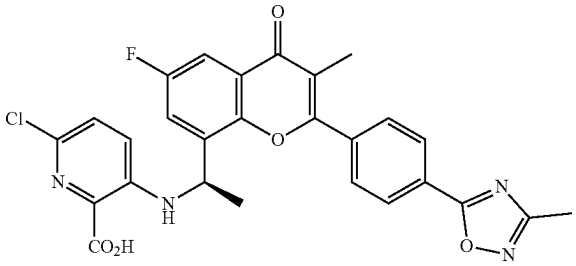
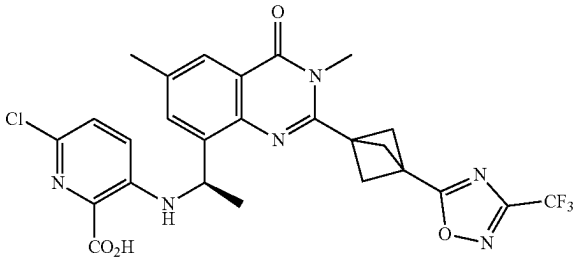
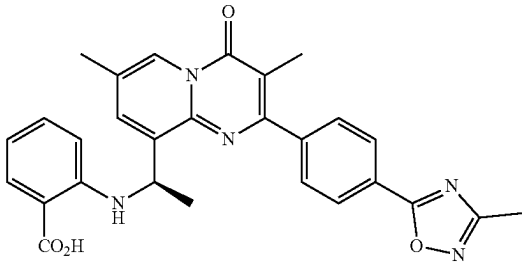
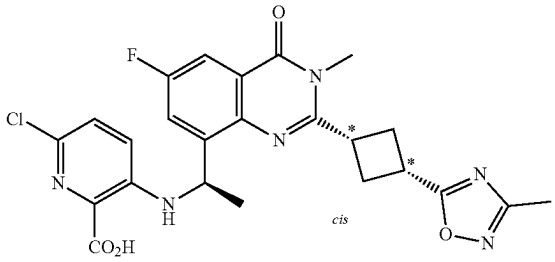
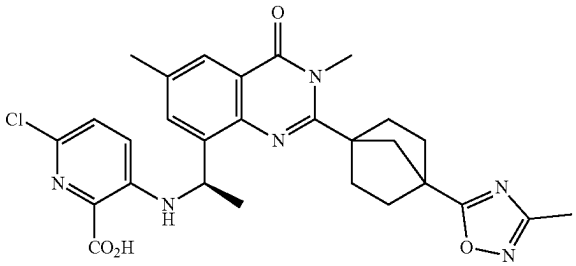
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
315		535.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.33-8.18 (m, 2H), 8.21 (s, 1H, FA), 8.09-8.01 (m, 2H), 7.71-7.60 (m, 1H), 7.51-7.45 (m, 1H), 7.18-6.86 (m, 2H), 5.19-5.05 (m, 1H), 2.47 (s, 3H), 2.12 (s, 3H), 1.58 (d, J = 6.0 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.03 (1F).
316		575.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.73 (brs, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.35-7.26 (m, 1H), 7.22-7.11 (m, 1H), 5.46-5.34 (m, 1H), 3.65 (s, 3H), 2.99-2.85 (m, 6H), 2.39 (s, 3H), 1.72-1.58 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −65.30 (3F).
317		496.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.73 (s, 1H), 8.68-8.51 (m, 1H), 8.29-8.21 (m, 2H), 8.03-7.94 (m, 2H), 7.85-7.80 (m, 1H), 7.73-7.64 (m, 1H), 7.23-7.09 (m, 1H), 6.57-6.47 (m, 1H), 6.37-6.30 (m, 1H), 5.44-5.33 (m, 1H), 2.46 (s, 3H), 2.35 (s, 3H), 2.26 (s, 3H), 1.66-1.54 (m, 3 H).
318		513.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.15 (brs, 1H), 7.68-7.65 (m, 1H), 7.58-7.55 (m, 1H), 7.13-7.11 (m, 1H), 6.89-6.87 (m, 1H), 5.53-5.502 (m, 1H), 4.08-3.84 (m, 2H), 3.49 (s, 3H), 3.02-2.81 (m, 4H), 2.26 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.90 (1F).
319		549.4	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.63 (s, 1H), 8.30 (s, 1H, FA), 7.78 (s, 1H), 7.48 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.44-5.31 (m, 1H), 3.63 (s, 3H), 2.55-2.59 (m, 1H), 2.33-2.30 (m, 11H), 2.18-1.97 (m, 4H), 1.52 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

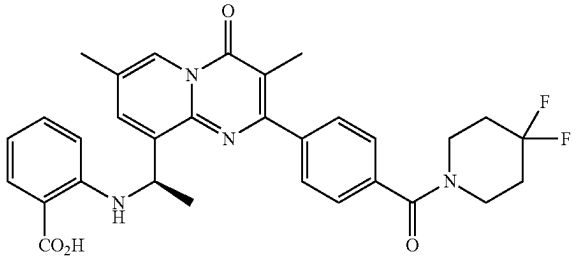
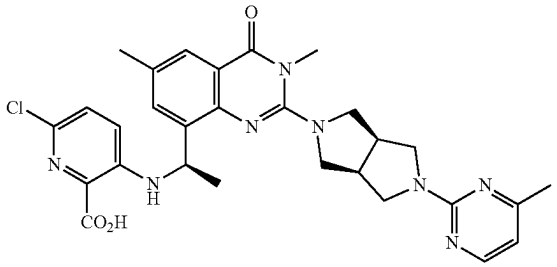
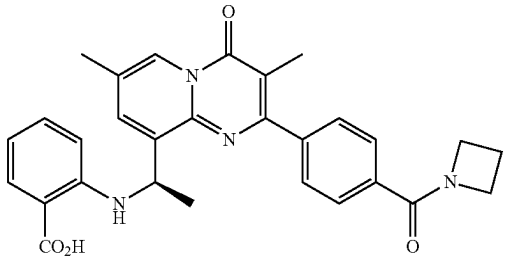
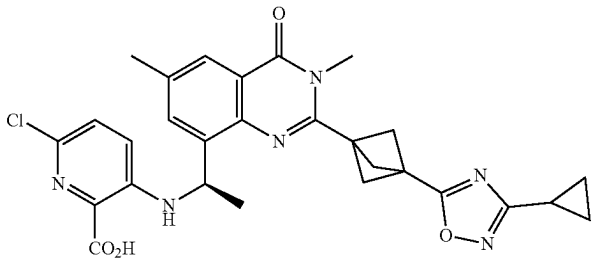
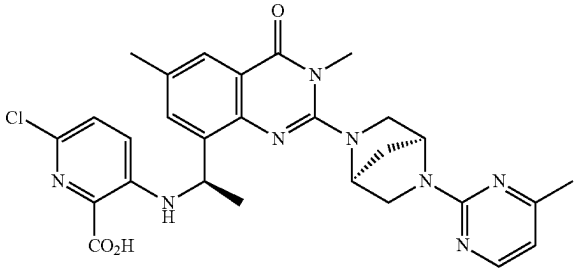
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
320		561.4	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.72 (s, 1H), 8.50 (s, 1H), 7.82-7.80 (m, 3H), 7.66-7.60 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H), 6.43 (t, J = 7.6 Hz, 1H), 6.23 (d, J = 8.4 Hz, 1H), 5.42-5.39 (m, 1H), 3.75-3.40 (m, 4H), 2.34 (s, 3H), 2.25 (s, 3H), 2.15-1.96 (m, 4H), 1.60 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −95.72 (2F).
321		575.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.33 (s, 1H), 8.18 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.36 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.73 (s, 1H), 6.48 (d, J = 5.2 Hz, 1H), 5.28 (d, J = 7.6 Hz, 1H), 3.86-3.75 (m, 4H), 3.63-3.50 (m, 4H), 3.45 (s, 3H), 3.08 (s, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 1.45 (d, J = 6.8 Hz, 3H).
322		497.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.72 (s, 1H), 7.85-7.74 (m, 5H), 7.66 (s, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.52 (t, J = 7.4 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 5.39 (s, 1H), 4.38 (t, J = 7.6 Hz, 2H), 4.08 (t, J = 7.8 Hz, 2H), 2.33 (s, 3H), 2.32-2.26 (m, 2H), 2.24 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
324		547.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.91 (brs, 1H), 8.54 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.67 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 5.45-5.30 (m, 1H), 3.63 (s, 3H), 2.93-2.67 (m, 6H), 2.39 (s, 3H), 2.20-2.08 (m, 1H), 1.67 (d, J = 6.8 Hz, 3H), 1.13-1.01 (m, 2H), 0.95-0.84 (m, 2H).
325		561.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, MeOD-d$_4$, ppm): δ 8.45 (brs, 1H, FA), 8.10 (d, J = 5.2 Hz, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 5.2 Hz, 1H), 5.46-5.38 (m, 1H), 5.07 (s, 1H), 4.86 (s, 1H), 4.05 (d, J = 10.6 Hz, 1H), 3.85 (dd, J = 9.2, 2.0 Hz, 1H), 3.67 (d, J = 10.2 Hz, 1H), 3.61-3.50 (m, 1H), 3.53 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H), 2.13-2.06 (m, 2H), 1.61 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

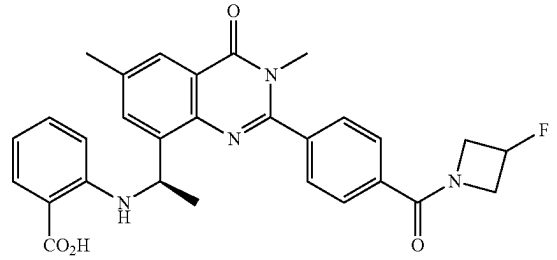
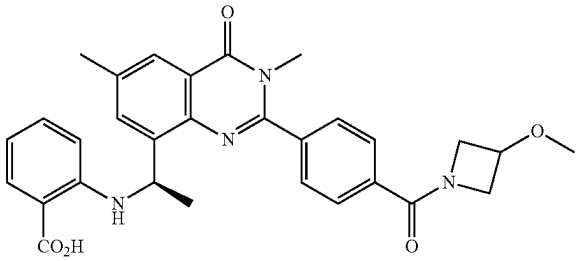
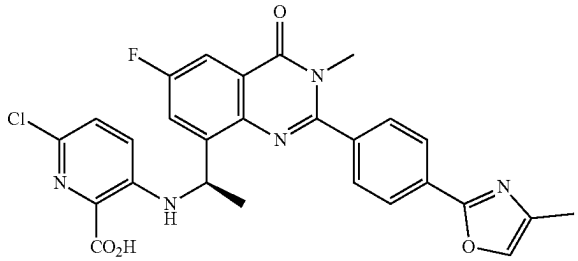
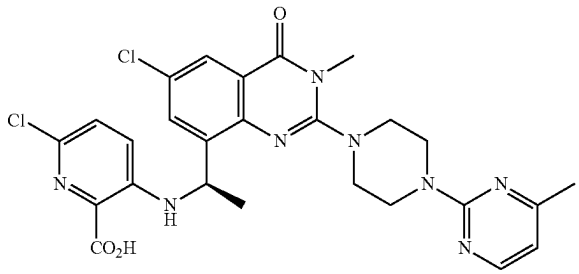
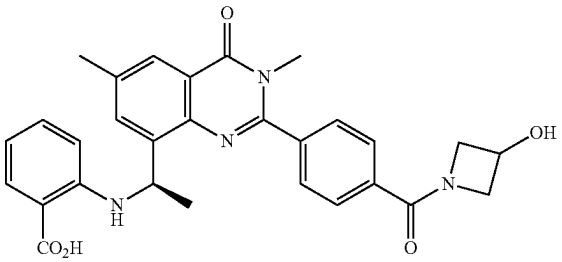
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
326		515.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.90-7.76 (m, 6H), 7.58 (s, 1H), 7.13-7.09 (m, 1H), 6.46 (t, J = 7.6 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 5.56-5.36 (m, 2H), 4.68-4.28 (m, 3H), 4.18-4.05 (m, 1H), 3.41 (s, 3H), 2.39 (s, 3H), 1.52 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −179.54 (1F).
327		527.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.90-7.76 (m, 6H), 7.58 (s, 1H), 7.06-7.04 (m, 1H), 6.45 (t, J = 6.8 Hz, 1H), 6.31 (d, J = 7.2 Hz, 1H), 5.51-5.37 (m, 1H), 4.56-4.44 (m, 1H), 4.32-4.21 (m, 3H), 3.92-3.83 (m, 1H), 3.41 (s, 3H), 3.23 (s, 3H), 2.39 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H).
328		534.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.05-8.50 (m, 1H), 8.17-8.10 (m, 2H), 8.04-7.97 (m, 1H), 7.96-7.89 (m, 2H), 7.80-7.73 (m, 1H), 7.65-7.54 (m, 1H), 7.24-7.08 (m, 1H), 6.95-6.77 (m, 1H), 5.52-5.37 (m, 1H), 3.44 (s, 3H), 2.20 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.92 (1F).
329		569.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.67-8.44 (m, 1H), 8.31-8.22 (d, J = 5.2 Hz, 1H), 7.92-7.84 (m, 1H), 7.77-7.65 (m, 1H), 7.36-7.25 (m, 1H), 7.17-6.98 (m, 1H), 6.65-6.51 (d, J = 4.8 Hz, 1H), 5.42-5.26 (m, 1H), 4.01-3.90 (m, 4H), 3.54 (s, 3H), 3.42-3.36 (m, 4H), 2.31 (s, 3H), 1.67-1.59 (m, 3 H).
330		513.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.00 (brs, 1H), 7.99-7.74 (m, 6H), 7.62-7.54 (m, 1H), 7.09-7.00 (m, 1H), 6.48-6.39 (m, 1H), 6.33-6.23 (m, 1H), 5.52-5.39 (m, 1H), 4.59-4.46 (m, 2H), 4.36-4.24 (m, 1H), 4.17-4.07 (m, 1H), 3.89-3.78 (m, 1H), 3.41 (s, 3H), 2.38 (s, 3H), 1.59-1.45 (m, 3H), 1.23 (s, 1H).

TABLE 2-continued

Characterization of exemplary compounds.

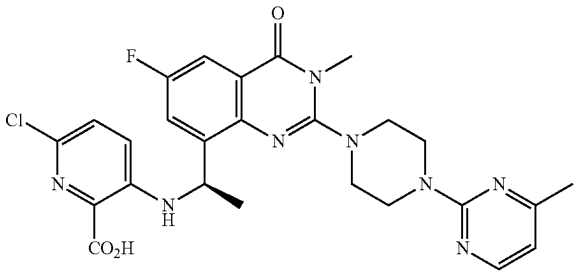
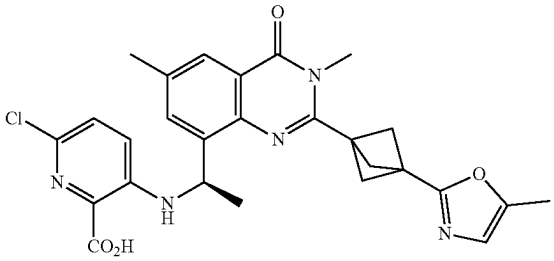
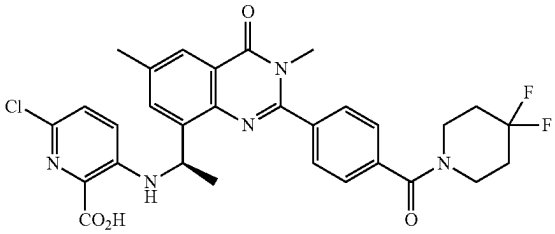
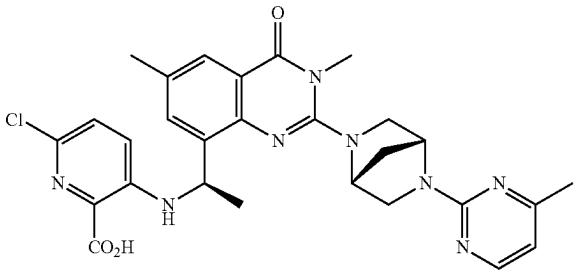
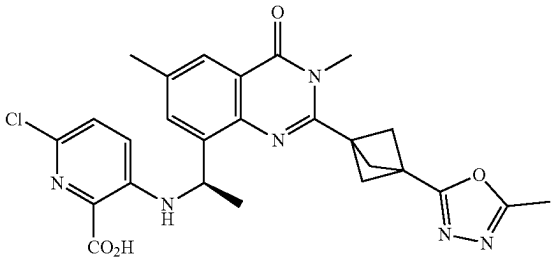
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
331		553.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.54 (brs, 1H), 8.26 (s, 1H, FA), 8.24-8.20 (m, 1H), 7.65-7.52 (m, 1H), 7.47-7.33 (m, 1H), 7.10-6.95 (m, 1H), 6.82-6.64 (m, 1H), 6.62-6.43 (m, 1H), 5.43-5.23 (m, 1H), 4.00-3.80 (m, 4H), 3.59-3.47 (m, 3H), 3.42-3.36 (m, 4H), 2.30 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H); ^{19}F NMR (4376 MHz, DMSO-d$_6$, ppm): δ −115.81 (1F).
332		520.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.10 (brs, 1H), 7.80 (s, 1H), 7.59 (s, 1H), 7.21-7.19 (m, 1H), 7.01-6.99 (m, 1H), 6.79 (d, J = 1.2 Hz, 1H), 5.41-5.38 (m, 1H), 3.65 (s, 3H), 2.75-2.68 (m, 6H), 2.37 (s, 3H), 2.34 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).
333		596.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.65 (brs, 1H 8.33 (s, 1H, FA), 7.87-7.84 (m, 3H), 7.65-7.63 (m, 2H), 7.53 (s, 1H,), 7.00 (d, J = 8.8 Hz, 1H), 6.68-6.66 (m, 1H), 5.40-5.37 (m, 1H), 3.75-3.70 (m, 4H), 3.42 (s, 3H), 2.37 (s, 3H), 2.08-2.00 (m, 4H), 1.50 (d, J = 6.4 Hz, 3H).
334		561.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.61 (brs, 1H), 8.34 (s, 1H, FA), 8.16 (d, J = 4.8 Hz, 1H), 7.62 (s, 1H), 7.35 (s, 1H), 7.03 (d, J = 4.8 Hz, 1H), 6.65 (s, 1H), 6.48 (d, J = 4.8 Hz, 1H), 5.31-5.27 (m, 1H), 5.00 (s, 1H), 4.85 (s, 1H), 3.98-3.95 (m, 1H), 3.87-3.85 (m, 1H), 3.61-3.59 (m, 2H), 3.47-3.44 (m, 3H), 2.25-2.20 (m, 6H), 2.05-1.97 (m, 2H), 1.54-1.52 (d, J = 6.4 Hz, 3H).
335		521.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.03 (brs, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 5.45-5.35 (m, 1H), 3.65 (s, 3H), 2.85-2.70 (m, 6H), 2.50 (s, 3H). 2.37 (s, 3H), 1.65-1.55 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

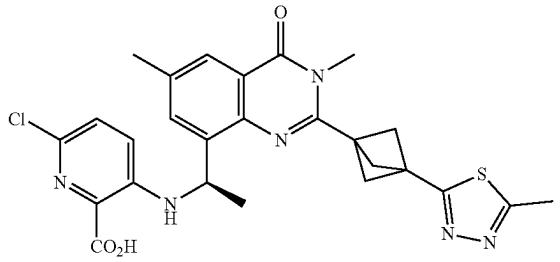
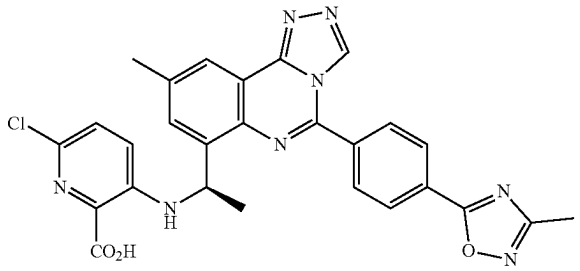
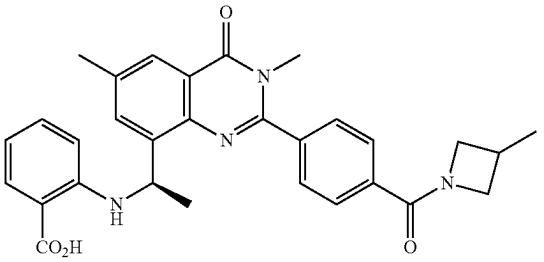
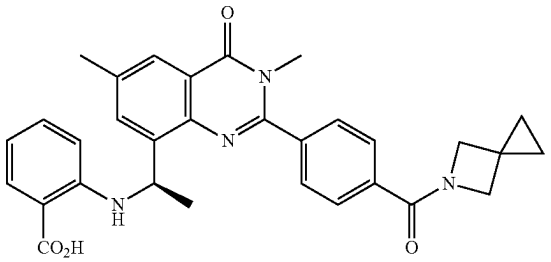
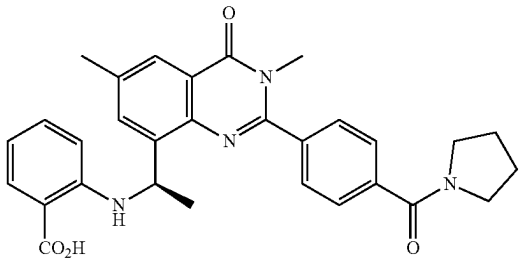
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
336		537.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.45 (brs, 1H), 7.80 (s, 1H), 7.57 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 5.46-5.35 (m, 1H), 3.66 (s, 3H), 2.91-2.65 (m, 9H), 2.37 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H).
337		541.4	^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 8.99 (s, 1H), 8.42-8.32 (m, 3H), 8.16-8.05 (m, 2H), 7.54 (s, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.75-5.60 (m, 1H), 2.57-2.43 (m, 6H), 1.68 (d, J = 6.8 Hz, 3H).
338		511.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.41 (s, 1H), 7.90-7.74 (m, 6H), 7.58 (d, J = 1.6 Hz, 1H), 7.22-7.11 (m, 1H), 6.50 (t, J = 7.6 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.53-5.43 (m, 1H), 4.47 (t, J = 8.2 Hz, 1H), 4.19 (d, J = 9.2 Hz, 1H), 3.94-3.88 (m, 1H), 3.65 (dd, J = 9.6, 5.6 Hz, 1H), 3.41 (s, 3H), 2.81-2.67 (m, 1H), 2.40 (s, 3H), 1.54 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H).
339		523.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.40 (s, 1H), 7.91-7.80 (m, 5H), 7.78 (dd, J = 8.0, 1.6 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.20-7.10 (m, 1H), 6.50 (t, J = 7.6 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.52-5.41 (m, 1H), 4.41 (s, 2H), 4.16 (s, 2H), 3.41 (s, 3H), 2.40 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H), 0.73-0.62 (m, 4H).
340		511.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.41 (s, 1H), 7.89 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.78 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 1.6 Hz, 1H), 7.19-7.14 (m, 1H), 6.50 (t, J = 7.2 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.52-5.44 (m, 1H), 3.48 (dt, J = 19.6, 6.4 Hz, 4H), 3.42 (s, 3H), 2.40 (s, 3H), 1.95-1.78 (m, 4H), 1.54 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

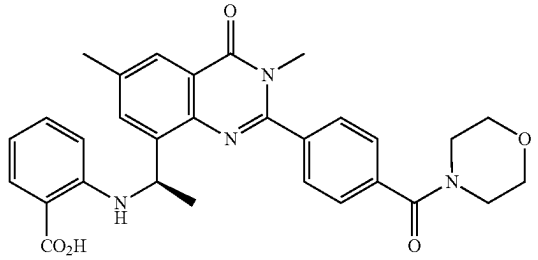
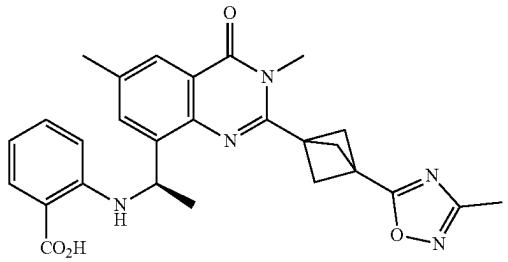
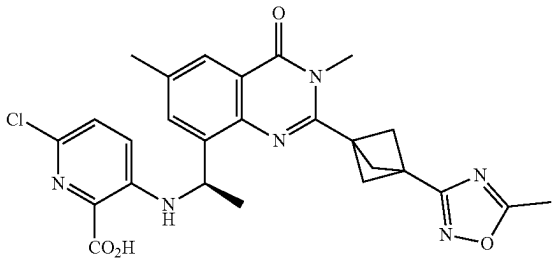
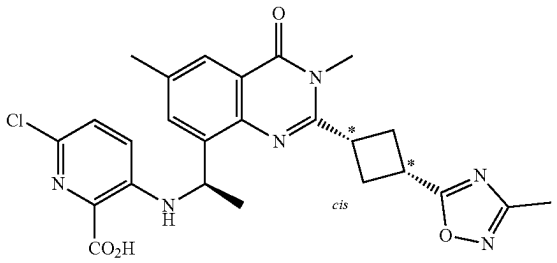
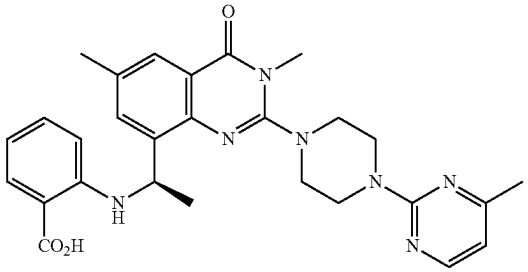
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
341		527.5	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.69-8.43 (brs, 1H), 7.92-7.82 (m, 3H), 7.79 (d, J = 7.6 Hz, 1H), 7.65-7.52 (m, 3H), 7.19-7.06 (m, 1H), 6.48 (t, J = 7.2 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 5.54-5.42 (m, 1H), 3.80-3.53 (m, 6H), 3.51-3.40 (m, 5H), 2.39 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H).
342		486.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.87-7.73 (m, 2H), 7.58 (s, 1H), 7.15-7.01 (m, 1H), 6.52-6.32 (m, 2H), 5.52-5.39 (m, 1H), 3.65 (s, 3H), 2.91-2.76 (m, 6H), 2.41-2.25 (m, 6H), 1.57 (d, J = 6.4 Hz, 3H).
343		521.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.70 (s, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.33-7.30 (m, 1H), 7.18-7.15 (m, 1H), 5.40-5.37 (m, 1H), 3.65 (s, 3H), 2.78-2.69 (m, 6H), 2.59 (s, 3H), 2.39 (s, 3H), 1.66 (d, J = 6.4 Hz, 3H).
344		509.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.38 (brs, 1H), 7.80 (s, 1H), 7.54 (s, 1H), 7.06-7.04 (m, 1H), 6.85-6.83 (m, 1H), 5.51-5.48 (m, 1H), 4.05-3.96 (m, 1H), 3.93-3.83 (m, 1H), 3.48 (s, 3H), 3.05-2.77 (m, 4H), 2.35 (s, 3H), 2.26 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
345		514.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.11 (brs, 1H), 8.25 (d, J = 4.8 Hz, 1H), 7.81-7.62 (m, 2H), 7.49 (s, 1H), 6.82-6.70 (m, 1H), 6.56 (d, J = 5.2 Hz, 1H), 6.32-6.20 (m, 1H), 6.11 (d, J = 8.0 Hz, 1H), 5.35-5.21 (m, 1H), 4.05-3.90 (m, 4H), 3.55 (s, 3H), 3.32-3.15 (m, 4H), 2.30 (s, 6H), 1.47 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

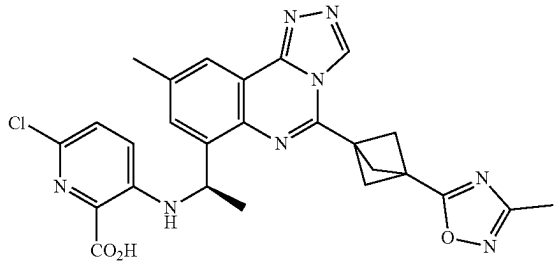
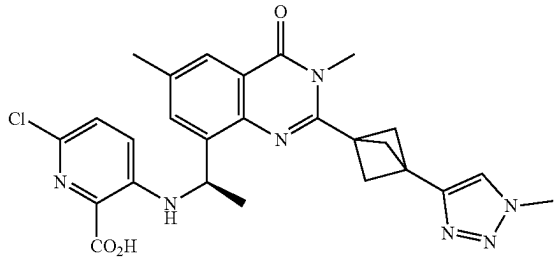
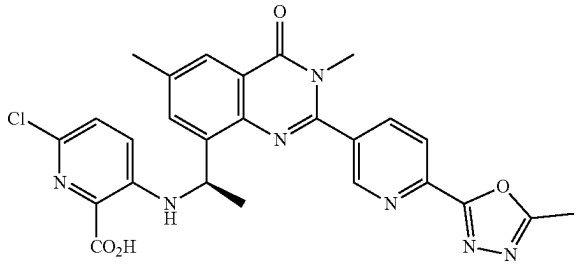
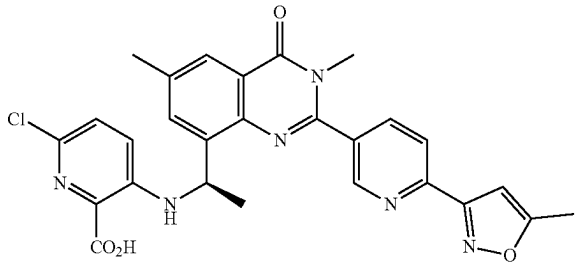
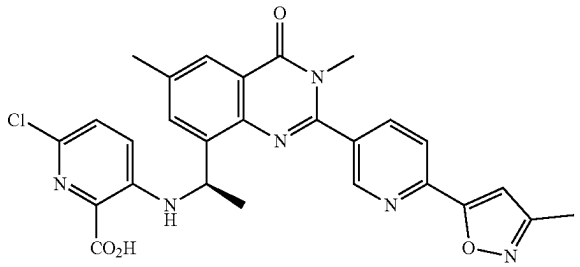
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
346		531.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.84 (brs, 1H), 8.75 (s, 1H), 8.16 (s, 1H), 7.79 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 5.59-5.56 (m, 1H), 2.99-2.92 (m, 6H), 2.53 (s, 3H), 2.38 (s, 3H), 1.74 (d, J = 6.4 Hz, 3H).
347		520.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.76-8.51 (m, 1H), 7.98 (s, 1H), 7.85-7.78 (m, 1H), 7.68-7.60 (m, 1H), 7.37-7.28 (m, 1H), 7.23-7.13 (m, 1H), 5.48-5.32 (m, 1H), 4.02 (s, 3H), 3.66 (s, 3H), 2.71-2.65 (m, 3H), 2.64-2.59 (m, 3H), 2.38 (s, 3H), 1.69-1.61 (m, 3H).
348		532.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.58-8.95 (m, 2H), 8.52-8.45 (m, 1H), 8.37-8.30 (m, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.15-7.05 (m, 1H), 6.88-6.74 (m, 1H), 5.47-5.34 (m, 1H), 3.47 (s, 3H), 2.66 (s, 3H), 2.40 (s, 3H), 1.58-1.50 (m, 3H).
349		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.22 (m, 1H), 8.40-8.38 (m, 1H), 8.19-8.17 (m, 1H), 7.90 (s, 1H), 7.59 (s, 1H), 7.18-7.01 (m, 1H), 6.89-6.72 (m, 2H), 5.48-5.30 (m, 1H), 3.48 (s, 3H), 2.55 (s, 3H), 2.40 (s, 3H), 1.55 (d, J = 4.8 Hz, 3H).
350		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.12 (s, 2H), 8.43-8.41 (m, 1H), 8.18-8.11 (m, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.14-7.11 (m, 2H), 6.85-6.83 (m, 1H), 5.43-5.40 (m, 1H), 3.48 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H), 1.55 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

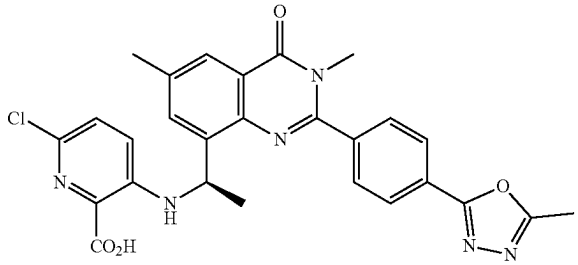
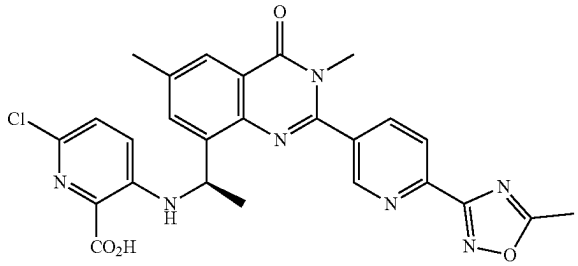
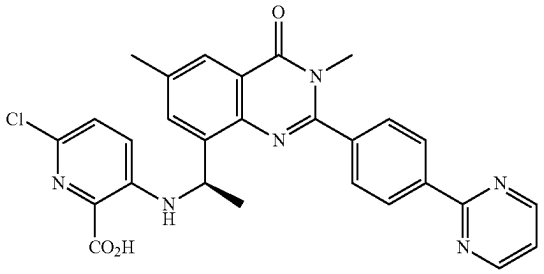
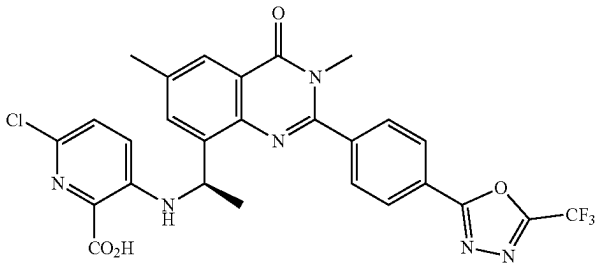
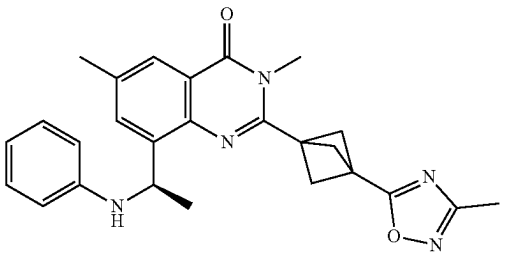
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
351		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.94 (brs, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.87 (s, 1H), 7.56 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 5.38-5.25 (m, 1H), 3.43 (s, 3H), 2.62 (s, 3H), 2.38 (s, 3H), 1.49 (d, J = 6.4 Hz, 3H).
352		531.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.81 (brs, 1H), 8.19-8.17 (m, 2H), 7.97-7.90 (m, 3H), 7.60 (s, 1H), 7.24-7.14 (m, 1H), 6.95-6.84 (m, 1H), 5.44-5.41 (m, 1H), 3.43 (s, 3H), 2.71 (s, 3H), 2.40 (s, 3H), 1.56 (d, J = 6.6 Hz, 3H).
353		527.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.91 (brs, 1H), 8.98 (d, J = 4.9 Hz, 2H), 8.57 (d, J = 8.2 Hz, 2H), 8.00-7.84 (m, 3H), 7.62-7.46 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 5.52-5.30 (m, 1H), 3.46 (s, 3H), 2.39 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H).
354		585.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.08 (brs, 1H), 8.33-8.23 (m, 2H), 8.10-8.00 (m, 2H), 7.90 (s, 1H), 7.59 (s, 1H), 7.19-7.09 (m, 1H), 6.90-6.79 (m, 1H), 5.45-5.34 (m, 1H), 3.43 (s, 3H), 2.40 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −64.19 (3F).
355		442.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.77 (s, 1H), 7.64 (s, 1H), 7.05-6.90 (m, 2H), 6.53-6.33 (m, 3H), 6.21 (d, J = 7.6 Hz, 1H), 5.45-5.35 (m, 1H), 3.65 (s, 3H), 2.82 (s, 6H), 2.45-2.30 (m, 6H), 1.47 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

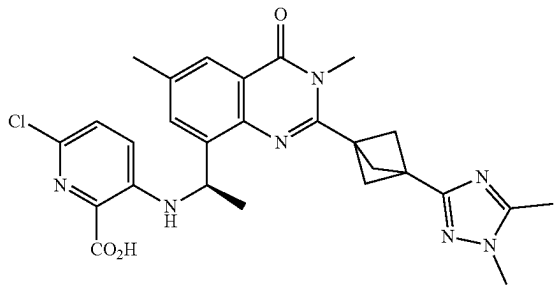
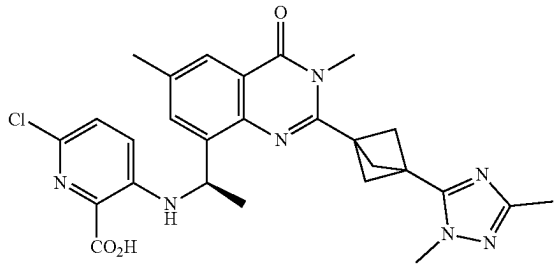
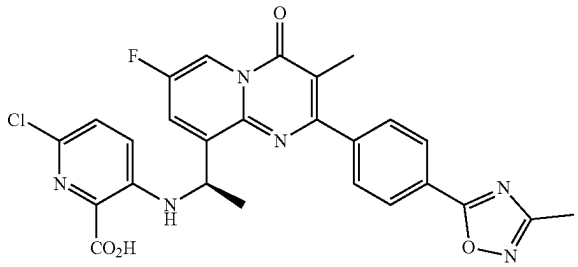
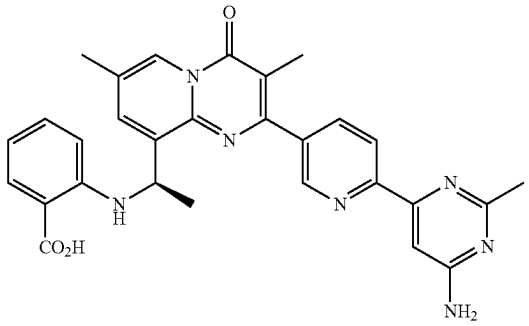
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
356		534.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.83 (brs, 1H), 7.81 (s, 1H), 7.62 (s, 1H), 7.28-7.26 (m, 1H), 7.12-7.10 (m, 1H), 5.41-5.38 (m, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 2.65-2.57 (m, 6H), 2.38 (s, 3H), 2.35 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H).
357		534.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.33 (s, 1H), 7.80 (s, 1H), 7.56 (s, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 5.44-5.40 (m, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.82-2.75 (m, 6H), 2.36 (s, 3H), 2.18 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
358		535.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.48 (s, 1H), 8.86-8.85 (m, 1H), 8.26-8.24 (m, 2H), 7.99-7.97 (m, 2H), 7.77 (s, 1H), 7.05 (s, 1H), 6.77 (s, 1H), 5.40-5.30 (m, 1H), 2.46 (s, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
359		521.4	As 1.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.11 (brs, 1H), 8.71 (s, 1H), 8.33 (s, 1H, FA), 8.20 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 3H), 7.63 (s, 1H), 7.13 (s, 1H), 7.09-7.02 (m, 1H), 6.62 (s, 2H), 6.51-6.42 (m, 1H), 6.28-6.20 (m 1H), 5.39-5.37 (m, 1H), 2.33 (s, 6H), 2.28 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

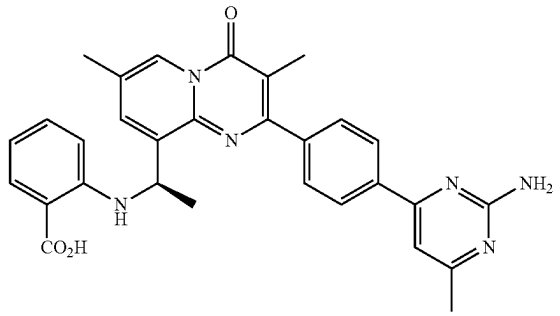
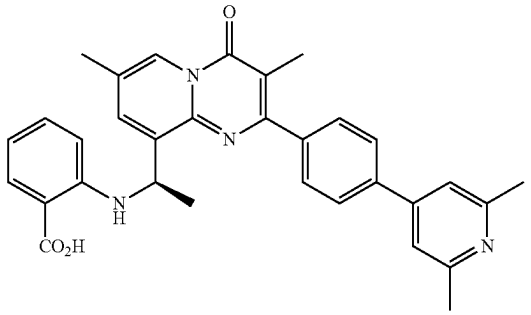
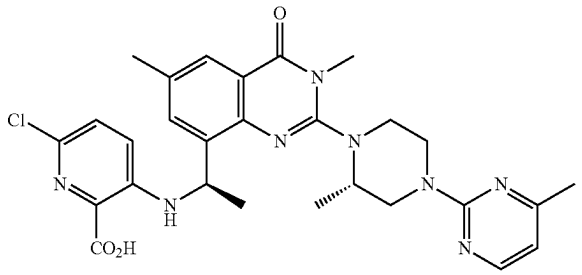
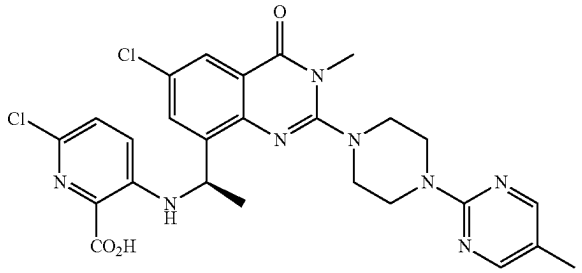
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
360		521.4	As 2.0 FA salts. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.39 (brs, 1H), 8.71 (s, 1H), 8.38 (s, 2H, FA) 8.14-8.09 (m, 2H), 7.86-7.84 (m, 3H), 7.61 (s, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.87 (s, 2H), 6.78 (s, 1H), 6.45 (t, J = 7.2 Hz, 1H), 6.20 (d, J = 8.0 Hz, 1H), 5.38-5.37 (m, 1H), 2.41 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
361		519.5	As 1.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.17 (s, 1H), 8.71 (s, 1H), 8.32 (s, 1H, FA), 7.94-7.82 (m, 5 H), 7.63 (s, 1H), 7.45 (s, 2H), 7.06 (t, J = 8.4 Hz, 1H), 6.47 (t, J = 7.2 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1H), 5.40-5.38 (m, 1H), 2.51 (s, 6H), 2.33 (s, 3H), 2.28 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
362		563.3	1H NMR (400 MHz, MeOH-d4, ppm): δ 8.16 (d, J = 4.8 Hz, 1H), 7.82 (s, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.50 (d, J = 4.8 Hz, 1H), 5.48-5.39 (m, 1H), 4.23-4.12 (m, 1H), 4.01-3.79 (m, 4H), 3.65 (s, 3H), 3.54-3.45 (m, 1H), 3.27-3.21 (m, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H).
363		569.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.28 (s, 2H), 7.87 (d, J = 2.4 Hz, 1H), 7.71 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.09-7.03 (m, 1H), 5.33 (t, J = 6.8 Hz, 1H), 3.90-3.88 (m, 4H), 3.54 (s, 3H), 3.39-3.37 (m, 4H), 2.10 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

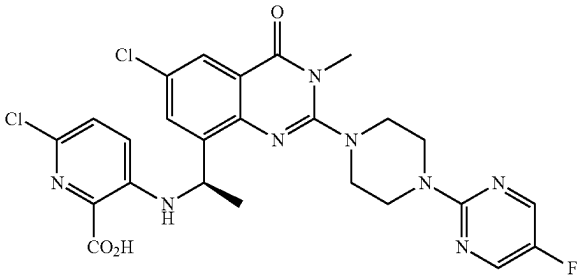
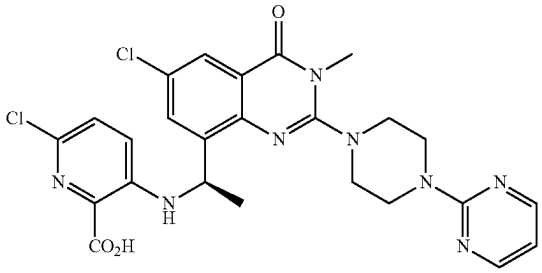
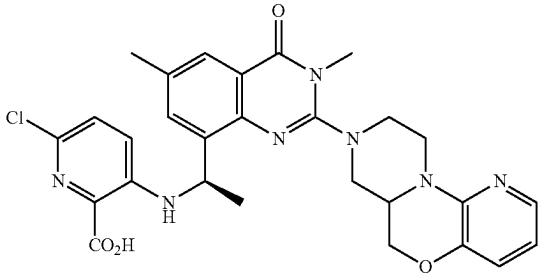
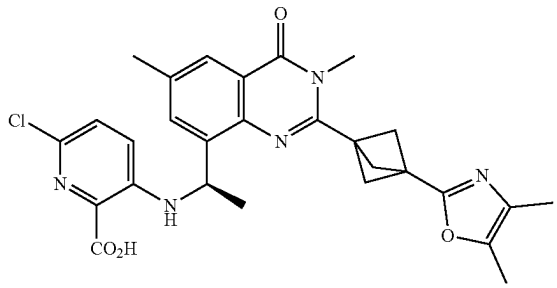
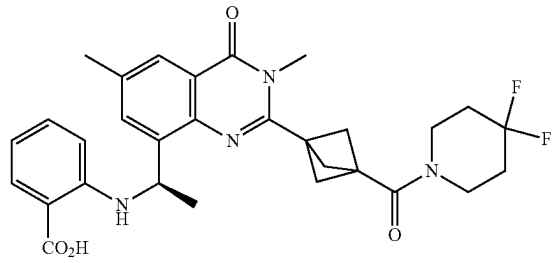
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
364		573.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.83 (brs, 1H), 8.51 (s, 2H), 7.86 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.38-5.24 (m, 1H), 4.00-3.81 (m, 4H), 3.54 (s, 3H), 3.44-3.39 (m, 4H), 1.61 (d, J = 6.4 Hz, 3H).
365		555.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.69 (brs, 1H), 8.41 (d, J = 4.8 Hz, 2H), 7.87 (d, J = 2.4 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.73-6.61 (m, 1H), 5.40-5.23 (m, 1H), 3.95 (t, J = 4.8 Hz, 4H), 3.54 (s, 3H), 3.40 (d, J = 4.4 Hz, 4H), 1.62 (d, J = 6.8 Hz, 3H).
366		562.2	As 1.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.57 (brs, 1H), 8.32 (s, 1H, FA), 7.75-7.72 (m, 2H), 7.44 (s, 1H), 7.03-7.01 (m, 2H), 6.76 (s, 1H), 6.66-6.63 (m, 1H), 5.32-5.30 (m, 1H), 4.48-4.36 (m, 2H), 4.04-3.98 (m, 2H), 3.78-3.76 (m, 2H), 3.53 (s, 3H), 3.01-2.99 (m, 2H), 2.79-2.73 (m, 1H), 2.30 (s, 3H), 1.53-1.52 (d, J = 6.4 Hz, 3H).
367		534.4	1H NMR (400 MHz, MeOH-d4, ppm): δ 7.86 (s, 1H), 7.64 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.62-5.51 (m, 1H), 3.75 (s, 3H), 2.77 (s, 6H), 2.38 (s, 3H), 2.25 (s, 3H), 2.07 (s, 3H), 1.61 (d, J = 8.0 Hz, 3H).
368		551.6	As 2.0 TFA salts. 1H NMR (400 MHz, MeOH-d4, ppm): δ 7.90-7.80 (m, 2H), 7.58 (s, 1H), 7.11 (t, J = 6.8 Hz, 1H), 6.55-6.40 (m, 2H), 5.60-5.50 (m, 1H), 3.90-3.80 (m, 2H), 3.75-3.65 (m, 5H), 2.84-2.70 (m, 6H), 2.38 (s, 3H), 2.15-1.95 (m, 4H), 1.70-1.60 (m, 3H); 19F NMR (376 MHz, MeOD-d4, ppm): δ −77.37 (6F), −99.16 (2F).

TABLE 2-continued

Characterization of exemplary compounds.

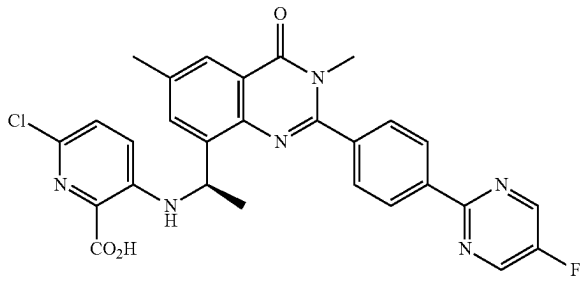
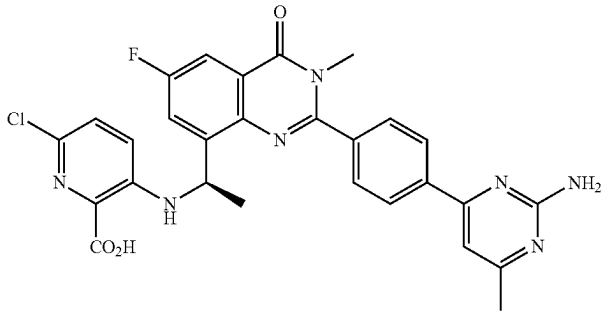
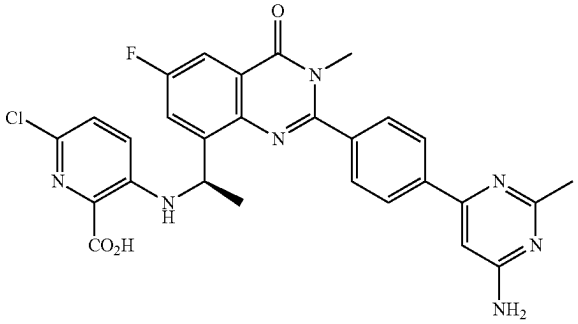
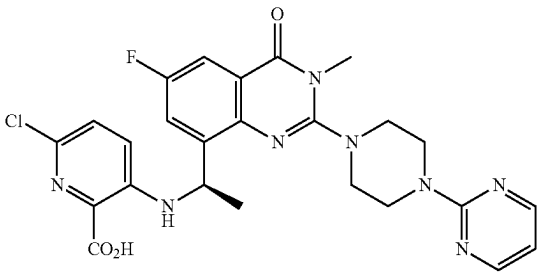
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
369		545.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.07 (s, 2H), 8.51 (d, J = 8.4 Hz, 2H), 7.99-7.85 (m, 3H), 7.60 (s, 1H), 7.28-7.13 (m, 1H), 6.97-6.83 (m, 1H), 5.50-5.36 (m, 1H), 3.45 (s, 3H), 2.41 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −139.30 (1F).
370		560.2	As 2.0 TFA salts. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.39 (d, J = 7.2 Hz, 1H), 8.36-8.27 (m, 2H), 7.99-7.92 (m, 2H), 7.79 (dd, J = 8.4, 3.2 Hz, 1H), 7.71 (dd, J = 9.2, 3.2 Hz, 1H), 7.41 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 5.53-5.41 (m, 1H), 3.45 (s, 3H), 2.44 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm) δ −74.48 (6F), −111.80 (1F).
371			As 1.0 TFA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.45-8.35 (m, 1H), 8.10-7.88 (m, 4H), 7.80 (dd, J = 8.4, 3.2 Hz, 1H), 7.72 (dd, J = 9.2, 2.8 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 9.2 Hz, 1H), 6.91-6.77 (m, 1H), 5.51-5.33 (m, 1H), 3.44 (s, 3H), 2.56 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.64 (1F).
372		539.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.41 (d, J = 4.8 Hz, 2H), 7.65-7.54 (m, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.76-6.65 (m, 1H), 5.42-5.31 (m, 1H), 4.01-3.90 (m, 4H), 3.55 (s, 3H), 3.46-3.35 (m, 4H), 1.64 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.77 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

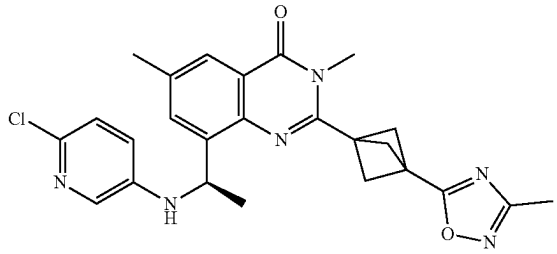
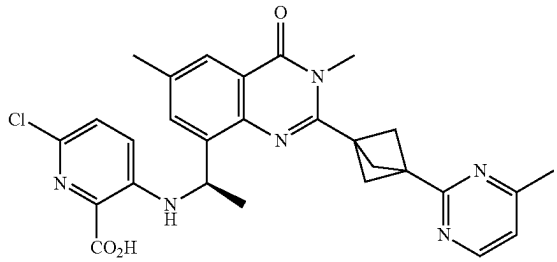
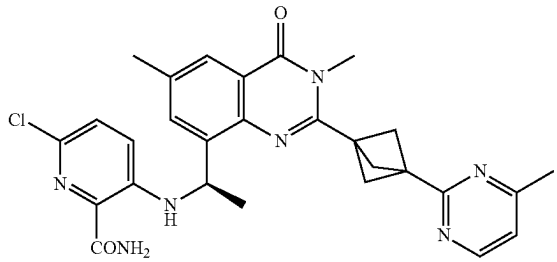
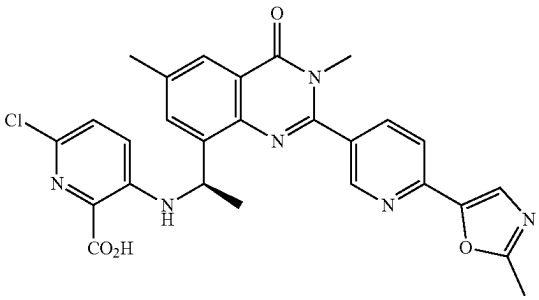
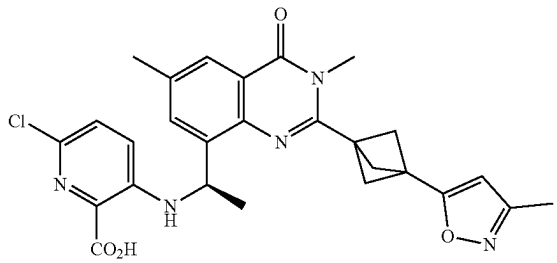
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
373		477.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.70 (s, 1H), 7.78-7.58 (m, 2H), 7.15-7.03 (m, 1H), 6.95-6.85 (m, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.50-5.37 (m, 1H), 3.65 (s, 3H), 2.82 (s, 6H), 2.38 (s, 3H), 2.35 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H).
374		531.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.02 (brs, 1H), 8.63 (s, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.30 (s, 1H), 7.24-7.21 (m, 1H), 7.05-7.03 (m, 1H), 5.44-5.41 (m, 1H), 3.68 (s, 3H), 2.73-2.66 (m, 6H), 2.47 (s, 3H), 2.38 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H).
375		530.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.14-9.12 (m, 1H), 8.63 (s, 1H), 7.84-7.82 (m, 2H), 7.60-7.57 (m, 2H), 7.32-7.29 (m, 2H), 7.12-7.10 (m, 1H), 5.46-5.40 (m, 1H), 3.68 (s, 3H), 2.74-2.66 (m, 6H), 2.47 (s, 3H), 2.39 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H).
376		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.63 (brs, 1H), 9.10-8.91 (m, 1H), 8.48-8.30 (m, 1H), 7.98-7.85 (m, 2H), 7.84-7.70 (m, 1H), 7.65-7.41 (m, 1H), 7.13-6.88 (m, 1H), 6.84-6.57 (m, 1H), 5.63-5.26 (m, 1H), 3.49 (s, 3H), 2.54 (s, 3H), 2.38 (s, 3H), 1.53 (d, J = 6.8 Hz, 3H).
377		520.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.70 (brs, 1H), 7.81 (s, 1H), 7.62 (s, 1H), 7.27-7.19 (m, 1H), 7.18-6.99 (m, 1H), 6.30 (s, 1H), 5.41-5.38 (m, 1H), 3.65 (s, 3H), 2.73-2.68 (m, 6H), 2.38 (s, 3H), 2.22 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

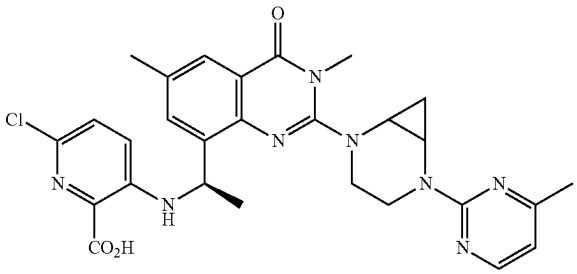
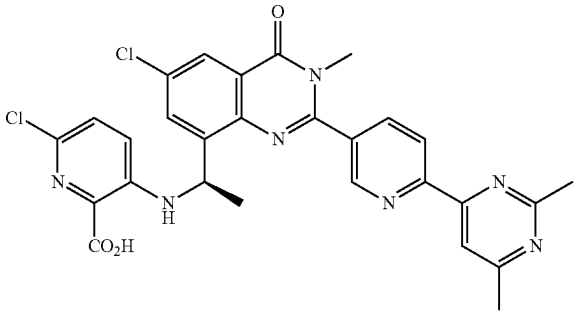
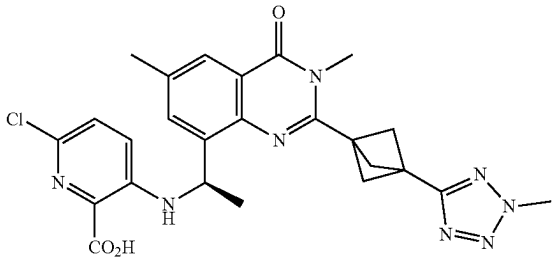
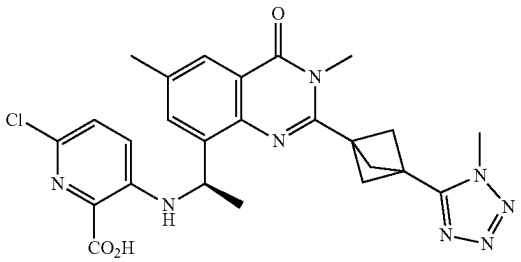
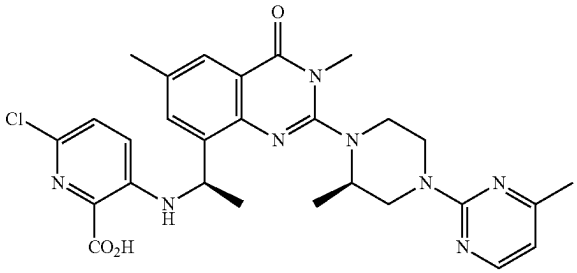
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
378		561.2	As 1.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.71 (brs, 1H), 8.42 (s, 1H, FA), 8.28-8.13 (m, 1H), 7.65 (s, 1H), 7.38-7.35 (m, 1H), 7.07-6.62 (m, 1H), 6.62-6.46 (m, 2H), 5.35-5.21 (m, 1H), 4.27-4.09 (m, 1H), 4.05-3.88 (m, 1H), 3.61 (s, 3H), 3.58-3.51 (m, 2H), 3.23-3.15 (m, 2H), 2.30-2.13 (m, 6H), 1.48 (dd, J = 16.8, 6.4 Hz, 3H), 1.28-1.21 (m, 1H), 0.40-0.30 (m, 1H).
380		556.2	As 1.0 FA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.67 (s, 1H), 9.16 (s, 1H), 8.59 (d, J = 8.2 Hz, 1H), 8.43 (s, 1H, FA), 8.26 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.57 (s, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.42-5.34 (m, 1H), 3.49 (s, 3H), 2.71 (s, 3H), 2.56 (s, 3H), 2.39 (s, 3H), 1.53 (d, J = 6.7 Hz, 3H).
381		521.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.85 (brs, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 7.29-7.27 (m, 1H), 7.13-7.10 (m, 1H), 5.42-5.39 (m, 1H), 4.36 (s, 3H), 3.67 (s, 3H), 2.82-2.74 (m, 6H), 2.39 (s, 3H), 1.65 (d, J = 6.8 Hz, 3H).
382		521.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.85 (s, 1H), 7.83 (s, 1H), 7.63 (s, 1H), 7.29-7.27 (m, 1H), 7.13-7.11 (m, 1H), 5.44-5.41 (m, 1H), 4.15 (s, 3H), 3.68 (s, 3H), 2.95-2.86 (m, 6H), 2.39 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H).
383		563.5	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.24 (d, J = 5.2 Hz, 1H), 7.74 (s, 1H), 7.48 (s, 1H), 7.05 (s, 1H), 6.81 (s, 1H), 6.54 (d, J = 5.0 Hz, 1H), 5.51-5.19 (m, 1H), 4.32-4.07 (m, 1H), 4.00 (dd, J = 12.6, 4.8 Hz, 1H), 3.89-3.79 (m, 2H), 3.71-3.69 (m, 1H), 3.55 (s, 3H), 3.45-3.41 (m, 1H), 3.31-3.19 (m, 1H), 2.33-2.30 (m, 6H), 1.53 (d, J = 6.4 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

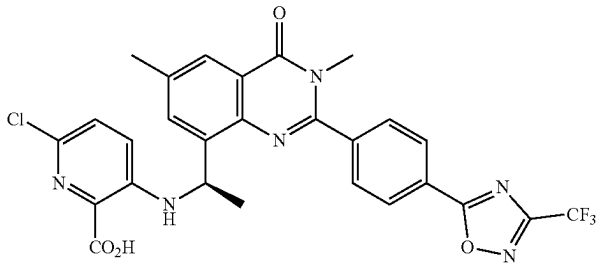
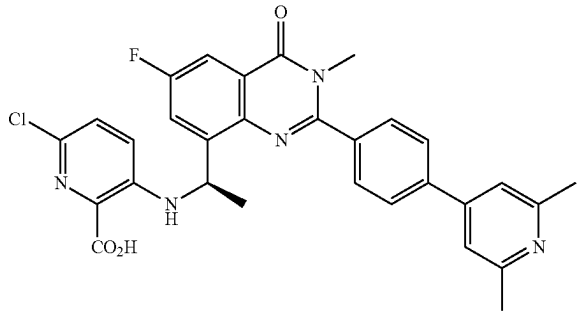
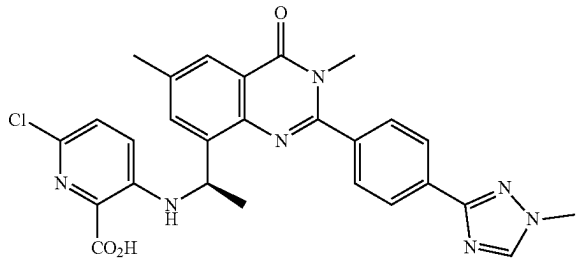
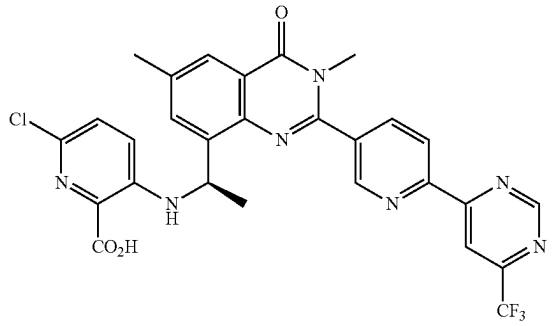
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
384		585.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.66 (brs, 1H), 8.38 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.92 (s, 1H), 7.64 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 9.2 Hz, 1H), 5.47-5.36 (m, 1H), 3.42 (s, 3H), 2.42 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −65.27 (3F).
385		558.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.96 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.78 (dd, J = 8.4, 3.2 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.47 (s, 2H), 7.25 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 5.52-5.41 (m, 1H), 3.46 (s, 3H), 2.63-2.52 (m, 6H), 1.60 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −111.98 (1F).
386		530.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.96 (s, 1H), 8.60 (s, 1H), 8.16 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 3H), 7.55 (s, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.45-5.30 (m, 1H), 3.97 (s, 3H), 3.45 (s, 3H), 2.38 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H).
387		596.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (brs, 1H), 9.65 (s, 1H), 9.22 (d, J = 1.6 Hz, 1H), 8.79 (d, J = 1.2 Hz, 1H), 8.70 (d, J = 8.0 Hz, 1H), 8.52 (dd, J = 8.0, 2.4 Hz, 1H), 8.47 (brs, 1H), 7.93 (s, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 9.2 Hz, 1H), 7.05 (d, J = 9.2 Hz, 1H), 5.49-5.40 (m, 1H), 3.49 (s, 3H), 2.43 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

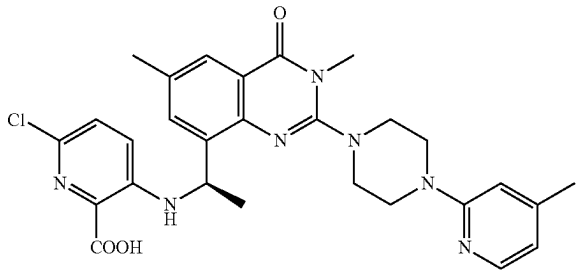
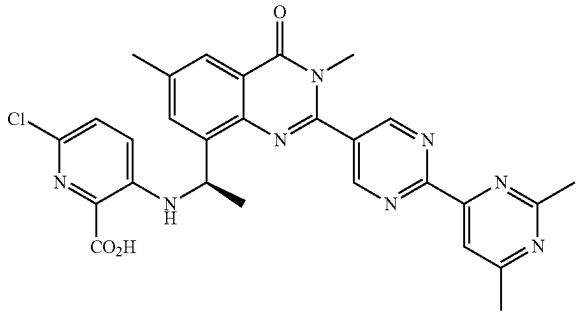
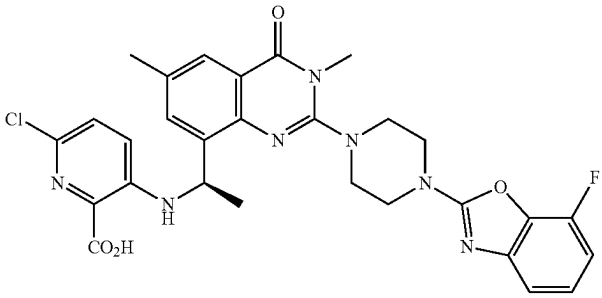
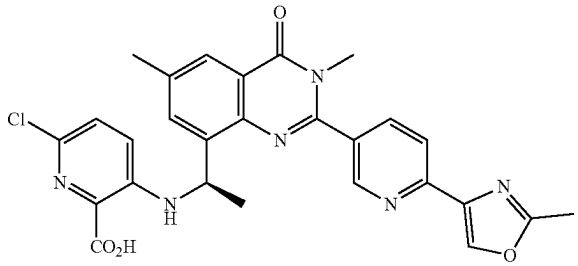
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
388		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.12 (brs, 1H), 8.00 (d, J = 5.2 Hz, 1H), 7.73 (s, 1H), 7.47 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.74 (s, 1H), 6.53 (d, J = 5.2 Hz, 1H), 5.51-5.20 (m, 1H), 3.68 (t, J = 5.2 Hz, 4H), 3.54 (s, 3H), 3.34 (s, 4H), 2.32 (s, 3H), 2.23 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).
389		557.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.47 (s, 2H), 8.69 (brs, 1H), 8.17 (s, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 5.43 (t, J = 7.0 Hz, 1H), 3.54 (s, 3H), 2.71 (s, 3H), 2.59 (s, 3H), 2.43 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H).
390		592.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.64 (s, 1H), 7.76 (s, 1H), 7.53 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.18 (s, 2H), 7.10-6.92 (m, 2H), 5.44-5.28 (m, 1H), 3.93-3.79 (m, 4H), 3.55 (s, 3H), 3.48-3.42 (m, 4H), 2.34 (s, 3H), 1.61 (d, J = 4.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −137.01 (1F).
391		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.49-9.10 (m, 1H), 9.03-8.95 (m, 1H), 8.63 (s, 1H), 8.36-8.25 (m, 1H), 8.01-7.91 (m, 1H), 7.91-7.84 (m, 1H), 7.63-7.41 (m, 1H), 7.17-6.93 (m, 1H), 6.87-6.67 (m, 1H), 5.54-5.25 (m, 1H), 3.47 (s, 3H), 2.53 (s, 3H), 2.39 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

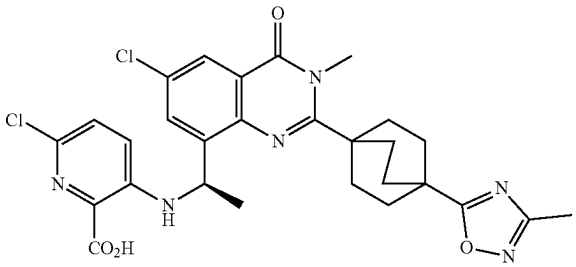
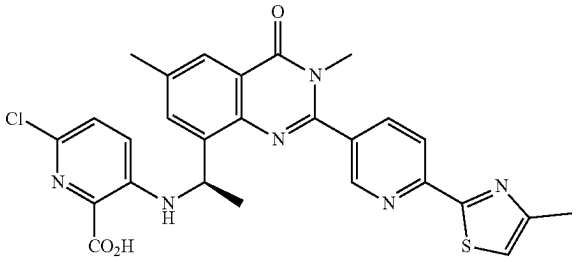
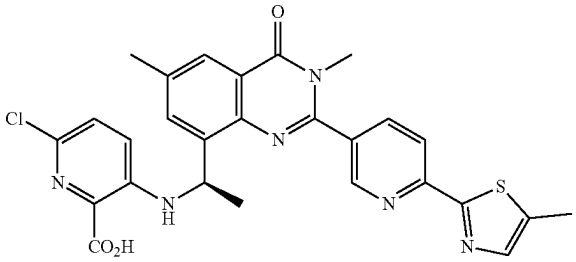
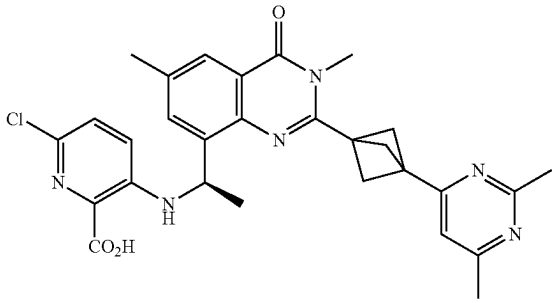
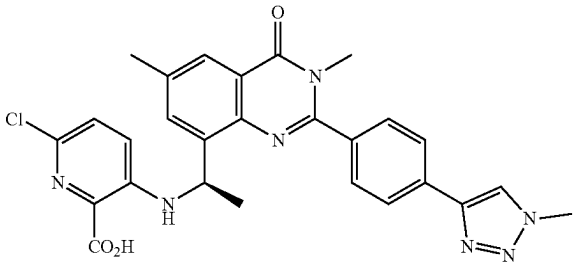
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
392		583.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.23 (brs, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.65 (s, 1H), 7.14 (s, 1H), 6.77 (s, 1H), 5.43-5.40 (m, 1H), 3.71 (s, 3H), 2.32 (s, 3H), 2.27-2.25 (m, 6H), 2.08-2.04 (m, 6H), 1.59 (s, J = 6.4 Hz, 3H).
393		547.2	^{1}H NMR (400 MHz, DMSO, ppm): δ 9.18-9.06-9.01 (m, 1H), 8.41-8.34 (m, 1H), 8.30-8.21 (m, 1H), 7.94-7.85 (m, 1H), 7.65-7.56 (m, 1H), 7.55-7.49 (m, 1H), 7.18-7.07 (m, 1H), 6.91-6.79 (m, 1H), 5.49-5.33 (m, 1H), 3.49 (s, 3H), 2.49-2.48 (m, 3H), 2.40 (s, 3H), 1.63-1.50 (m, 3H).
394		547.2	^{1}H NMR (400 MHz, DMSO, ppm): δ 9.09-8.98 (m, 1H), 8.68 (brs, 1H), 8.41-8.34 (m, 1H), 8.27-8.21 (m, 1H), 7.93-7.88 (m, 1H), 7.80-7.74 (m, 1H), 7.66-7.58 (m, 1H), 7.28-7.21 (m, 1H), 7.03-6.92 (m, 1H), 5.51-5.39 (m, 1H), 3.49 (s, 3H), 2.58-2.49 (m, 3H), 2.41 (s, 3H), 1.63-1.54 (m, 3H).
395		545.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.55 (d, J = 7.2 Hz, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.27-7.16 (m, 2H), 5.48-5.36 (m, 1H), 3.67 (s, 3H), 2.72-2.62 (m, 6H), 2.56 (s, 3H), 2.42 (s, 3H), 2.39 (s, 3H), 1.67 (d, J = 6.8 Hz, 3H).
396		530.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.25 (brs, 1H), 8.36 (s, 1H), 8.07-7.97 (m, 2H), 7.92-7.80 (m, 3H), 7.56 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 5.46-5.36 (m, 1H), 4.24 (s, 3H), 3.46 (s, 3H), 2.38 (s, 3H), 1.53 (d, J = 6.6 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

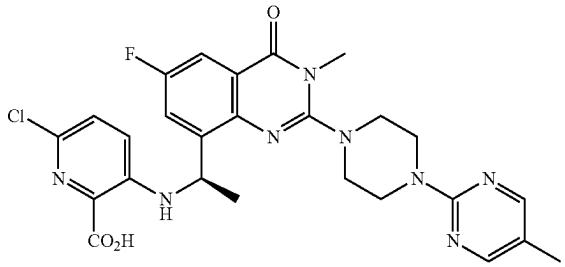
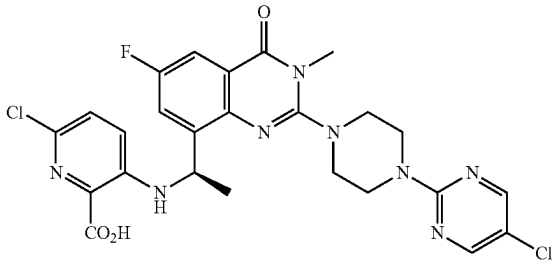
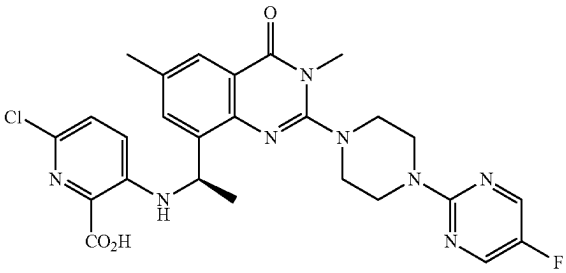
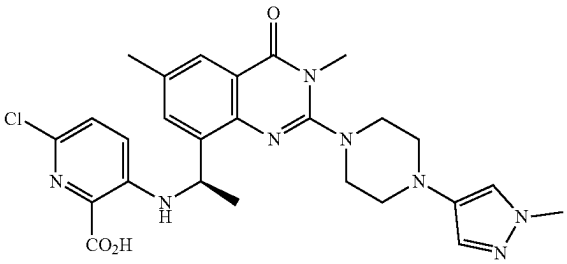
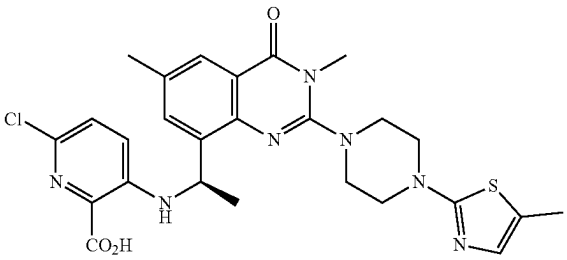
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
397		553.2	^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.40 (s, 2H), 8.38-8.28 (m, 1H), 7.82-7.72 (m, 1H), 7.41-7.31 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.39-5.29 (m, 1H), 4.16-4.05 (m, 4H), 3.67 (s, 3H), 3.45-3.35 (m, 4H), 2.25 (s, 3H), 1.67 (d, J = 8.0 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ −113.58 (1F).
398		573.4	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.50 (s, 2H), 7.64-7.45 (m, 2H), 7.26-7.14 (m, 1H), 6.97-6.85 (m, 1H), 5.40-5.30 (m, 1H), 3.98-3.88 (m, 4H), 3.55 (s, 3H), 3.45-3.35 (m, 4H), 1.67-1.55 (m, 3H); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −115.74 (1F).
399		553.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.94 (d, J = 7.2 Hz, 1H), 8.50 (s, 2H), 7.70 (s, 1H), 7.43 (s, 1H), 6.95-6.85 (m, 1H), 6.63-6.53 (m, 1H), 5.33-5.22 (m, 1H), 3.99-3.88 (m, 4H), 3.54 (s, 3H), 3.43-3.23 (m, 4H), 2.31 (s, 3H), 1.49 (d, J = 6.8, 3H); ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ −156.23 (1F).
400		537.2	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 9.93 (d, J = 7.2 Hz, 1H), 7.71 (s, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.32 (s, 1H), 7.21 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.41-5.30 (m, 1H), 3.74 (s, 3H), 3.51 (s, 3H), 3.49-3.35 (m, 4H), 3.11-2.97 (m, 4H), 2.31 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H).
401		554.4	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 9.95 (d, J = 7.2 Hz, 1H), 7.70 (s, 1H), 7.44 (s, 1H), 6.93-6.83 (m, 2H), 6.61 (d, J = 8.8 Hz, 1H), 5.31-5.21 (m, 1H), 3.62-3.46 (m, 7H), 3.47-3.37 (m, 4H), 2.37-2.27 (m, 6H), 1.49 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

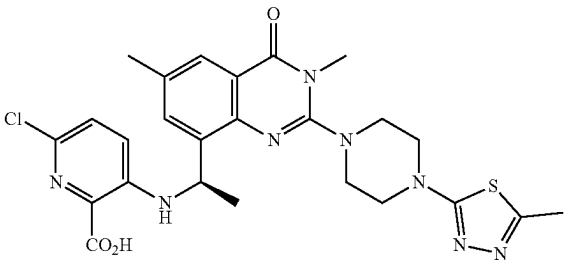
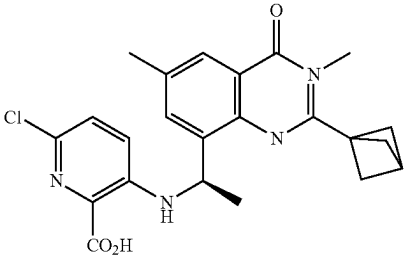
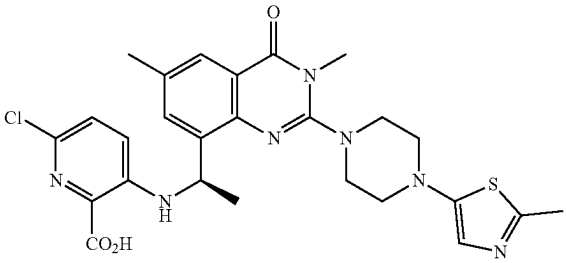
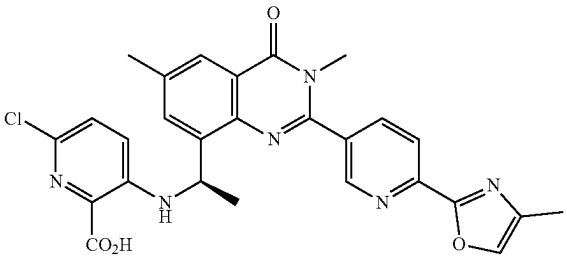
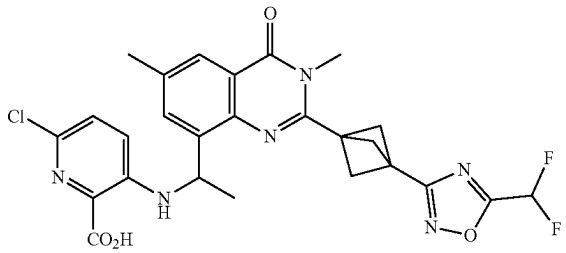
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
402		555.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.31 (brs, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 5.40-5.25 (m, 1H), 3.70-3.55 (m, 4H), 3.52 (s, 3H), 3.45-3.20 (m, 4H), 2.53 (s, 3H), 2.31 (s, 3H), 1.60-1.50 (m, 3H).
403		439.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.51 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.35 (d, J = 9.2 Hz, 1H), 7.20 (d, J = 9.2 Hz, 1H), 5.45-5.34 (m, 1H), 3.62 (s, 3H), 2.59 (s, 1H), 2.46-2.30 (m, 9H), 1.64 (d, J = 6.8 Hz, 3H).
404		554.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.56 (d, J = 6.0 Hz, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 9.2 Hz, 1H), 6.88 (s, 1H), 5.41-5.30 (m, 1H), 3.51 (s, 3H), 3.48-3.29 (m, 8H), 3.26-3.19 (m, 3H), 2.33 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H).
405		531.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 9.05 (s, 1H), 8.36 (m, 1H), 8.29 (m, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.66 (s, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 5.55 (q, J = 6.0 Hz, 1H), 3.59 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H).
406		557.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.89 (s, 1H), 7.82 (s, 1H), 7.63-7.37 (m, 2H), 7.28-7.26 (m, 1H), 7.11-7.09 (m, 1H), 5.42-5.38 (m, 1H), 3.66 (s, 3H), 2.85-2.76 (m, 6H), 2.38 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −121.62 (2F).

TABLE 2-continued

Characterization of exemplary compounds.

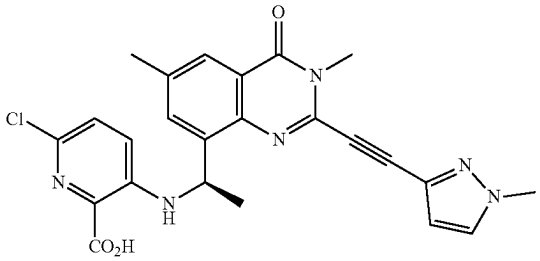
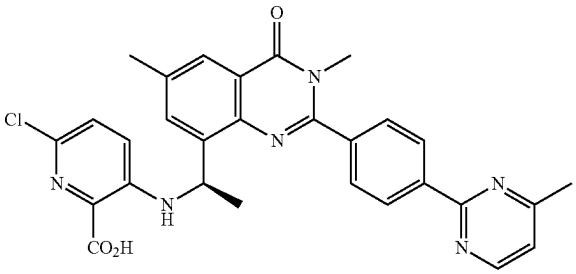
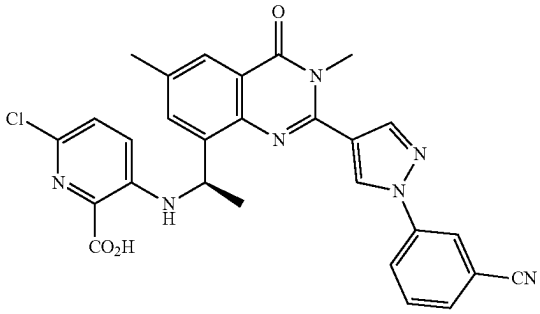
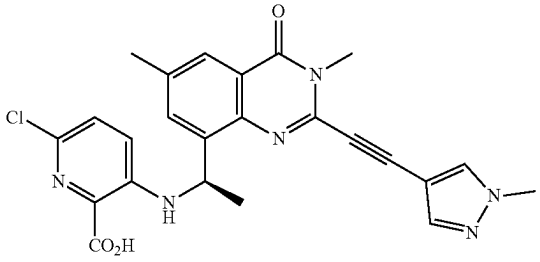
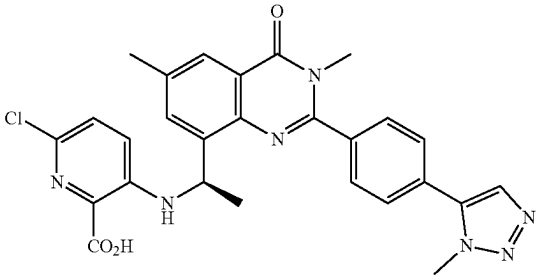
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
407		477.2	As 1.0 FA salt, 1H NMR (400 MHz, DMSO-d6, ppm): δ 9.81 (s, 1H), 8.46 (s, 1H, FA), 7.91 (d, J = 2.0 Hz, 1H), 7.84 (s, 1H), 7.52 (s, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.56 (s, 1H), 5.45-5.36 (m, 1H), 3.94 (s, 3H), 3.72 (s, 3H), 2.35 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H).
408		541.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.83-8.72 (m, 2H), 8.56 (d, J = 8.4 Hz, 2H), 8.18-8.15 (m, 3H), 7.61 (s, 1H), 7.40 (d, J = 4.0 Hz, 1H), 7.26-7.18 (m, 1H), 6.96-6.88 (m, 1H), 5.49-5.46 (m, 1H), 3.46 (s, 3H), 2.59 (s, 3H), 2.41 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H)
409		540.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.28 (s, 1H), 8.60 (brs, 1H), 8.54 (s, 1H), 8.52-8.51 (m, 1H), 8.36-8.34 (m, 1H), 7.89-7.86 (m, 2H), 7.82-7.78 (m, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 5.60-5.50 (m, 1H), 3.80 (s, 3H), 2.40 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H).
410		477.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 13.04 (s, 1H), 8.45 (s, 1H), 8.39 (s, 1H), 7.96 (s, 1H), 7.85 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 5.51-5.45 (m, 1H), 3.91 (s, 3H), 3.72 (s, 3H), 2.38 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H).
411		530.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.06 (brs, 1H), 8.66 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.94-7.80 (m, 3H), 7.57 (s, 1H), 7.20-7.06 (m, 1H), 6.85 (d, J = 8.8 Hz, 1H), 5.49-5.37 (m, 1H), 4.13 (s, 3H), 3.46 (s, 3H), 2.39 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

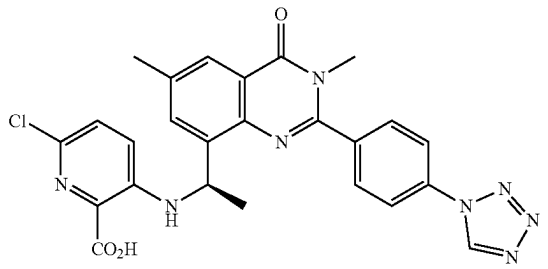
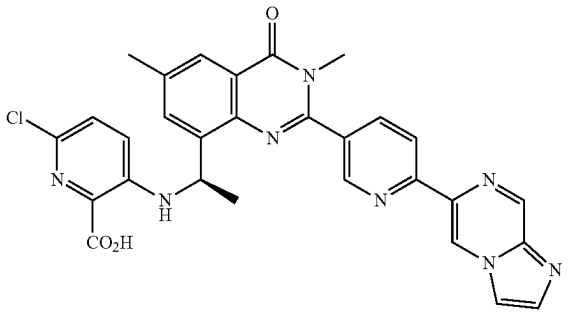
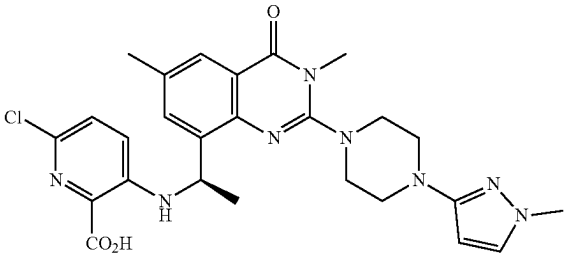
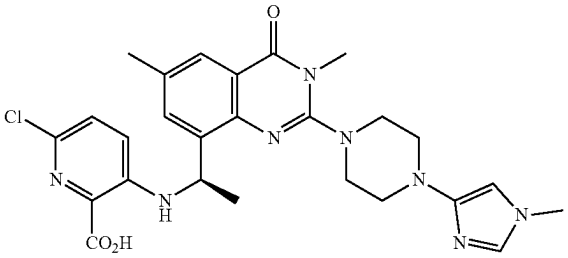
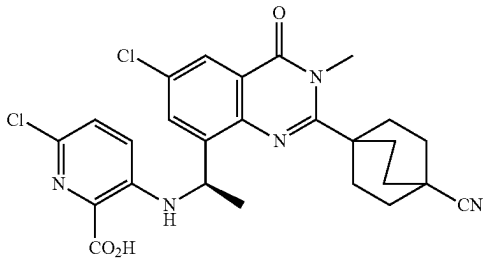
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
412		517.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 10.21 (s, 1H), 9.57 (brs, 1H), 8.18-8.02 (m, 4H), 7.89 (s, 1H), 7.55 (s, 1H), 7.05-6.95 (m, 1H), 6.78-6.62 (m, 1H), 5.45-5.30 (m, 1H), 3.46 (s, 3H), 2.38 (s, 3H), 1.52 (d, J = 6.4 Hz, 3H).
413		567.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 10.01 (d, J = 7.2 Hz, 1H), 9.66 (s, 1H), 9.24 (s, 1H), 9.11 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.43 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 8.34 (s, 1H), 7.90-7.80 (m, 2H), 7.57 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 5.40-5.30 (m, 1H), 3.52 (s, 3H), 2.39 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H).
414		537.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.51 (d, J = 7.6 Hz, 1H), 7.74 (s, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 9.2 Hz, 1H), 5.75 (s, 1H), 5.45-5.34 (m, 1H), 3.67 (s, 3H), 3.51 (s, 3H), 3.42-3.25 (m, 8H), 2.34 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H).
415		537.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.62 (brs, 1H), 8.51 (d, J = 7.2 Hz, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 6.95 (s, 1H), 5.40-5.28 (m, 1H), 3.75 (s, 3H), 3.51 (s, 3H), 3.48-3.36 (m, 4H), 3.32-3.17 (m, 4H), 2.35 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
416		526.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.84-8.27 (m, 1H), 7.97-7.87 (m, 1H), 7.80-7.68 (m, 1H), 7.33-7.21 (m, 1H), 7.00-6.85 (m, 1H), 5.49-5.33 (m, 1H), 3.67 (s, 3H), 2.24-2.00 (m, 12H), 1.63 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

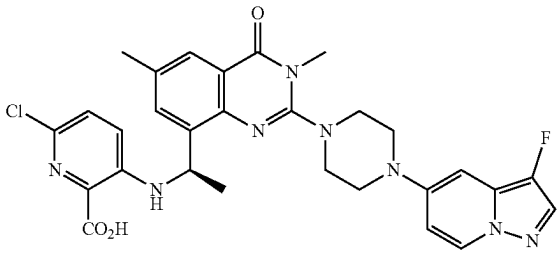
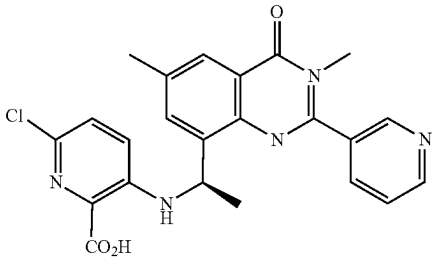
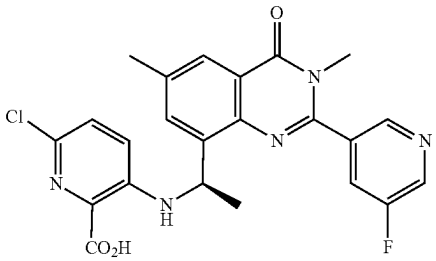
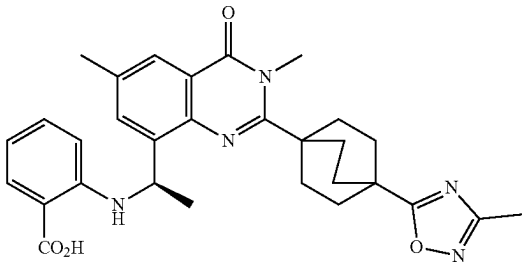
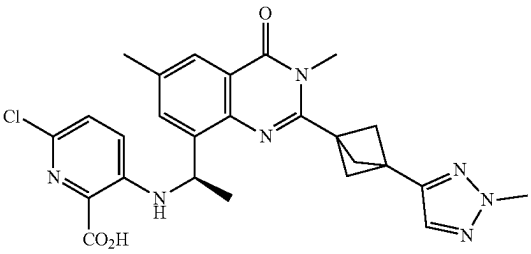
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
417		591.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.54 (d, J = 7.2 Hz, 1H), 8.42-8.35 (m, 1H), 7.92 (d, J = 3.6 Hz, 1H), 7.76 (s, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 6.89 (dd, J = 7.6 Hz, 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 5.45-5.30 (m, 1H), 3.55 (s, 3H), 3.50-3.43 (m, 4H), 3.42-3.38 (m, 4H), 2.35 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −186.76 (1F).
418		450.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.99 (d, J = 1.60 Hz, 1H), 8.81-8.74 (m, 1H), 8.58 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.65-7.59 (m, 2H), 7.25 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.50-5.39 (m, 1H), 3.44 (s, 3H), 2.41 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H).
419		468.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.88 (s, 1H), 8.81 (d, J = 2.8 Hz, 1H), 8.48 (d, J = 6.00 Hz, 1H), 8.27-8.20 (m, 1H), 7.92 (s, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 5.50-5.39 (m, 1H), 3.44 (s, 3H), 2.42 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −126.44 (1F).
420		528.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.92 (s, 1H), 7.83-7.74 (m, 2H), 7.55-7.50 (m, 1H), 7.10-7.02 (m, 1H), 6.47-6.40 (m, 1H), 6.36-6.28 (m, 1H), 5.60-5.40 (m, 1H), 3.71 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 2.31-2.21 (m, 6H), 2.11-2.02 (m, 6H), 1.58-1.51 (m, 3H).
421		520.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.62-8.45 (m, 1H), 7.83-7.79 (m, 1H), 7.69 (s, 1H), 7.67-7.63 (m, 1H), 7.39-7.33 (m, 1H), 7.25-7.18 (m, 1H), 5.47-5.33 (m, 1H), 4.12 (s, 3H), 3.65 (s, 3H), 2.71-2.59 (m, 6H), 2.39 (s, 3H), 1.71-1.63 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

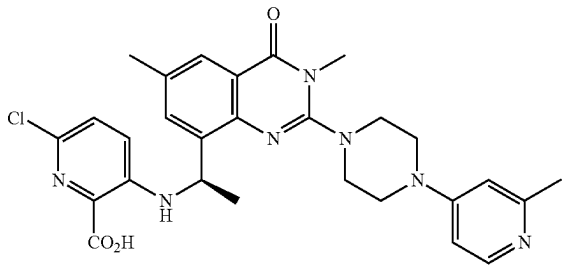
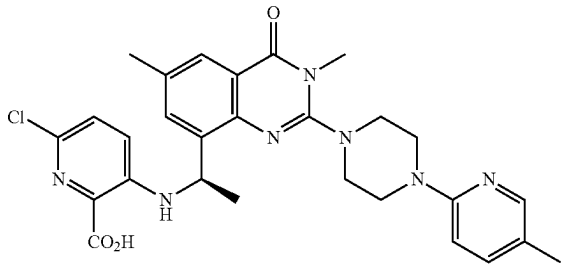
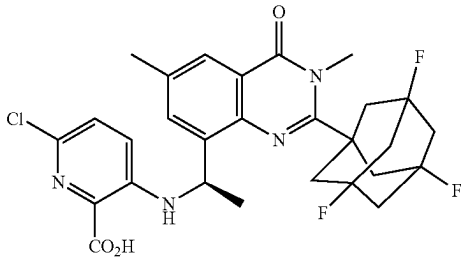
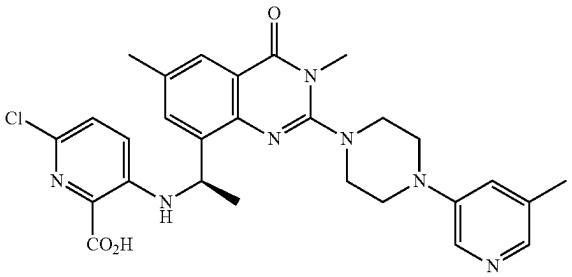
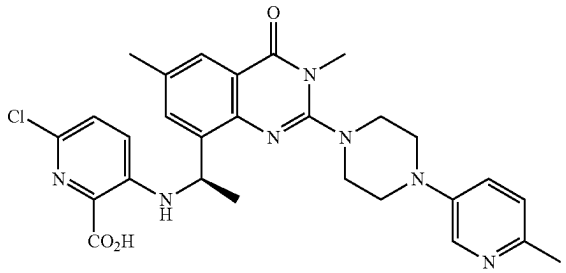
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
423		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.32 (s, 1H), 8.10 (d, J = 6.0 Hz, 1H), 7.73 (s, 1H), 7.48 (s, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 9.2 Hz, 2H), 6.77 (d, J = 6.0 Hz, 1H), 5.41-5.15 (m, 1H), 3.54 (s, 3H), 3.40-3.38 (m, 8H), 2.37 (s, 3H), 2.32 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).
424		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.71 (s, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.74 (s, 1H), 7.51 (s, 1H), 7.44-7.41 (m, 1H), 7.26-7.24 (m, 1H), 7.06-7.04 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.37-5.34 (m, 1H), 3.64-3.61 (m, 4H), 3.54 (s, 3H), 3.38-3.34 (m, 4H), 2.34 (s, 3H), 2.16 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H).
425		561.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.65 (s, 1H), 7.83 (s, 1H), 7.61 (s, 1H), 7.32-7.31 (m, 1H), 7.03-7.00 (m, 1H), 5.38-5.35 (m, 1H), 3.73 (s, 3H), 2.44-2.38 (m, 4H), 2.34-2.32 (m, 4H), 2.28-2.27 (m, 7H), 1.64-1.62 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −140.18 (3F).
426		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.41 (s, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.24 (t, J = 2.0 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 5.36 (t, J = 6.8 Hz, 1H), 3.54 (s, 3H), 3.42 (d, J = 3.2 Hz, 8H), 2.32 (s, 3H), 2.26 (s, 3H), 1.55 (d, J = 6.8 Hz, 3H).
427		548.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.01 (brs, 1H), 8.23 (d, J = 3.2 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 8.8, 3.2 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.96 (s, 1H), 5.53-5.23 (m, 1H), 3.54 (s, 3H), 3.50-3.38 (m 8H), 2.37 (s, 3H), 2.33 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

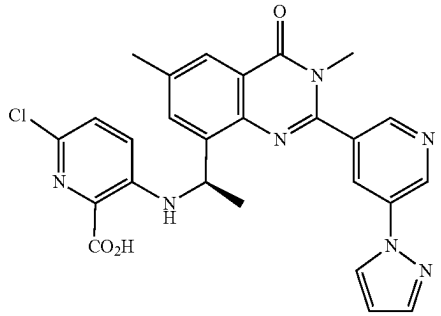
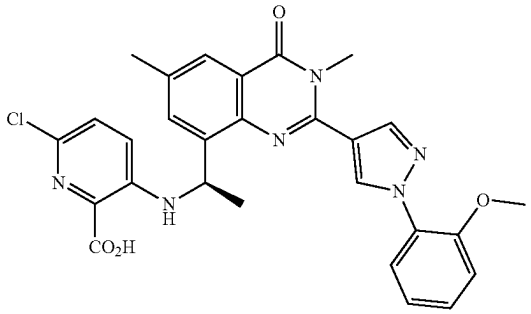
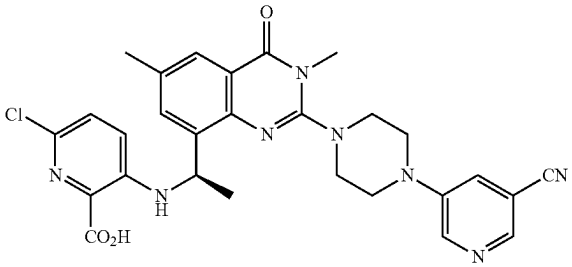
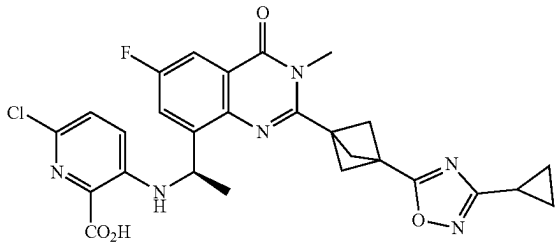
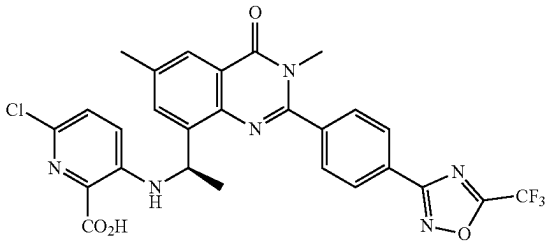
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
428		516.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.32 (d, J = 2.4 Hz, 1H), 8.92 (d, J = 1.6 Hz, 1H), 8.71 (d, J = 2.4 Hz, 1H), 8.67 (t, J = 2.0 Hz, 1H), 8.46 (d, J = 6.4 Hz, 1H), 7.94 (s, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 9.2 Hz, 1H), 6.69-6.64 (m, 1H), 5.48 (t, J = 6.8 Hz, 1H), 3.49 (s, 3H), 2.43 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
429		545.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.87 (s, 1H), 8.38 (s, 1H), 7.84 (s, 1H), 7.78-7.65 (m, 1H), 7.57 (s, 1H), 7.51-7.41 (m, 1H), 7.36-7.28 (m, 1H), 7.25-7.10 (m, 2H), 7.06-6.90 (m, 1H), 5.58-5.44 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 2.38 (s, 3H), 1.61 (s, 3H).
430		559.2	1H-NMR (400 MHz, DMSO-d6, ppm): δ 8.80 (brs, 1H), 8.67 (d, J = 3.2 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 7.88-7.86 (m, 1H), 7.75 (s, 1H), 7.51 (s, 1H), 7.26-7.18 (m, 1H), 7.10-6.95 (m, 1H), 5.40-5.30 (m, 1H), 3.58-3.38 (m, 11H), 2.33 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
431		551.2	1H NMR (400 MHz, DMSO-d6, ppm) δ 8.67-8.50 (m, 1H), 7.81-7.62 (m, 2H), 7.36 (d, J = 9.2 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 5.50-5.28 (m, 1H), 3.64 (s, 3H), 2.91-2.76 (m, 6H), 2.19-2.10 (m, 1H), 1.69 (d, J = 6.0 Hz, 3H), 1.13-1.01 (m, 2H), 0.96-0.84 (m, 2H). 19F NMR (376 MHz, DMSO-d6, ppm) δ −112.35 (1F).
432		585.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.07 (brs, 1H), 8.26 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.90 (s, 1H), 7.59 (s, 1H), 7.19-7.09 (m, 1H), 6.89-6.79 (m, 1H), 5.45-5.35 (m, 1H), 3.43 (s, 3H), 2.39 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −64.64 (3F).

TABLE 2-continued

Characterization of exemplary compounds.

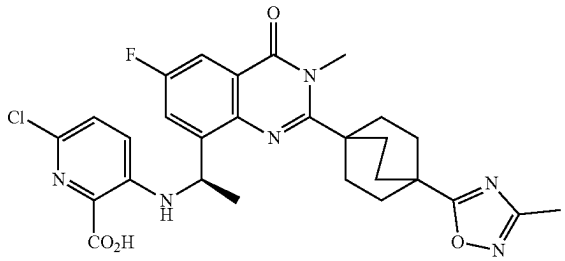
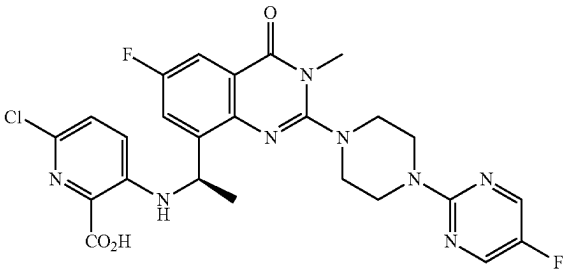
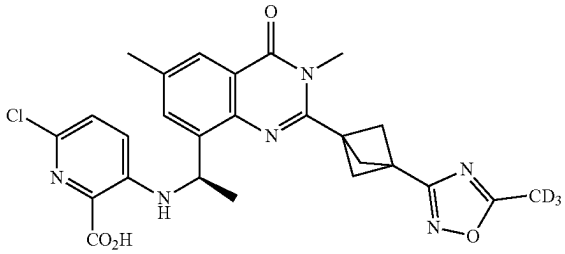
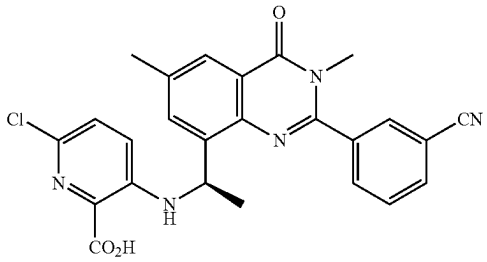
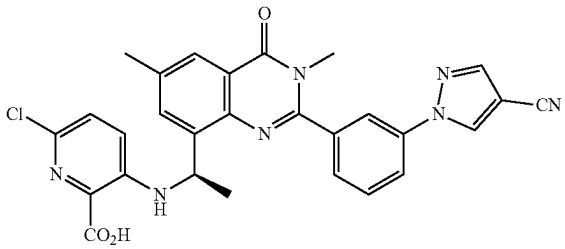
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
433		567.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.94 (brs, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.50-5.40 (m, 1H), 3.71 (s, 3H), 2.34 (s, 3H), 2.32-2.18 (m, 6H), 2.15-2.00 (m, 6H), 1.63 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.46 (1F).
434		557.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.33 (s, 2H), 7.70-7.60 (m, 1H), 7.49-7.39 (m, 1H), 7.21 (d, J = 9.2 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 5.52-5.41 (m, 1H), 4.05-3.92 (m, 4H), 3.66 (s, 3H), 3.48-3.37 (m, 4H), 1.69 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −117.05 (1F), −158.45 (1F).
435		524.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.56 (brs, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 5.43-5.32 (m, 1H), 3.65 (s, 3H), 2.80-2.66 (m, 6H), 2.39 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).
436		474.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.62 (brs, 1H), 8.29 (s, 1H), 8.18-8.03 (m, 2H), 7.91 (s, 1H), 7.85-7.75 (m, 1H), 7.61 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 5.55-5.40 (m, 1H), 3.40 (s, 3H), 2.41 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).
437		540.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.44 (s, 1H), 8.50-8.40 (m, 2H), 8.26 (s, 1H), 8.15-8.05 (m, 1H), 7.91 (s, 1H), 7.85-7.70 (m, 2H), 7.63 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H), 5.51-5.41 (m, 1H), 3.43 (s, 3H), 2.41 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

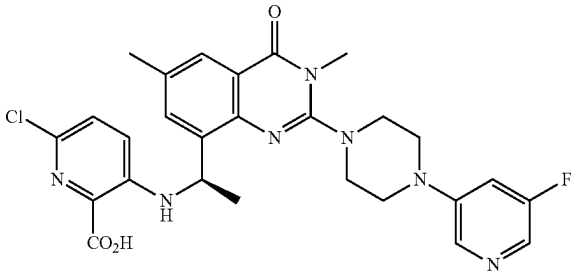
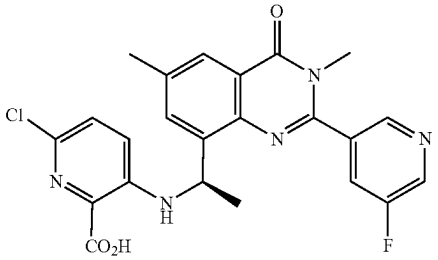
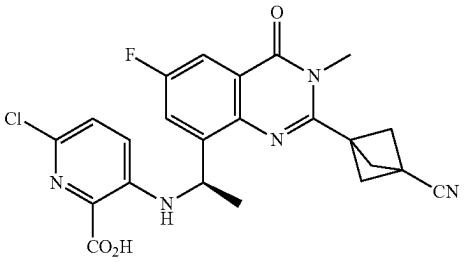
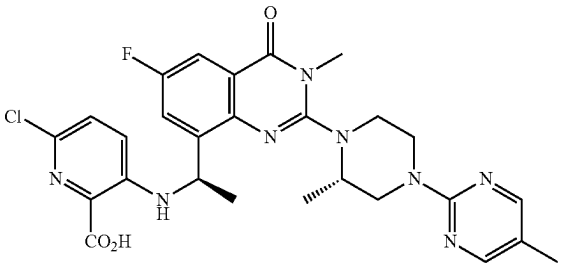
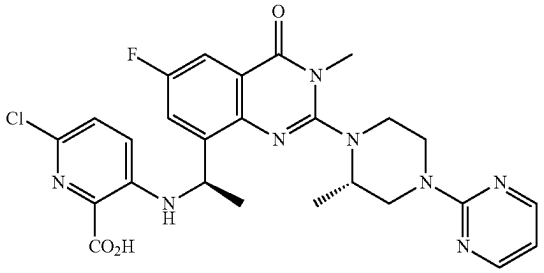
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
438		552.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.86 (s, 1H), 8.27 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.74 (s, 1H), 7.51 (s, 1H), 7.36-7.32 (m, 1H), 7.23-7.21 (m, 1H), 7.02-7.00 (m, 1H), 5.38-5.34 (m, 1H), 3.54 (s, 3H), 3.48-3.47 (m, 4H), 3.44-3.41 (m, 4H), 2.33 (s, 3H), 1.60-1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −127.77 (1F).
439		475.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.63 (brs, 1H), 9.28 (d, J = 2.4 Hz, 1H), 9.22 (d, J = 2.0 Hz, 1H), 8.83-8.81 (m, 1H), 8.29 (s, 1H, FA), 7.89 (s, 1H), 7.57 (s, 1H), 7.03-6.96 (m, 1H), 6.70 (brs, 1H), 5.43-5.33 (m, 1H), 3.44 (s, 3H), 2.39 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H).
440		468.2	^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 8.38 (d, J = 6.0 Hz, 1H), 7.79 (dd, J = 8.0, 2.4 Hz, 1H), 7.40 (dd, J = 8.4, 2.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.41-5.29 (m, 1H), 3.68 (s, 3H), 2.91-2.76 (m, 6H), 1.69 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, CDCl$_3$, ppm): δ −110.11 (1.0F).
441		567.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (s, 1H), 8.56 (s, 1H), 8.26 (d, J = 3.2 Hz, 2H), 7.66-7.54 (m, 2H), 7.26 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 5.39-5.31 (m, 1H), 4.22 (d, J = 12.4 Hz, 1H), 4.03 (dd, J = 12.8, 4.4 Hz, 1H), 3.89 (d, J = 8.4 Hz, 1H), 3.69 (dd, J = 12.8, 3.2 Hz, 1H), 3.59 (s, 2H), 3.55 (d, J = 3.2 Hz, 3H), 3.45 (t, J = 10.4 Hz, 2H), 2.10 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H), 1.16 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.62 (1.0F).
442		553.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (s, 1H), 8.48 (s, 1H), 8.40 (d, J = 4.4 Hz, 2H), 7.64-7.56 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.66 (t, J = 4.8 Hz, 1H), 5.36 (t, J = 6.8 Hz, 1H), 4.33-4.25 (m, 1H), 4.10 (dd J = 12.8, 4.4 Hz, 1H), 3.92 (dt, J = 7.6, 4.4 Hz, 1H), 3.73 (dd, J = 12.8, 3.2 Hz, 1H), 3.65-3.57 (m, 1H), 3.55 (s, 3H), 3.50-3.40 (m, 1H), 3.32 (s, 2H), 1.63 (d, J = 6.4 Hz, 3H), 1.16 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.62 (1.0F).

TABLE 2-continued

Characterization of exemplary compounds.

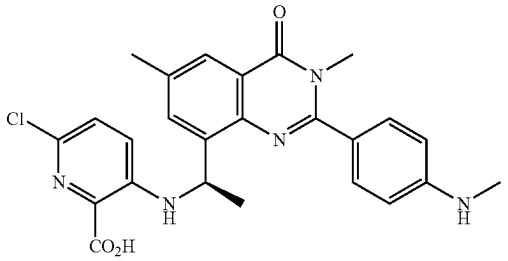
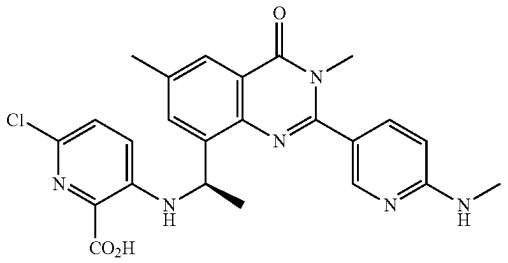
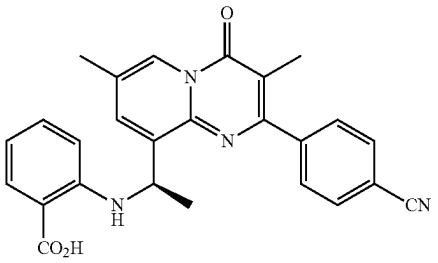
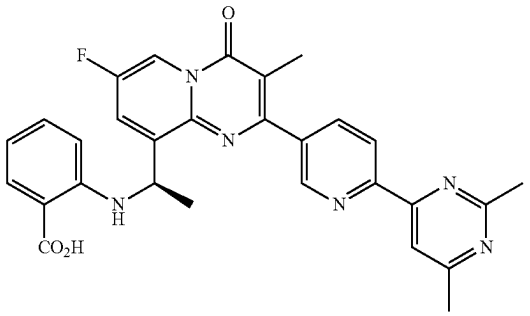
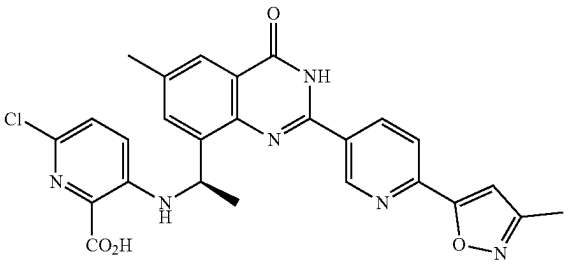
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
443		478.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.50-8.37 (m, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.68-7.51 (m, 3H), 7.29 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 6.28 (s, 1H), 5.50-5.47 (m, 1H), 3.51 (s, 3H), 2.76 (s, 3H), 2.38 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
444		479.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.55 (s, 1H), 8.53 (s, 1H), 7.89 (s, 2H), 7.56 (s, 1H), 7.23-7.04 (m, 2H), 6.86-6.55 (m, 2H), 5.49 (s, 1H), 3.58 (s, 3H), 2.92 (d, J = 4.8 Hz, 3H), 2.41 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
445		439.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.72 (s, 1H), 8.52 (s, 1H), 8.06-7.97 (m, 2H), 7.96-7.90 (m, 2H), 7.87-7.78 (m, 1H), 7.72-7.64 (m, 1H), 7.22-7.12 (m, 1H), 6.58-6.48 (m, 1H), 6.37-6.29 (m, 1H), 5.43-5.31 (m, 1H), 2.34 (s, 3H), 2.21 (s, 3H), 1.71-1.51 (m, 3H).
446		521.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.7 (brs, 1H), 9.12 (s, 1H), 8.82-8.32 (m, 4H), 8.13 (s, 1H), 7.90-7.61 (m, 2H), 7.17 (s, 1H), 6.66-6.23 (m, 2H), 5.40 (s, 1H), 2.69 (s, 3H), 2.55 (s, 3H), 2.40-2.25 (m, 6H), 1.62 (s, 3H).
447		517.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.51 (s, 1H), 8.79-8.76 (m, 1H), 8.22 (s, 1H), 8.12-8.10 (m, 1H), 7.90-7.82 (m, 1H), 7.56 (s, 1H), 7.12 (s, 1H), 7.05-7.03 (m, 1H), 6.81-6.80 (m, 1H), 5.58-5.55 (m, 1H), 2.41-2.36 (m, 3H), 2.36-2.34 (m, 3H), 1.60 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

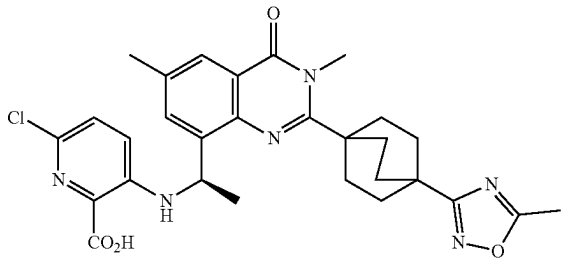
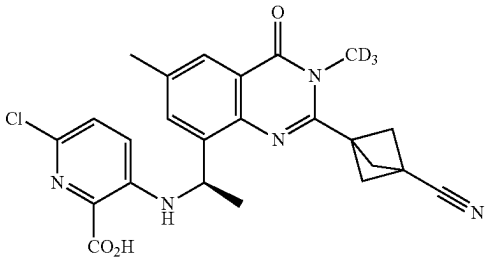
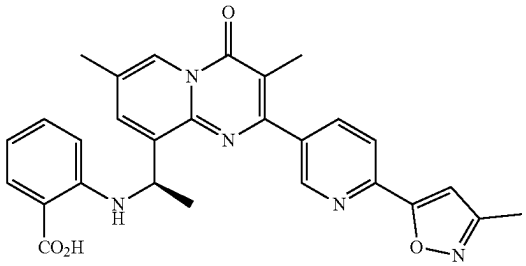
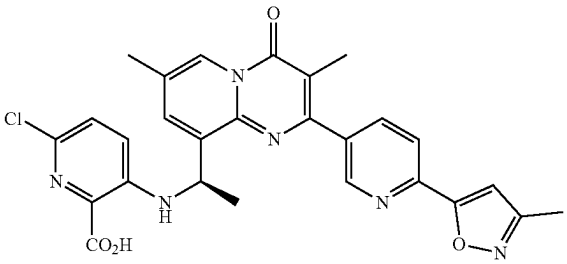
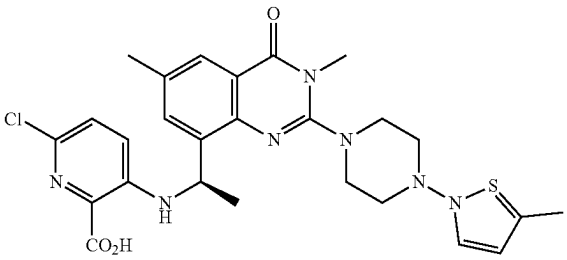
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
448		563.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.40 (brs, 1H), 8.23 (s, 1H, FA), 7.78 (s, 1H), 7.49 (s, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.59-5.26 (m, 1H), 3.71 (s, 3H), 2.56 (s, 3H), 2.34 (s, 3H), 2.25 (d, J = 5.2 Hz, 6H), 1.98 (t, J = 7.6 Hz, 6H), 1.55 (d, J = 6.4 Hz, 3H).
449		467.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (brs, 1H), 8.68 (brs, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.16 (s, 1H), 5.43-5.24 (m, 1H), 2.90-2.87 (m, 3H), 2.82-2.80 (m, 3H), 2.39 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).
450		496.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.31 (d, J = 6.8 Hz, 1H), 9.10 (d, J = 2.4 Hz, 1H), 8.71 (s, 1H), 8.37 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.78 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.08 (s, 1H), 6.90-6.78 (m, 1H), 6.40-6.27 (m, 1H), 6.06 (d, J = 8.4 Hz, 1H), 5.40-5.20 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H).
451		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.01 (d, J = 6.8 Hz, 1H), 9.10 (d, J = 1.6 Hz, 1H), 8.72 (s, 1H), 8.38 (dd, J = 8.0, 2.0 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.08 (s, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.35-5.22 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 2.29 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).
452		536.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.86 (s, 1H), 7.73 (s, 1H), 7.67 (d, J = 2.4 Hz, 1 H), 7.50 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 6.8 Hz, 1H), 6.02 (d, J = 1.60 Hz, 1H), 5.42-5.31 (m, 1H), 4.42-4.28 (m, 1H), 3.79-3.63 (m, 2H), 3.52 (s, 3H), 3.18-2.98 (m, 3H), 2.34 (s, 3H), 2.16 (s, 3H), 2.14-1.98 (m, 3H), 1.58 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

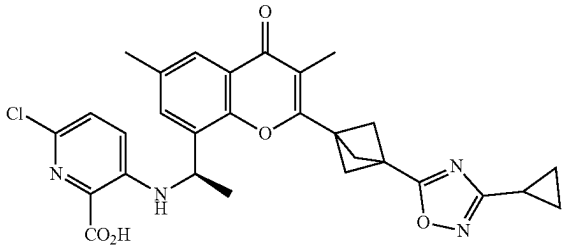
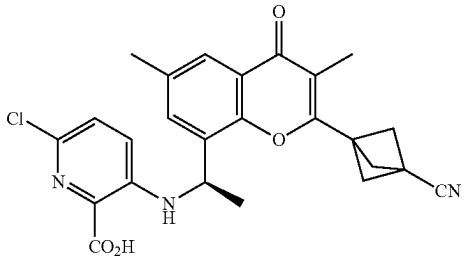
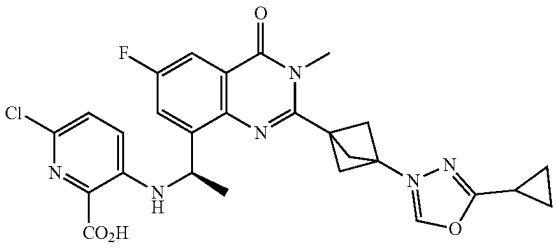
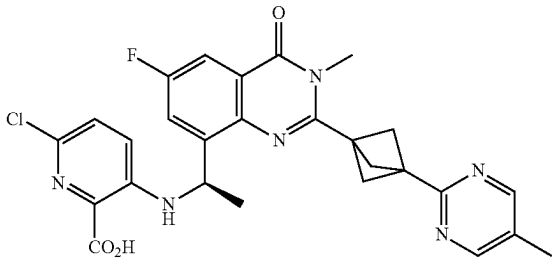
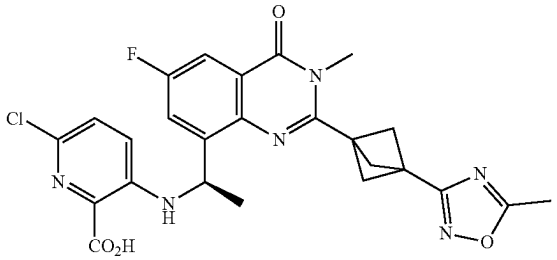
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
453		547.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.09 (brs, 1H), 8.47 (brs, 1H), 7.71 (s, 1H), 7.54 (s, 1H), 7.41-7.27 (m, 1H), 7.17-7.03 (m, 1H), 5.21-5.07 (m, 1H), 2.92-2.72 (m, 6H), 2.35 (s, 3H), 2.19-2.10 (m, 1H), 2.05 (s, 3H), 1.72-1.56 (m, 3 H), 1.14-1.01 (m, 2H), 0.97-0.83 (m, 2H).
454		464.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.13 (brs, 1H), 8.45-8.35 (m, 1H), 7.73-7.67 (m, 1H), 7.58-7.53 (m, 1H), 7.40-7.33 (m, 1H), 7.13-7.06 (m, 1H), 5.20-5.05 (m, 1H), 2.88-2.81 (m, 6H), 2.34 (s, 3H), 2.00 (s, 3H), 1.63 (d, J = 6.4 Hz, 3 H).
456		551.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.96 (brs, 1H), 8.63-8.47 (m, 1H), 7.76 (dd, J = 9.2, 2.4 Hz, 1H), 7.69 (dd, J = 8.4, 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 5.47-5.34 (m, 1H), 3.65 (s, 3H), 2.78-2.66 (m, 6H), 2.39-2.30 (m, 1H), 1.70 (d, J = 6.4 Hz, 3H), 1.28-1.21 (m, 2H), 1.15-1.08 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d$_6$): δ −112.46 (1F).
457		535.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.97 (brs, 1H), 8.64 (s, 2H), 8.61-8.54 (m, 1H), 7.78-7.72 (m, 1H), 7.71-7.66 (m, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 5.47-5.37 (m, 1H), 3.68 (s, 3H), 2.78-2.65 (m, 6H), 2.28 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.64 (1F).
458		525.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.74-8.54 (m, 1H), 7.79-7.64 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 5.50-5.32 (m, 1H), 3.66 (s, 3H), 2.82-2.68 (m, 6H), 2.60 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.46 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

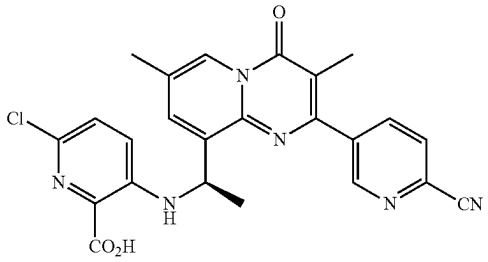
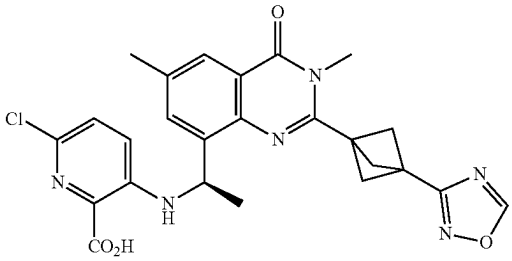
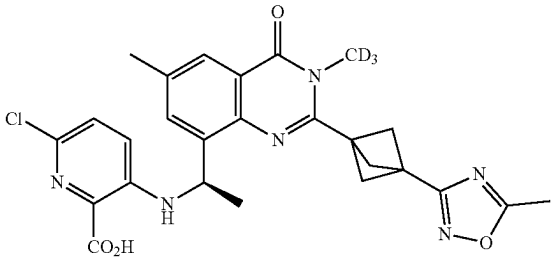
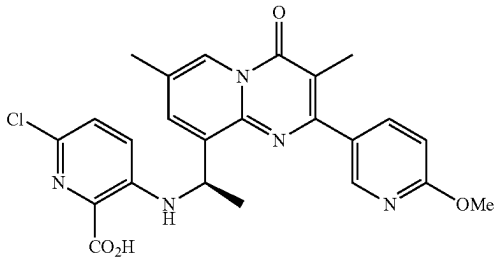
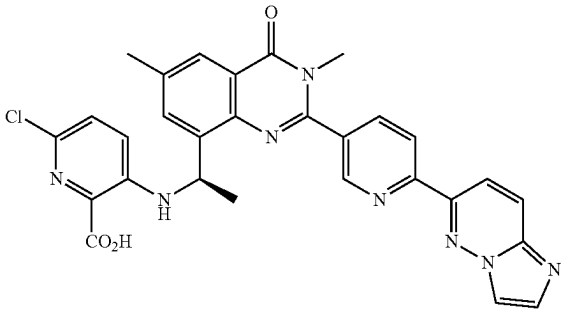
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
459		475.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.12 (d, J = 1.2 Hz, 1H), 8.74 (s, 1H), 8.62 (s, 1H), 8.43-8.40 (m, 1H), 8.24-8.16 (m, 1H), 7.76 (s, 1H), 7.25-7.23 (m, 1H), 6.96-6.94 (m, 1H), 5.37-5.34 (m, 1H), 2.36 (s, 3H), 2.24 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).
460		507.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 12.97 (brs, 1H), 9.62 (s, 1H), 8.77 (s, 1H), 7.82 (s, 1H), 7.64 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 5.44-5.31 (m, 1H), 3.66 (s, 3H), 2.86-2.71 (m, 6H), 2.39 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H).
461		524.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 12.93 (brs, 1H), 8.56 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.67 (d, J = 1.2 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 5.43-5.24 (m, 1H), 2.78-2.73 (m, 6H), 2.60 (s, 3H), 2.40 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).
462		480.0	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.69 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.50 (s, 1H), 8.11-8.08 (m, 1H), 7.70 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.98-6.93 (m, 2H), 5.40-5.37 (m, 1H), 3.93 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).
463		567.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.18 (s, 1H), 8.53-8.42 (m, 4H), 8.34 (d, J = 9.2 Hz, 1H), 8.25 (d, J = 9.2 Hz, 1H), 7.93 (s, 2H), 7.66 (s, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 5.53-5.42 (m, 1H), 3.51 (s, 3H), 2.43 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

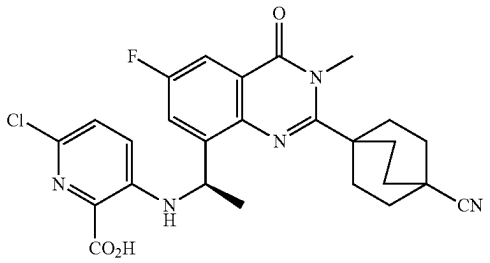
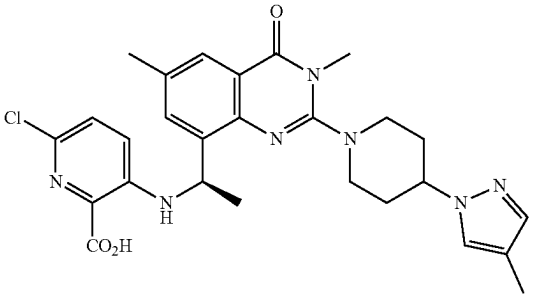
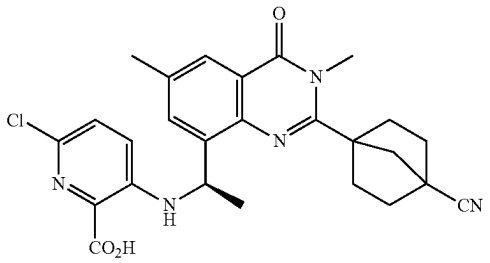
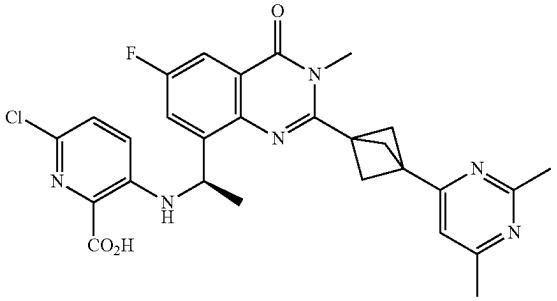
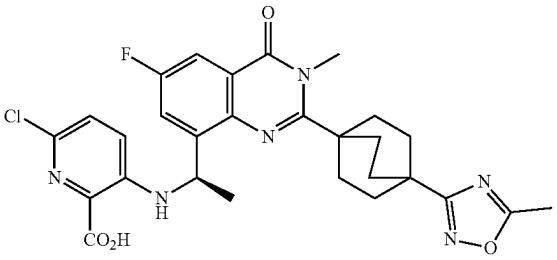
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
464		510.2	As 1.0 TFA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 13.03 (brs, 1H), 8.40 (d, J = 8.4 Hz, 1H), 7.70-7.60 (m, 2H), 7.33 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 5.50-5.40 (m, 1H), 3.67 (s, 3H), 2.25-1.90 (m, 12H), 1.65 (d, J = 6.8 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −73.76 (3F), −112.34 (1F).
465		536.3	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.62 (s, 1H), 7.74 (s, 1H), 7.57 (s, 1H), 7.52 (d, J = 1.2 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.25 (s, 1H), 7.08 (d, J = 8.8 Hz, 1H), 5.43-5.33 (m, 1H), 4.43-4.29 (m, 1H), 3.71 (d, J = 12.80 Hz, 2H), 3.51 (s, 3H), 3.18-2.98 (m, 2H), 2.34 (s, 3H), 2.24-2.06 (m, 4H), 2.01 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
466		492.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 12.95 (s, 1H), 8.49 (s, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.36-7.34 (m, 1H), 7.14-7.11 (m, 1H), 5.42-5.38 (m, 1H), 3.58 (s, 3H), 2.67-2.65 (m, 1H), 2.44-2.42 (m, 1H), 2.38 (s, 3H), 2.28-2.14 (m, 4H), 2.04-2.00 (m, 4H), 1.65 (d, J = 6.4 Hz, 3H).
467		549.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.07-8.74 (m, 1H), 7.74-7.62 (m, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 5.52-5.38 (m, 1H), 3.70 (s, 3H), 2.75-2.64 (m, 6H), 2.58 (s, 3H), 2.44 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −112.52 (1F).
468		567.3	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.40 (brs, 1H), 7.72-7.60 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 5.55-5.40 (m, 1H), 3.71 (s, 3H), 2.56 (s, 3H), 2.35-2.15 (m, 6H), 2.05-1.95 (m, 6H), 1.67 (d, J = Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −112.50 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

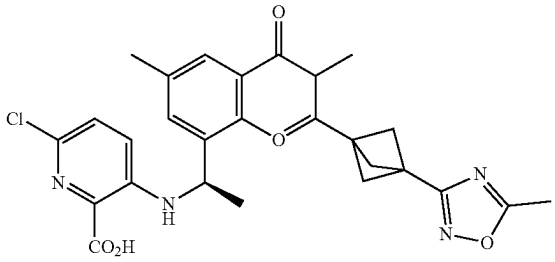
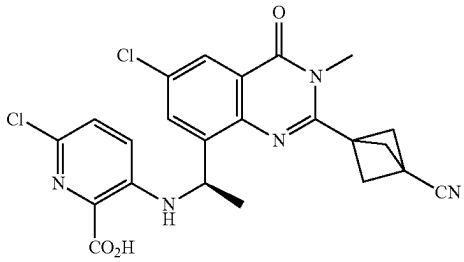
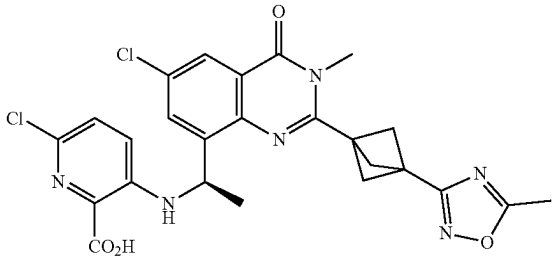
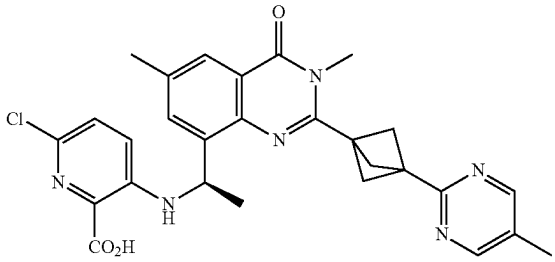
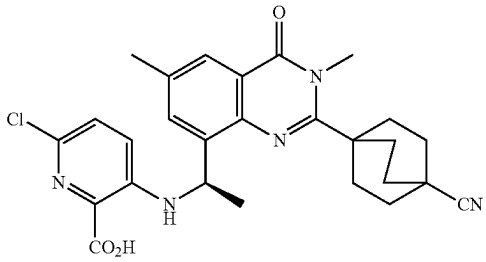
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
469		521.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.07 (brs, 1H), 8.44 (brs, 1H), 7.74-7.68 (m, 1H), 7.58-7.51 (m, 1H), 7.39-7.31 (m, 1H), 7.16-7.07 (m, 1H), 5.24-5.05 (m, 1H), 2.74-2.69 (m, 6H), 2.59 (s, 3H), 2.35 (s, 3H), 2.06 (s, 3H), 1.65 (d, J = 6.8 Hz, 3 H).
470		484.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.61-8.50 (m, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.36-5.32 (m, 1H), 3.58 (s, 3H), 2.91 (d, J = 9.2 Hz, 3H), 2.83 (d, J = 9.2 Hz, 3H), 1.68 (d, J = 6.8 Hz, 3H).
471		541.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.63 (s, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 5.39-5.36 (m, 1H), 3.66 (s, 3H), 2.79 (d, J = 9.2 Hz, 3H), 2.72 (d, J = 9.2 Hz, 3H), 2.60 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H).
472		531.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.62 (s, 2H), 8.57 (s, 1H), 7.83 (s, 1H), 7.66 (s, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 9.2 Hz, 1H), 5.47-5.30 (m, 1H), 3.68 (s, 3H), 2.78-2.62 (m, 6H), 2.40 (s, 3H), 2.28 (s, 3H), 1.68 (d, J = 6.8 Hz, 3H).
473		506.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.48 (brs, 1H), 8.28 (s, 1H, FA), 7.77 (s, 1H), 7.48 (s, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.71-6.68 (m, 1H), 5.42-5.37 (m, 1H), 3.84 (s, 3H), 2.33 (s, 3H), 2.20-2.17 (m, 6H), 2.12-2.03 (m, 6H), 1.53 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

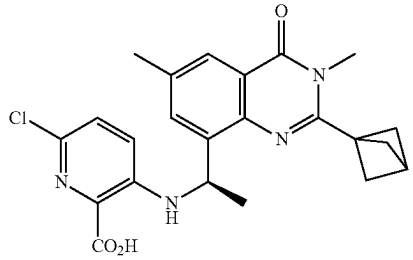
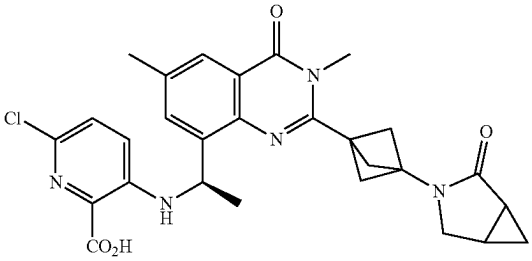
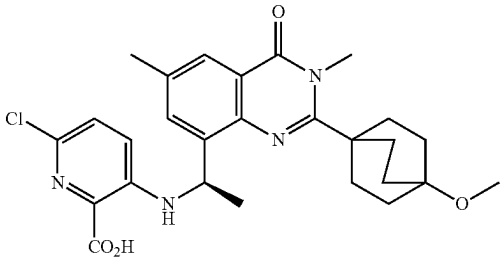
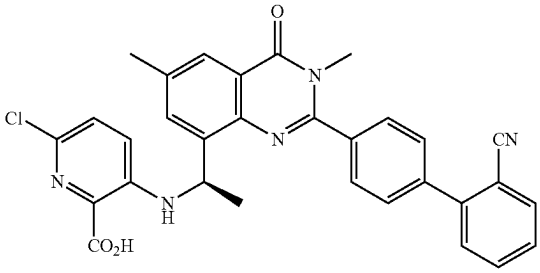
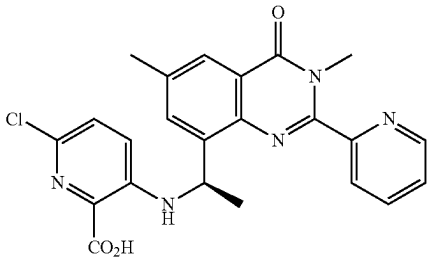
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
474		459.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.52 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 5.42-5.35 (m, 1H), 3.63 (s, 3H), 2.61 (s, 1H), 2.47-2.32 (m, 6H), 1.68 (d, J = 6.8 Hz, 3H).
475		534.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.68 (brs, 1H), 7.77 (s, 1H), 7.49 (s, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.43-5.32 (m, 1H), 3.62-3.45 (m, 4H), 3.41-3.25 (m, 1H), 2.62-2.51 (m, 6H), 2.33 (s, 3H), 1.99-1.86 (m, 1H), 1.85-1.70 (m, 1H), 1.51 (d, J = 6.8 Hz, 3H), 1.15-1.01 (m, 1H), 0.57-0.44 (m, 1H).
476		511.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.47 (brs, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.51-5.32 (m, 1H), 3.66 (s, 3H), 3.11 (s, 3H), 2.36 (s, 3H), 2.31-2.15 (m, 6H), 1.85-1.65 (m, 6H), 1.60 (d, J = 6.8 Hz, 3H).
477		550.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.02 (d, J = 7.6 Hz, 1H), 8.00-7.90 (m, 2H), 7.89 (s, 1H), 7.88-7.78 (m, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.72-7.61 (m, 1H), 7.58 (brs, 1H), 7.20-7.05 (m, 1H), 6.90-6.70 (m, 1H), 5.55-5.40 (m, 1H), 3.47 (s, 3H), 2.40 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H).
478		450.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.01 (d, J = 7.2 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.16-8.00 (m, 2H), 7.88 (s, 1H), 7.65-7.55 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 5.38-5.28 (m, 1H), 3.50 (s, 3H), 2.38 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

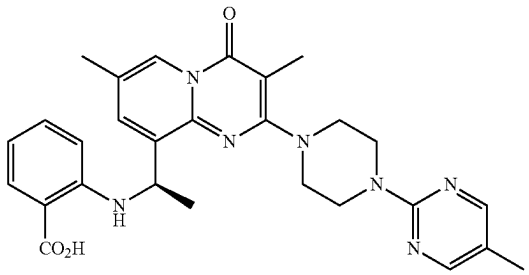
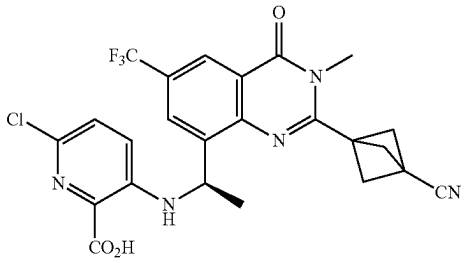
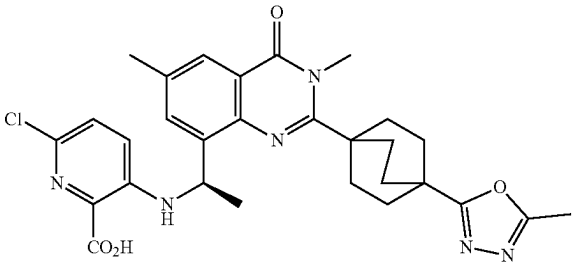
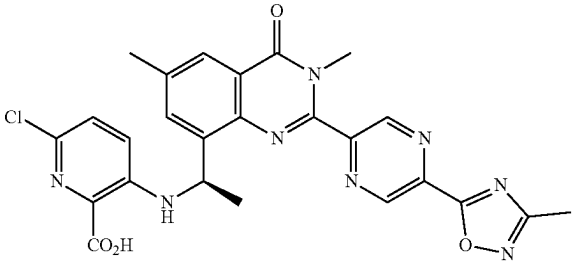
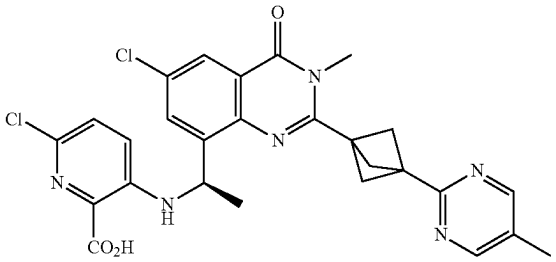
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
479		514.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.83 (s, 1H), 8.59 (s, 1H), 8.26 (s, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.13-7.10 (m, 1H), 6.51-6.47 (m, 1H), 6.30 (d, J = 8.4 Hz, 1H), 5.29-5.28 (m, 1H), 3.85-3.80 (m, 4H), 3.52-3.50 (m, 4H), 2.27 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
481		518.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.66 (s, 1H), 8.25 (s, 1H), 8.19 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 5.57-5.25 (m, 1H), 3.60 (s, 3H), 2.94 (dd, J = 9.2, 1.2 Hz, 3H), 2.86 (d, J = 9.2 Hz, 3H), 1.71 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −60.83 (3F).
482		563.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.98 (brs, 1H), 8.51 (s, 1H), 7.80 (s, 1H), 7.58 (s, 1H), 7.38-7.25 (m, 1H), 7.11-6.94 (m, 1H), 5.54-5.33 (m, 1H), 3.70 (s, 3H), 2.47 (s, 3H), 2.37 (s, 3H), 2.32-2.17 (m, 6H), 2.11-1.93 (m, 6H). 1.63 (d, J = 6.4 Hz, 3H).
483		533.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.53-9.50 (m, 2H), 7.94 (s, 1H), 7.65 (s, 1H), 7.13 (s, 1H), 6.91 (s, 1H), 5.46-5.43 (m, 1H), 3.61 (s, 3H), 2.53 (s, 3H), 2.42 (s, 3H), 1.59 (s, 3H).
484		551.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.64 (s, 2H), 7.95 (d, J = 2.4 Hz, 1H), 7.85-7.80 (m, 1H), 7.29-7.27 (m, 1H), 7.15-7.05 (m, 1H), 5.41 (t, J = 6.4 Hz, 1H), 3.68 (s, 3H), 2.75-2.67 (m, 6H), 2.28 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

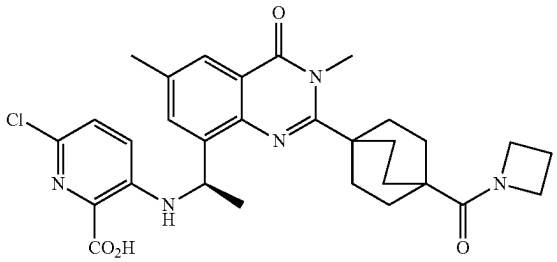
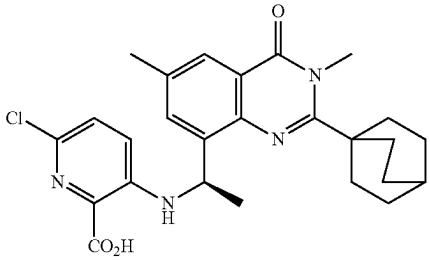
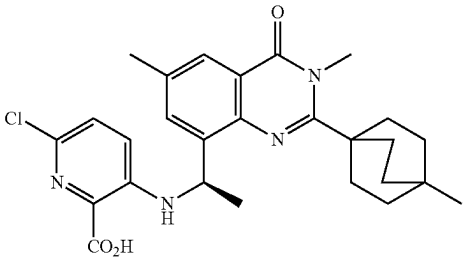
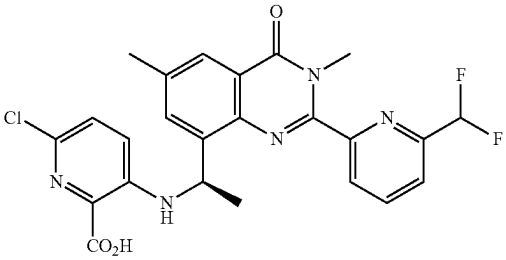
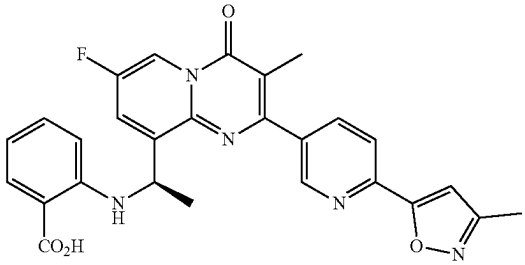
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
485		564.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.73 (s, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.42 (t, J = 6.6 Hz, 1H), 4.37 (s, 2H), 3.83 (d, J = 8.8 Hz, 2H), 3.67 (s, 3H), 2.35 (s, 3H), 2.14-2.12 (m, 8H), 1.84 (t, J = 7.6 Hz, 6H), 1.58 (d, J = 6.4 Hz, 3H).
486		481.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.48 (brs, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 5.52-5.40 (m, 1H), 3.68 (s, 3H), 2.36 (s, 3H), 2.20-2.00 (m, 6H), 1.76-1.65 (m, 7H), 1.61 (d, J = 6.4 Hz, 3H).
487		495.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.45-8.35 (m, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 5.50-5.37 (m, 1H), 3.67 (s, 3H), 2.36 (s, 3H), 2.20-2.03 (m, 6H), 1.62 (d, J = 6.4 Hz, 3H), 1.54-1.43 (m, 6H), 0.86 (s, 3H).
488		500.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.42 (d, J = 6.8 Hz, 1H), 8.30 (t, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.97-7.89 (m, 2H), 7.65 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.09 (t, J = 54.8 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H), 5.51-5.42 (m, 1H), 3.51 (s, 3H), 2.42 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.91 (2F).
489		500.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.35-10.25 (m, 1H), 9.10 (s, 1H), 8.83 (s, 1H), 8.42-8.30 (m, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.85-7.70 (m, 2H), 7.08 (s, 1H), 6.91-6.79 (m, 1H), 6.37 (t, J = 7.2 Hz, 1H), 6.13 (d, J = 8.0 Hz, 1H), 5.40-5.25 (m, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 1.65-1.50 (m, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −132.65 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

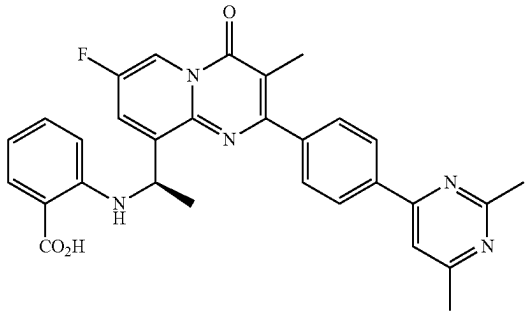
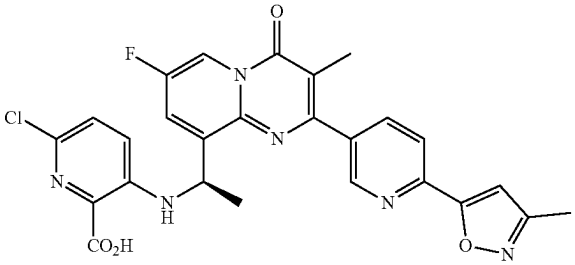
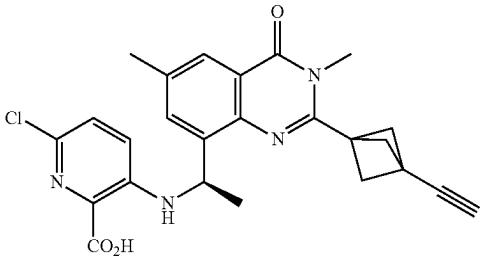
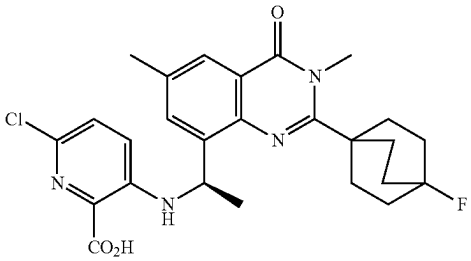
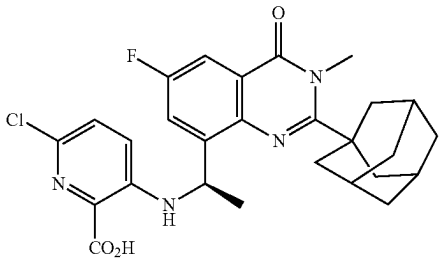
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
490		524.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 10.28 (d, J = 7.6 Hz, 1H), 8.86-8.75 (m, 1H), 8.34 (d, J = 8.4 Hz, 2H), 7.97-7.86 (m, 3H), 7.87-7.77 (m, 1H), 7.76-7.66 (m, 1H), 6.88-6.77 (m, 1H), 6.42-6.32 (m, 1H), 6.15-6.05 (m, 1H), 5.37-5.27 (m, 1H), 3.32 (s, 3H), 2.67 (s, 3H), 2.29 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H).
491		535.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 10.07 (d, J = 7.2 Hz, 1H), 9.11 (d, J = 1.6 Hz, 1H), 8.90-8.80 (m, 1H), 8.46-8.35 (m, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.81-7.70 (m, 1H), 7.09 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.34-5.22 (m, 1H), 2.36 (s, 3H), 2,31 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −132.66 (1F).
492		463.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.51 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 7.66 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 5.41-5.29 (m, 1H), 3.58 (s, 3H), 3.22 (s, 1H), 2.66 (d, J = 9.2 Hz, 3H), 2.58 (d, J = 9.2 Hz, 3H), 2.39 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H).
493		499.2	As 1.0 TFA salt. 1H NMR (400 MHz, DMSO-d6, ppm): δ 8.42 (d, J =32 6.8 Hz, 1H), 7.79 (s, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 5.50-5.36 (m, 1H), 3.66 (s, 3H), 2.41-2.22 (m, 9H), 1.95-1.85 (m, 6H), 1.62 (d, J = 6.4 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −74.95 (3F, TFA), −148.25 (1F).
494		511.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.41 (d, J = 6.0 Hz, 1H), 7.70-7.60 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 5.55-5.44 (m, 1H), 3.76 (s, 3H), 2.30-2.16 (m, 6H), 2.11 (s, 3H), 1.87-1.70 (m, 6H), 1.67 (d, J = 6.4 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −112.58 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

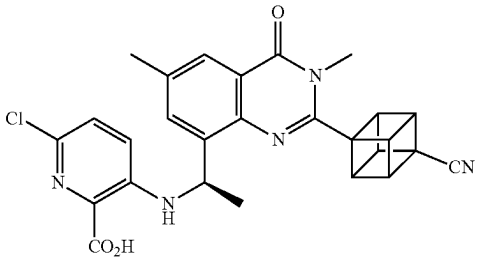
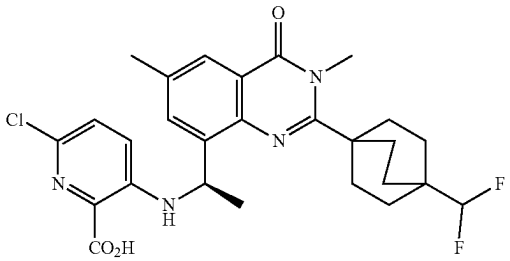
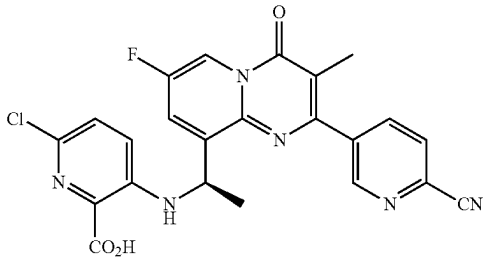
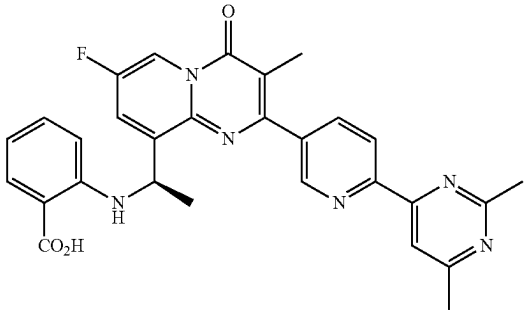
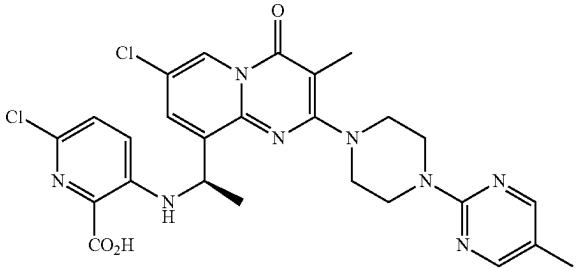
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
495		500.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.22 (s, 1H), 7.81 (s, 1H), 7.52 (s, 1H), 7.13-6.98 (m, 1H), 6.84-6.65 (m, 1H), 5.48-5.35 (m, 1H), 4.69-4.58 (m, 3H), 4.53-4.40 (m, 3H), 3.41 (s, 3H), 2.35 (s, 3H), 1.55 (d, J = 6.4 Hz, 3H).
496		531.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 12.97 (s, 1H), 8.46 (s, 1H), 7.80 (s, 1H), 7.58 (s, 1H), 7.34-7.32 (m, 1H), 7.05-7.02 (m, 1H), 5.92-5.64 (m, 1H), 5.54-5.33 (m, 1H), 3.68 (s, 3H), 2.37 (s, 3H), 2.17-2.13 (m, 6H), 1.66-1.62 (m, 9H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −128.31 (2F).
497		479.0	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.13 (s, 1H), 8.89-8.85 (m, 1H), 8.46-8.41 (m, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.20 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 5.33 (s, 1H), 2.26 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −132.39 (1F).
498		525.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.12 (d, J = 1.6 Hz, 1H), 8.89-8.84 (m, 1H), 8.59 (d, J = 8.4 Hz, 2H), 8.42-8.36 (m, 1H), 8.14 (s, 1H), 7.89-7.79 (m, 2H), 7.22-7.14 (m, 1H), 6.61-6.52 (m, 1H), 6.39 (d, J = 8.8 Hz, 1H), 5.40 (s, 1H), 2.70 (s, 3H), 2.56 (s, 3H), 2.32 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −132.79 (1F).
499		569.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.87 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.26 (s, 2H), 7.70 (s, 1H), 7.23-7.21 (m, 1H), 6.93-6.91 (m, 1H), 5.24-5.21 (m, 1H), 3.86-3.83 (m, 4H), 3.56-3.55 (m, 4H), 2.14 (s, 3H), 2.10 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

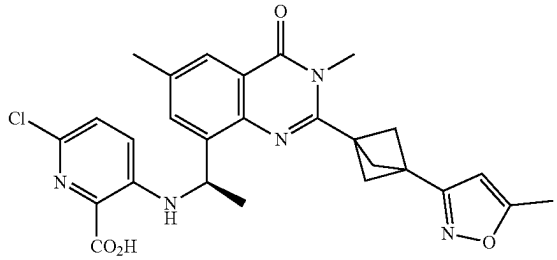
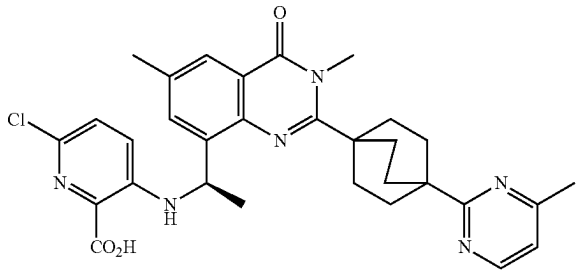
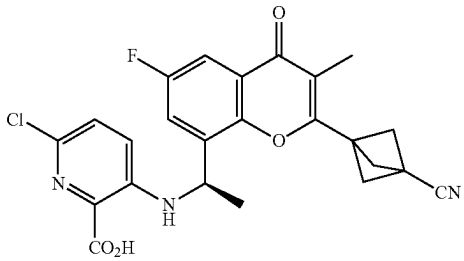
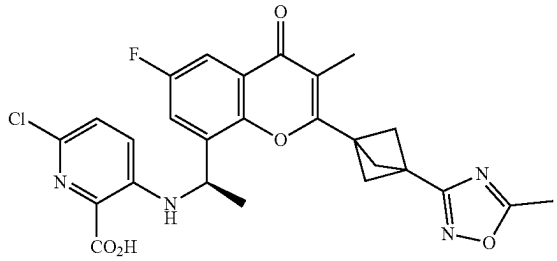
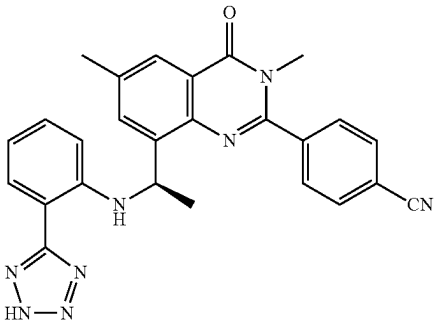
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
500		520.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.43 (s, 1H), 7.79 (s, 1H), 7.54 (s, 1H), 7.09 (s, 1H), 6.84 (s, 1H), 6.27 (s, 1H), 5.46-5.33 (m, 1H), 3.65 (s, 3H), 2.68-2.61 (m, 6H), 2.39 (s, 3H), 2.36 (s, 3H), 1.57 (d, J = 6.0 Hz, 3H).
501		573.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.59 (d, J = 5.2 Hz, 1H), 7.79 (s, 1H), 7.53 (s, 1H), 7.22-7.11 (m, 2H), 6.91-6.71 (m, 1H), 5.51-5.49 (m, 1H), 3.72 (s, 3H), 2.45 (s, 3H), 2.35 (s, 3H), 2.34-2.31 (m, 6H), 2.25-2.04 (m, 6H), 1.61-1.57 (m, 3H).
502		468.0	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.95-8.67 (m, 1H), 7.63-7.50 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.21-5.02 (m, 1H), 2.90-2.81 (m, 6H), 2.01 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −115.22 (1F).
503		525.1	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.60-8.40 (m, 1H), 7.64-7.55 (m, 2H), 7.33 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 5.25-5.12 (m, 1H), 2.77-2.69 (m, 6H), 2.59 (s, 3H), 2.07 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).
504		463.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.65 (brs, 1H), 8.21-7.83 (m, 6H), 7.68-7.54 (m, 1H), 7.02-6.91 (m, 1H), 6.63-6.51 (m, 1H), 6.43-6.32 (m, 1H), 5.58-5.42 (m, 1H), 3.40 (s, 3H), 2.35 (s, 3H), 1.59 (d, J = 6.0 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

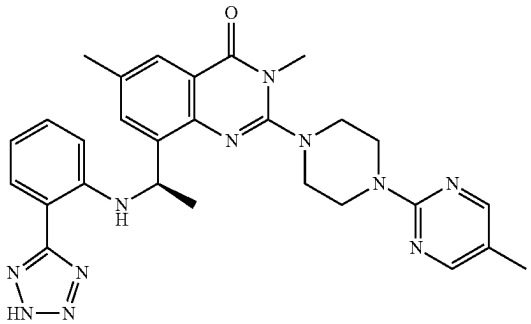
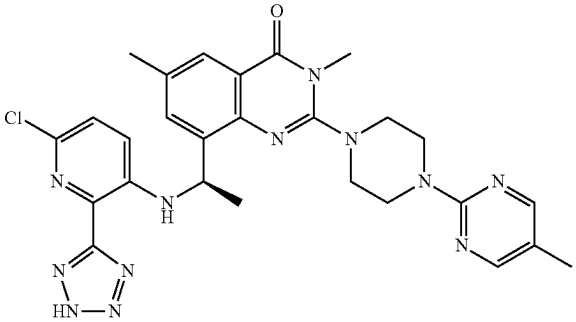
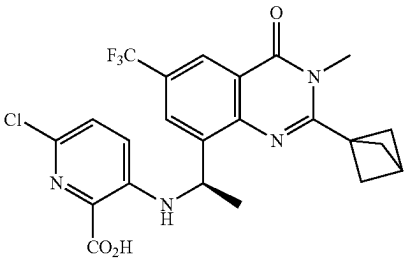
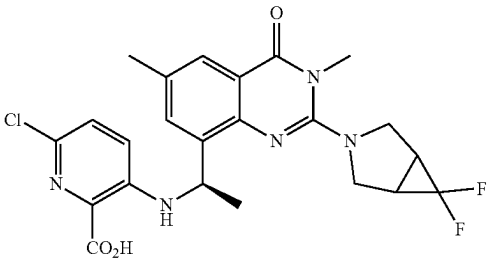
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
505		538.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.27 (s, 2H), 7.80-7.69 (m, 2H), 7.51 (s, 1H), 7.20-7.10 (m, 1H), 6.70-6.60 (m, 2H), 5.50-5.40 (m, 1H), 3.92-3.80 (m, 4H), 3.55 (s, 3H), 3.40-3.30 (m, 4H), 2.30 (s, 3H), 2.10 (s, 3H), 1.70-1.60 (m, 3H)
507		573.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.40 (s, 1 H), 8.27 (s, 2 H), 7.75 (s, 1 H), 7.54 (s, 1 H), 7.28 (d, J = 9.2 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 1 H), 5.50-5.38 (m, 1 H), 3.90 (s, 4 H), 3.55 (s, 3 H), 3.36 (s, 4 H), 2.31 (s, 3 H), 2.10 (s, 3 H), 1.70 (d, J = 6.8 Hz, 3 H).
508		493.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.55 (s, 1H), 8.22 (s, 1H), 7.91 (s, 1H), 7.08 (s, 1H), 6.80 (s, 1H), 5.63-5.22 (m, 1H), 3.65 (s, 3H), 2.61 (s, 1H), 2.41 (q, J = 9.2 Hz, 6H), 1.61 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −60.91 (3F).
509		490.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.52 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H), 5.62-5.00 (m, 1H), 4.17 (d, J = 11.2 Hz, 1H), 4.03 (d, J = 11.2 Hz, 1H), 3.95-3.78 (m, 2H), 3.44 (s, 3H), 2.64 (d, J = 10.8 Hz, 2H), 2.31 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm) δ −127.31 (1F), −150.95 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

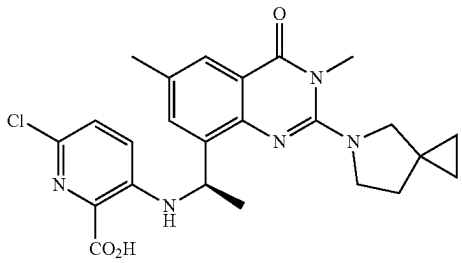
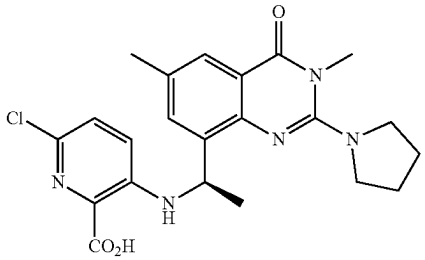
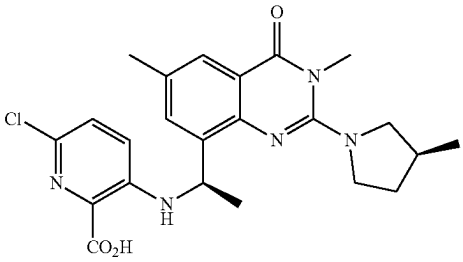
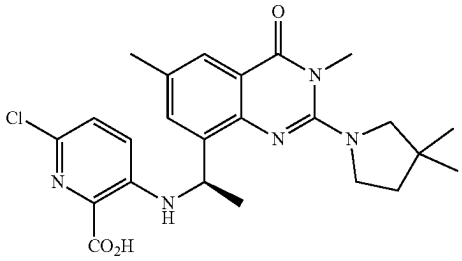
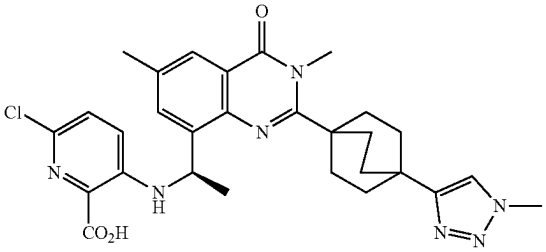
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
510		468.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.94 (brs, 1H), 8.42 (d, J = 6.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 5.32 (t, J = 6.8 Hz, 1H), 3.75 (t, J = 6.2 Hz, 2H), 3.50-3.47 (m, 2H), 3.46 (s, 3H), 2.30 (s, 3H), 1.89-1.82 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H), 0.63-0.61 (m, 4H).
511		442.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.57 (s, 1H), 7.66 (s, 1H), 7.55-7.21 (m, 2H), 7.03 (s, 1H), 5.29-5.28 (m, 1H), 3.64-3.51 (m, 4H), 3.46 (s, 3H), 2.29 (s, 3H), 1.99-1.79 (m, 4H), 1.59 (s, 3H).
512		456.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.67 (s, 1H), 7.66 (s, 1H), 7.39 (s, 1H), 7.33-7.11 (m, 1H), 7.06-6.80 (m, 1H), 5.33-5.18 (m, 1H), 3.72-3.57 (m, 3H), 3.45 (s, 3H), 3.25-3.17 (m, 1H), 2.35-2.21 (m, 4H), 2.10-1.98 (m, 1H), 1.62-1.46 (m, 4H), 1.15-1.02 (m, 3H).
513		470.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.59 (s, 1H), 7.66 (s, 1H), 7.41 (s, 1H), 7.31-7.16 (m, 1H), 7.10-6.91 (m, 1H), 5.35-5.22 (m, 1H), 3.75-3.63 (m, 2H), 3.44 (s, 3H), 3.30-3.24 (m, 2H), 2.29 (s, 3H), 1.76-1.69 (m, 2H), 1.63-1.52 (m, 3H), 1.09 (s, 6H).
514		562.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.99 (brs, 1H), 8.52 (brs, 1H), 7.82-7.80 (m, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.48-5.44 (m, 1H), 3.99 (s, 3H), 3.72 (s, 3H), 2.37 (s, 3H), 2.26-2.24 (m, 6H), 1.96-1.92 (m, 6H), 1.64 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

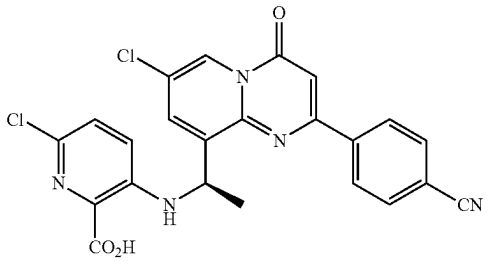
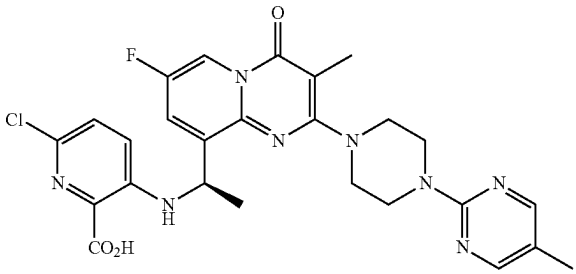
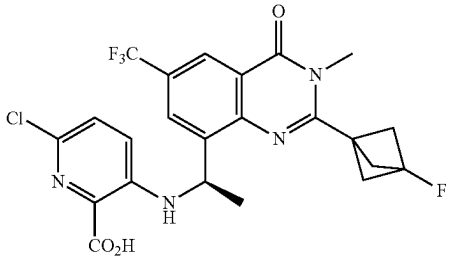
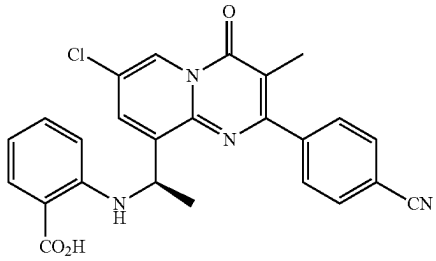
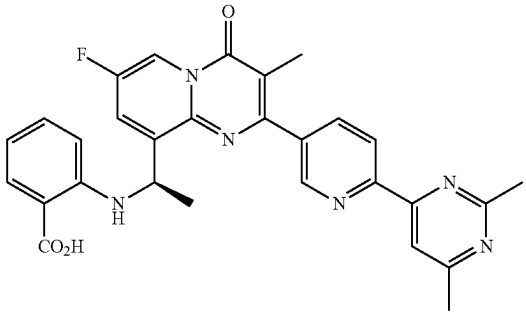
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
515		460.0	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.78 (s, 1H), 8.47 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.84 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.19 (s, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.59-5.55 (m, 1H), 2.36 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H).
516		553.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.89-8.76 (m, 1H), 8.73-8.68 (m, 1H), 8.26 (s, 2H), 7.84-7.75 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 5.65-5.25 (m, 1H), 3.93-3.78 (m, 4H), 3.60-3.46 (m, 4H), 2.14 (s, 3H), 2.09 (s, 3H), 1.65 (d, J = 6.8 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −135.89 (1F).
517		511.2	1H NMR (400 MHz, DMSO-d6, ppm) δ 12.97 (brs, 1H), 8.75 (brs, 1H), 8.25 (s, 1H), 8.14 (s, 1H), 7.38-7.28 (m, 1H), 7.26-7.14 (m, 1H), 5.47-5.36 (m, 1H), 3.60 (s, 3H), 2.79 (d, J = 9.2 Hz, 3H), 2.70 (d, J = 9.2 Hz, 3H), 1.69 (d, J = 6.8 Hz, 3H); 19F NMR (376 MHz, DMSO-d6, ppm): δ −148.38 (1F), −60.75 (3F).
518		459.2	1H NMR (400 MHz, DMSO-d6, ppm) δ 8.88-8.86 (m, 2H), 8.05-8.03 (m, 2H), 7.95-7.93 (m, 2H), 7.84 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.14-7.10 (m, 1H), 6.56-6.52 (m, 1H), 6.31 (d, J = 8.4 Hz, 1H), 5.33-5.31 (m, 1H), 2.24 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H).
519		541.2	1H NMR (400 MHz, DMSO-d6, ppm) δ 9.46 (brs, 1H), 9.12 (s, 1H), 8.88 (s, 1H), 8.59 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 7.6 Hz, 1H), 8.13 (s, 1H), 7.87 (s, 1H), 7.64 (s, 1H), 7.03-6.99 (m, 1H), 6.49 (s, 1H), 6.25 (s, 1H), 5.35-5.33 (m, 1H), 2.70 (s, 3H), 2.56 (s, 3H), 2.32 (s, 3H), 1.61 (d, J = 4.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

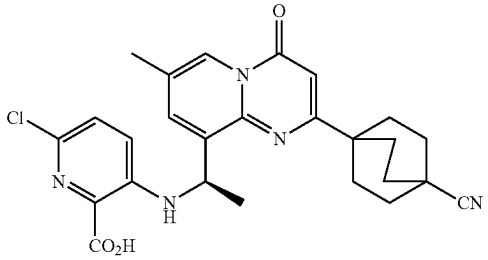
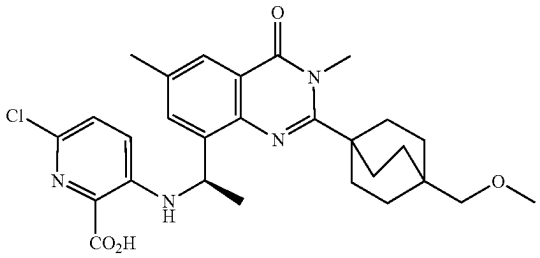
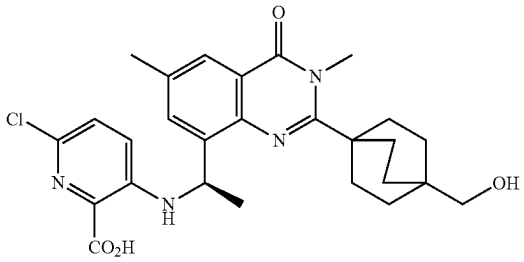
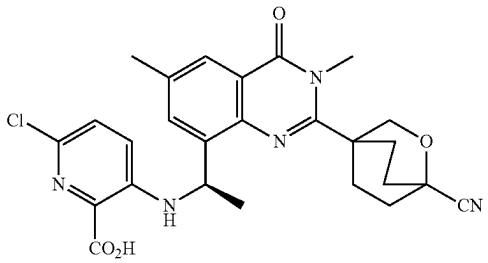
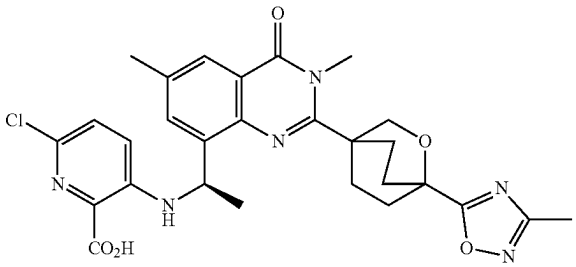
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
520		492.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 8.68 (s, 1H), 7.76 (s, 1H), 7.24-7.22 (m, 1H), 6.89 (s, 1H), 6.31 (s, 1H), 5.38-5.25 (m, 1H), 2.32 (s, 3H), 2.02-1.91 (m, 12H), 1.62 (d, J = 6.4 Hz, 3H).
521		525.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.85 (brs, 1H), 7.78 (s, 1H), 7.53 (s, 1H), 7.23-7.21 (m, 1H), 6.90-6.88 (m, 1H), 5.45-5.42 (m, 1H), 3.66 (s, 3H), 3.25 (s, 3H), 3.03 (s, 2H), 2.35 (s, 3H), 2.13-2.10 (m, 6H), 1.59-1.52 (m, 9H).
522		511.3	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.62 (brs, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.29-7.27 (m, 1H), 6.98-6.96 (m, 1H), 5.46-5.43 (m, 1H), 4.43 (s, 1H), 3.67 (s, 3H), 3.11 (s, 2H), 2.36 (s, 3H), 2.12-2.08 (m, 6H), 1.61-1.51 (m, 3H), 1.52-1.48 (m, 6H).
523		508.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.48-8.35 (m, 1H), 7.83-7.77 (m, 1H), 7.62-7.54 (m, 1H), 7.38-7.31 (m, 1H), 7.06-6.96 (m, 1H), 5.44-5.26 (m, 1H), 4.50-4.27 (m, 2H), 3.66 (s, 3H), 2.68-2.56 (m, 2H), 2.37 (s, 3H), 2.36-2.19 (m, 4H), 2.13-2.01 (m, 2H), 1.61 (d, J = 6.4 Hz, 3H).
524		565.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.01 (brs, 1H), 8.50-8.35 (m, 1H), 7.86-7.77 (m, 1H), 7.63-7.55 (m, 1H), 7.40-7.30 (m, 1H), 7.09-6.97 (m, 1H), 5.50-5.26 (m, 1H), 4.63-4.30 (m, 2H), 3.71 (s, 3H), 2.75-2.63 (m, 2H), 2.40-2.30 (m, 8H), 2.28-2.10 (m, 4H), 1.63 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

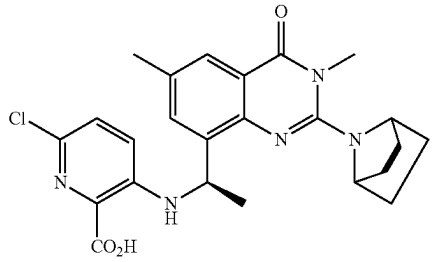
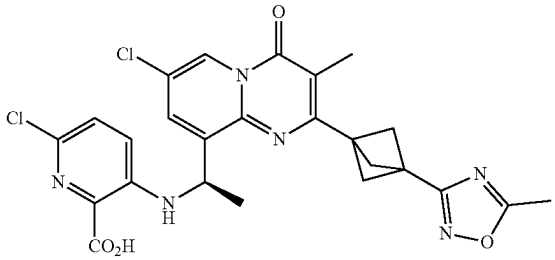
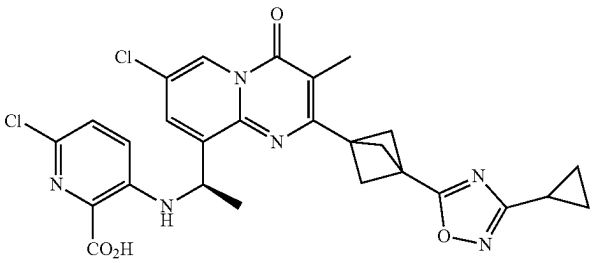
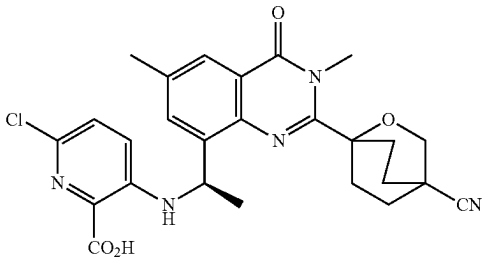
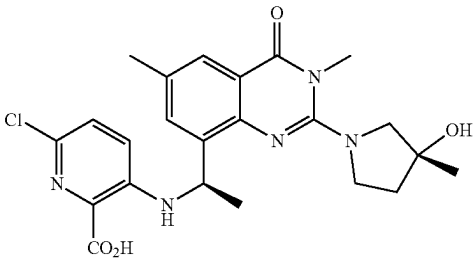
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
525		468.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.54 (brs, 1H), 7.78-7.59 (m, 1H), 7.46-7.37 (m, 1H), 7.28-7.12 (m, 1H), 6.99-6.73 (m, 1H), 5.53-5.25 (m, 1H), 4.49-4.26 (m, 2H), 3.53 (s, 3H), 2.30 (s, 3H), 1.98-1.87 (m, 4H), 1.55 (d, J = 6.4 Hz, 3H), 1.52-1.44 (m, 4H).
526		525.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.59 (brs, 1H), 8.74 (brs, 1H), 8.24 (s, 1H, FA), 7.72-7.70 (m, 1H), 7.08-7.06 (m, 1H), 6.88-6.70 (m, 1H), 5.28-5.25 (m, 1H), 2.66-2.60 (m, 6H), 2.58 (s, 3H), 2.29 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −133.53 (1F).
528		551.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.94 (brs, 1H), 9.15 (brs, 1H), 8.77-8.64 (m, 1H), 7.97-7.72 (m, 1H), 7.39-7.12 (m, 1H), 7.07-6.89 (m, 1H), 5.30-5.27 (m, 1H), 2.82-2.69 (m, 6H), 2.27 (s, 3H), 2.18-2.06 (m, 1H), 1.68 (d, J = 6.4 Hz, 3H), 1.13-1.02 (m, 2H), 0.93-0.85 (m, 2H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −133.51 (1F).
529		508.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.49 (brs, 1H), 7.86-7.80 (m, 1H), 7.65-7.57 (m, 1H), 7.36-7.27 (m, 1H), 7.06-6.96 (m, 1H), 5.43-5.30 (m, 1H), 4.23-4.12 (m, 2H), 3.73 (s, 3H), 2.61-2.53 (m, 1H), 2.49-2.43 (m, 1H), 2.41-2.30 (m, 4H), 2.29-2.14 (m, 5H), 1.64-1.56 (m, 3 H).
530		472.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.95 (brs, 1H), 8.45 (d, J = 6.4 Hz, 1H), 7.68-7.65 (m, 1H), 7.45-7.41 (m, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 5.38-5.26 (m, 1H), 4.93-4.75 (m, 1H), 4.02-3.90 (m, 1H), 3.60-3.52 (m, 2H), 3.44 (s, 3H), 3.31-3.28 (m, 1H), 2.29 (s, 3H), 1.93-1.79 (m, 2H), 1.59 (d, J = 6.4 Hz, 3H), 1.35 (s, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

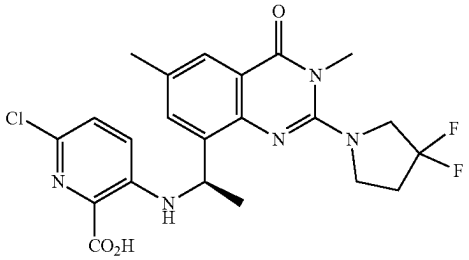
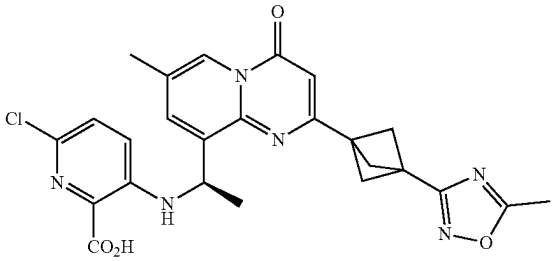
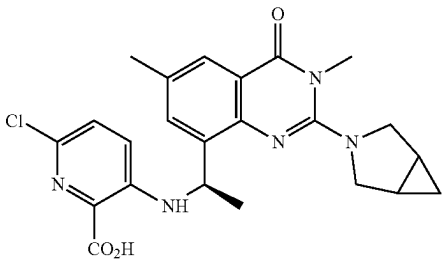
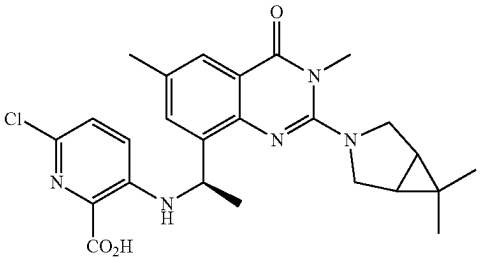
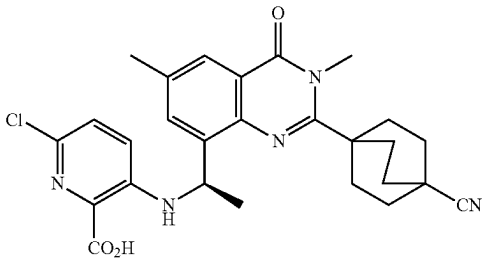
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
531		478.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.96 (brs, 1H), 8.61 (brs, 1H), 7.71 (s, 1H), 7.48 (s, 1H), 7.30-7.26 (m, 1H), 7.10-6.99 (m, 1H), 5.35-5.27 (m, 1H), 4.01 (t, J = 13.2 Hz, 2H), 3.80 (t, J = 7.2 Hz, 2H), 3.47 (s, 3H), 2.50-2.31 (m, 2H), 2.32 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −99.60 (2F).
532		507.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.81 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.26-7.23 (m, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.43 (s, 1H), 5.51 (q, J = 6.4 Hz, 1H), 2.60 (s, 3H), 2.58 (s, 6H), 2.40 (s, 3H), 1.75 (dd, J = 6.6, 1.6 Hz, 3H).
533		454.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.57 (s, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 9.2 Hz, 1H), 5.31 (t, J = 6.8 Hz, 1H), 3.95 (d, J = 10.4 Hz, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.55-3.44 (m, 2H), 3.42 (s, 3H), 2.30 (s, 3H), 1.62-1.58 (m, 5H), 0.61-0.56 (m, 1H), 0.38-0.33 (m, 1H).
534		482.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.61 (s, 1H), 7.67-7.63 (m, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.29 (q, J = 6.4 Hz, 1H), 3.86-3.80 (m, 2H), 3.80-3.72 (m, 1H), 3.69 (d, J = 10.8 Hz, 1H), 3.44 (s, 3H), 2.28 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H), 1.53-1.45 (m, 2H), 1.03 (s, 3H), 0.93 (s, 3H).
535		497.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.81 (brs, 1H), 7.78 (s, 1H), 7.53 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.45-5.35 (m, 1H), 4.44 (brs, 1H), 3.66 (s, 3H), 2.35 (s, 3H), 2.30-2.10 (m, 6H), 1.75-1.62 (m, 6H), 1.60-1.50 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

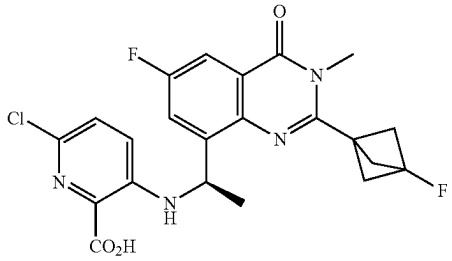
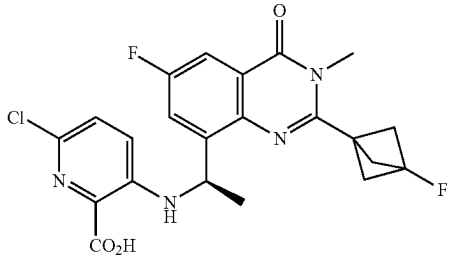
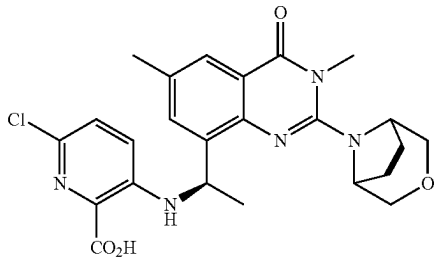
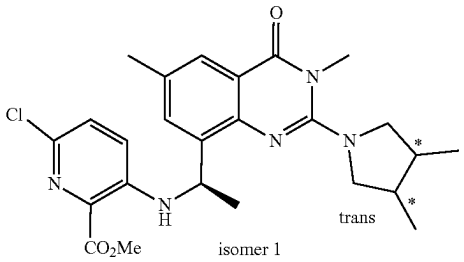
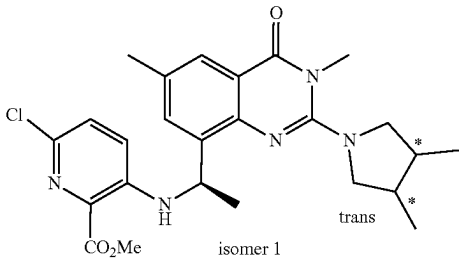
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
536		461.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.26 (brs, 1H), 7.70-7.50 (m, 2H), 7.20-7.10 (m, 1H), 6.89 (brs, 1H), 5.40-5.30 (m, 1H), 3.58 (s, 3H), 2.76-2.64 (m, 6H), 1.61 (d, J = 8.0 Hz, 3H).
537		477.0	1H NMR (400 MHz, MeOH-d4, ppm): δ 8.00 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.06-6.94 (m, 1H), 6.78-6.66 (m, 1H), 5.54-5.40 (m, 1H), 3.69 (s, 3H), 2.75-2.65 (m, 6H), 1.62 (d, J = 6.8 Hz, 3H); 19F NMR (376 MHz, MeOH-d4, ppm): δ −152.49 (1F).
538		548.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.41 (s, 1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 7.24 (s, 1H), 7.08-7.06 (d, J = 8.4 Hz, 1H), 6.82-6.80 (d, J = 8.4 Hz, 1H), 5.37-5.34 (d, J = 6.4 Hz, 1H), 3.54 (s, 3H), 3.38 (s, 8H), 2.32 (s, 3H), 2.26 (s, 3H), 1.56-1.54 (d, J = 10.8 Hz, 1H).
540	 obtained from intermediate 540-p1.	470.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.47-8.35 (m, 1H), 7.67 (d, J = 1.2 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 5.37-5.22 (m, 1H), 3.71-3.60 (m, 2H), 3.44 (s, 3H), 3.34-3.28 (m, 2H), 2.30 (s, 3H), 1.83-1.68 (m, 2H), 1.59 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 5.6 Hz, 6H).
541	 obtained from intermediate 540-p2.	470.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.58-8.38 (m, 1H), 7.67 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 5.35-5.22 (m, 1H), 3.61-3.53 (m, 2H), 3.45 (s, 3H), 3.36-3.32 (m, 2H), 2.31 (s, 3H), 1.84-1.70 (m, 2H), 1.61 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 5.6 Hz, 6H).

TABLE 2-continued

Characterization of exemplary compounds.

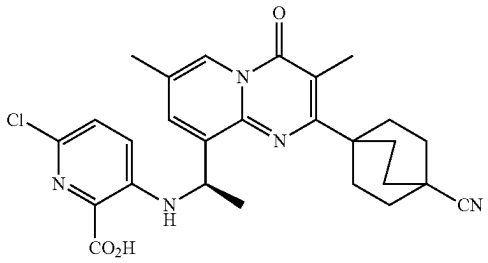
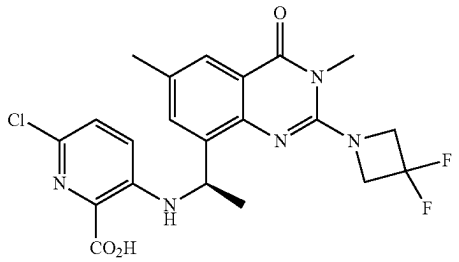
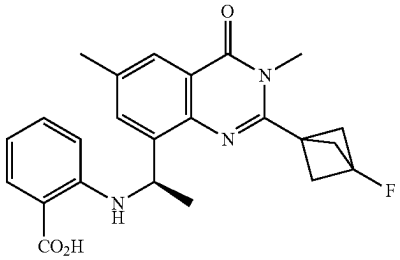
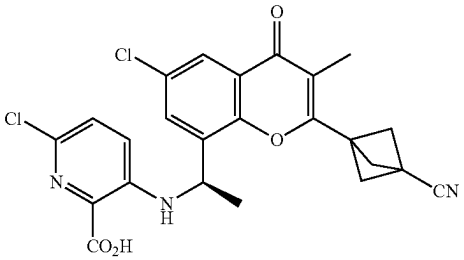
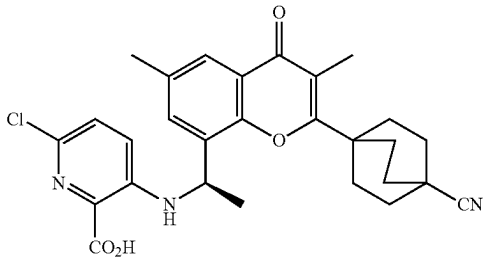
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
542		506.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.72 (s, 1H), 8.63 (s, 1H), 8.30 (s, 1H, FA), 7.51 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 5.35-5.14 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 2.12-2.01 (m, 12H), 1.57 (d, J = 6.4 Hz, 3H).
543		464.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.97 (brs, 1H), 8.57 (s, 1H), 7.72 (s, 1H), 7.50 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 5.33-5.30 (m, 1H), 4.80-4.67 (m, 4H), 3.39 (s, 3H), 2.32 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −98.95 (2F).
544		422.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.81-7.73 (m, 2H), 7.60 (s, 1H), 7.19-7.12 (m, 1H), 6.59-6,45 (m, 2H), 5.45-5.35 (m, 1H), 3.58 (s, 3H), 2.76-2.62 (m, 6H), 2.37 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −148.37 (1F).
545		484.2	^{1}H NMR (400 MHz, MeOH-d$_4$ppm): δ 7.94 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.18-5.07 (m, 1H), 2.87 (s, 6H), 2.10 (s, 3H), 1.71 (d, J = 6.8 Hz, 3H).
546		506.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.30 (d, J = 6.4 Hz, 1H), 7.69 (s, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 5.18-5.03 (m, 1H), 2.32 (s, 3H), 2.20-2.06 (m, 9H), 2.05-1.94 (m, 6H), 1.61 (d, J = 6.8 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

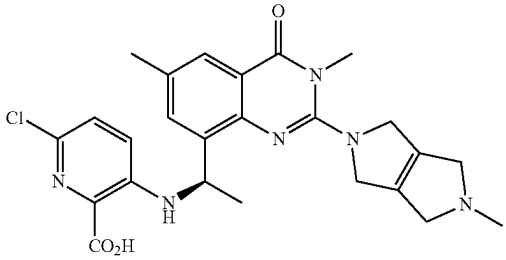
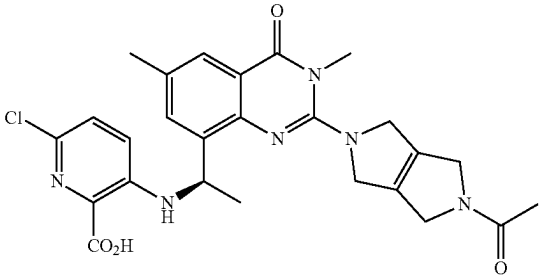
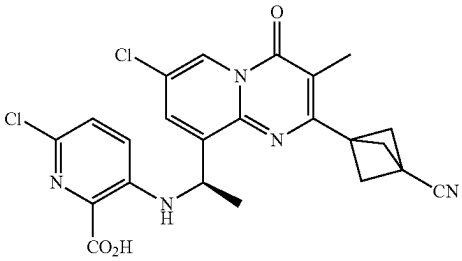
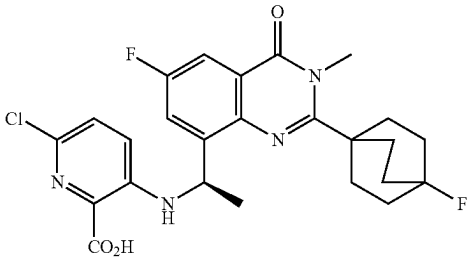
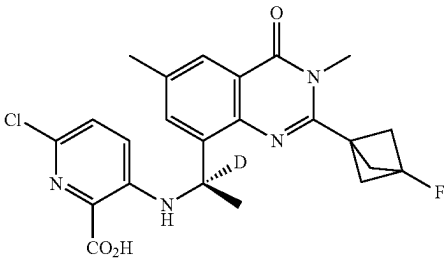
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
547		495.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.32-9.14 (m, 1 H), 7.66 (s, 1 H), 7.41 (s, 1 H), 7.10 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.28-5.17 (m, 1H), 4.47 (s, 4H), 3.82-3.61 (m, 4H), 3.50 (s, 3H), 2.72-2.60 (m, 3H), 2.28 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H).
548		523.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.79 (s, 1 H), 7.48 (d, J = 1.6 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H), 5.43-5.33 (m, 1H), 4.67-4.50 (m, 4H), 4.40 (s, 2H), 4.25 (s, 2H), 3.63 (s, 3H), 2.34 (s, 3H), 2.11 (s, 3H), 1.65 (d, J = 6.8 Hz, 3H).
549		464.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.68 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 5.42-5.37 (m, 1H), 2.82-2.79 (m, 6H), 2.35 (s, 3H), 2.29 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H).
550		503.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.82 (s, 1H), 7.65 (d, J = 5.6, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.50-5.31 (m, 1H), 3.68 (s, 3H), 2.40-2.25 (m, 6H), 1.95-1.90 (m, 6H), 1.61 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −112.4 (1F), −148.3 (1F).
551		458.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.83 (s, 1H), 7.80 (s, 1H), 7.62 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 3.57 (s, 3H), 2.73-2.64 (m, 6H), 2.38 (s, 3H), 1.61 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −148.4 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

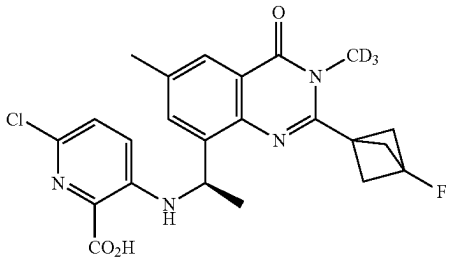
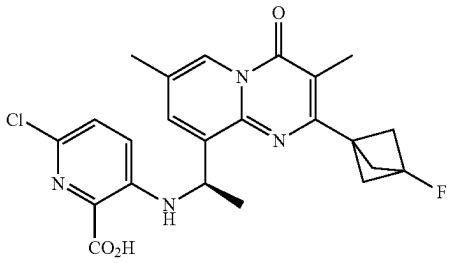
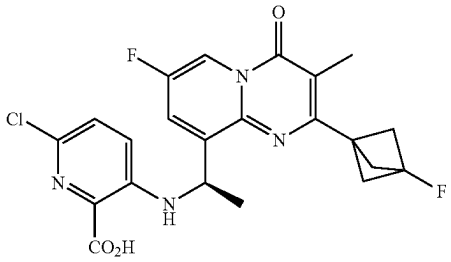
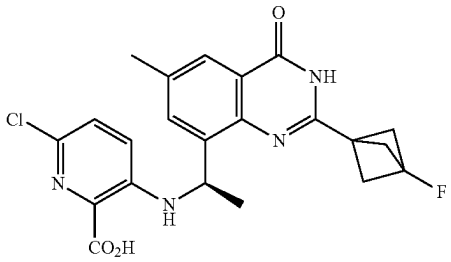
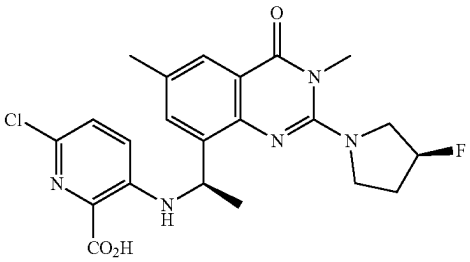
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
552		460.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.55 (d, J = 6.4 Hz, 1H), 7.82 (s, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 9.2 Hz, 1H), 5.56-5.03 (m, 1H), 2.75-2.65 (m, 6H), 2.39 (s, 3H), 1.65 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −148.36 (1F).
553		457.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.74-8.53 (m, 2H), 7.74 (s, 1H), 7.38-7.27 (m, 1H), 7.16-7.04 (m, 1H), 5.36-5.19 (m, 1H), 2.65-2.54 (m, 6H), 2.32 (s, 3H), 2.20 (s, 3H), 1.73-1.62 (m, 3H). ^{19}FNMR (376 MHz, DMSO-d$_6$, ppm): δ −145.52 (1F).
554		461.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.83-8.64 (m, 2H), 8.05-7.86 (m, 1H), 7.36-7.23 (m, 1H), 7.14-6.97 (m, 1H), 5.33-5.19 (m, 1H), 2.64-2.56 (m, 6H), 2.21 (s, 3H), 1.74-1.62 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −133.54 (1F), −145.58 (1F).
556		443.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.38 (brs, 1H), 9.36 (brs, 1H), 8.24 (s, 1H), 7.77 (s, 1H), 7.53 (s, 1H), 7.18-7.04 (m, 1H), 6.92-6.79 (m, 1H), 5.44-5.22 (m, 1H), 2.60-2.52 (m, 6H), 2.34 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −147.76 (1F).
557		460.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.98 (brs, 1H), 7.68 (s, 1H), 7.42 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 5.50-5.29 (m, 2H), 4.10-3.81 (m, 2H), 3.72-3.59 (m, 2H), 3.48 (s, 3H), 2.29 (s, 3H), 2.22-2.07 (m, 2H), 1.56 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

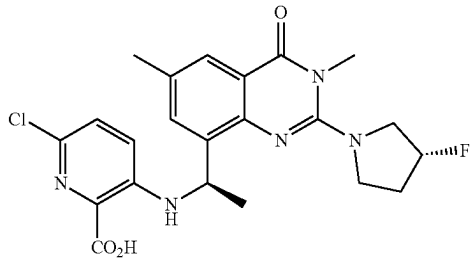
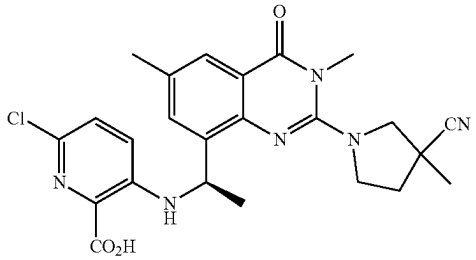
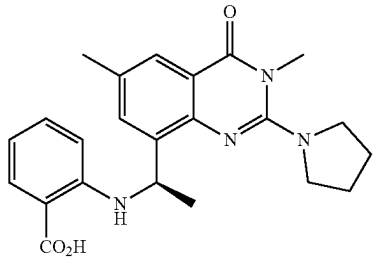
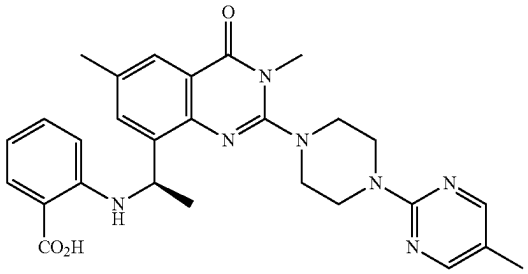
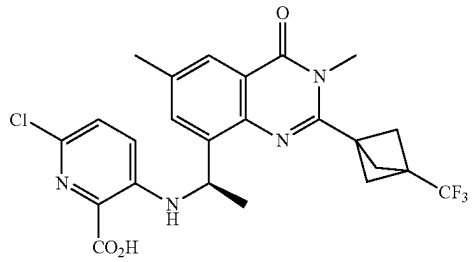
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
558		460.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.66 (brs, 1H), 7.69 (s, 1H), 7.44 (d, J = 1.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 5.51-5.38 (m, 1H), 5.30-5.27 (m, 1H), 4.06-3.85 (m, 2H), 3.75-3.62 (m, 2H), 3.48 (s, 3H), 2.33 (s, 3H), 2.31-2.07 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −176.82 (1F).
559		481.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.02-8.67 (m, 1H), 7.69 (s, 1H), 7.48-7.41 (m, 1H), 7.27-7.15 (m, 1H), 7.03-6.90 (m, 1H), 5.38-5.25 (m, 1H), 4.01-3.57 (m, 4H), 3.46 (d, J = 2.8 Hz, 3H), 2.45-2.37 (m, 1H), 2.30 (s, 3H), 2.15-2.04 (m, 1H), 1.56 (t, J = 5.6 Hz, 3H), 1.52 (d, J = 2.4 Hz, 3H).
560		407.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.96 (brs, 1H), 8.32 (s, 1H, FA), 7.80 (dd, J = 8.0, 2.0 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.42 (t, J = 7.2 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 5.39-5.29 (m, 1H), 3.58 (t, J = 3.6 Hz, 4H), 3.47 (s, 3H), 2.27 (s, 3H), 1.91 (t, J = 3.6 Hz, 4H), 1.50 (d, J = 6.4 Hz, 3H).
561		514.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.00 (brs, 1H), 8.27 (s, 2H), 7.79-7.78 (m, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.41 (t, J = 7.2 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 5.43-5.31 (m, 1H), 3.90 (t, J = 4.8 Hz, 4H), 3.55 (s, 3H), 3.34 (t, J = 4.8 Hz, 4H), 2.31 (s, 3H), 2.10 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H).
562		507.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.80 (s, 1H), 7.59 (s, 1H), 7.19-7.16 (m, 1H), 6.95-6.89 (m, 1H), 5.37 (t, J = 6.8 Hz, 1H), 3.62 (s, 3H), 2.60 (q, J = 9.6 Hz, 6H), 2.37 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −71.17 (3F).

TABLE 2-continued

Characterization of exemplary compounds.

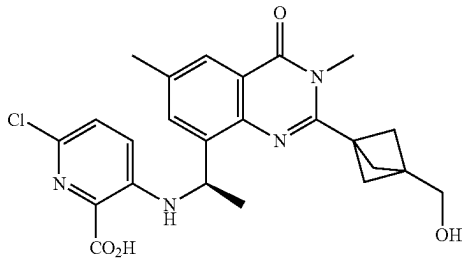
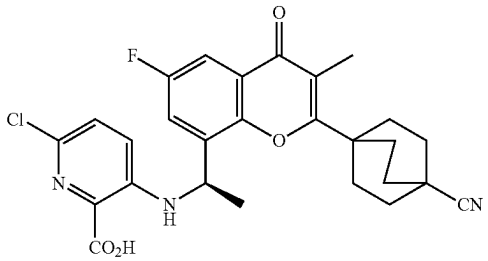
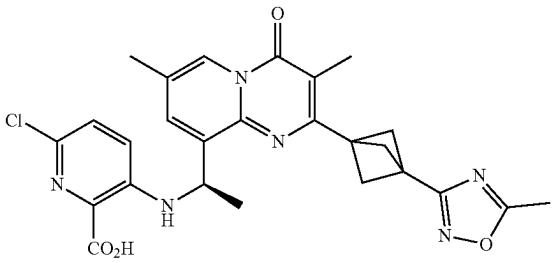
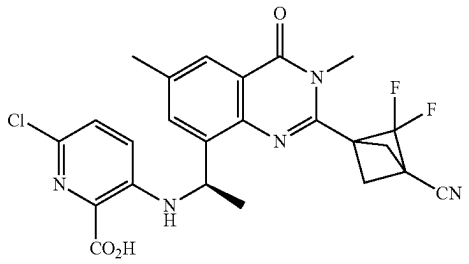
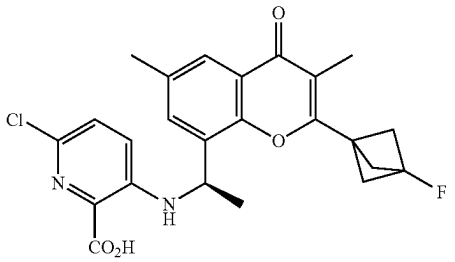
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
563		469.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.72 (s, 1H), 7.79 (s, 1H), 7.59 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 5.41 (t, J = 6.4 Hz, 1H), 4.64 (s, 1H), 3.61 (s, 3H), 3.50 (s, 2H), 2.34 (s, 3H), 2.24-2.17 (m, 6H), 1.62 (d, J = 6.8 Hz, 3H).
564		510.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.62 (dd, J = 8.0, 3.2 Hz, 1H), 7.45 (dd, J = 8.8, 3.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 9.2 Hz, 1H), 5.25-5.13 (m, 1H), 2.30-2.20 (m, 9H), 2.14-2.03 (m, 6H), 1.71 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −116.61 (1F).
565		521.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.70 (s, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 5.49-5.43 (m, 1H), 2.71 (s, 6H), 2.59 (s, 3H), 2.36 (s, 6H), 1.74 (d, J = 6.4 Hz, 3H).
566		500.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.47-8.31 (m, 1H), 7.89-7.80 (m, 1H), 7.70-7.61 (m, 1H), 7.35-7.27 (m, 1H), 7.12-7.00 (m, 1H), 5.52-5.37 (m, 1H), 3.54 (s, 3H), 3.09-2.89 (m, 4H), 2.39 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.63 (2F).
567		457.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.11 (brs, 1H), 8.42-8.35 (m, 1H), 7.75-7.68 (m, 1H), 7.59-7.49 (m, 1H), 7.41-7.32 (m, 1H), 7.14-7.05 (m, 1H), 5.18-5.05 (m, 1H), 2.72-2.64 (m, 6H), 2.35 (s, 3H), 2.01 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −145.66 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

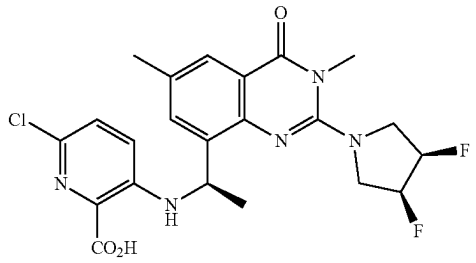
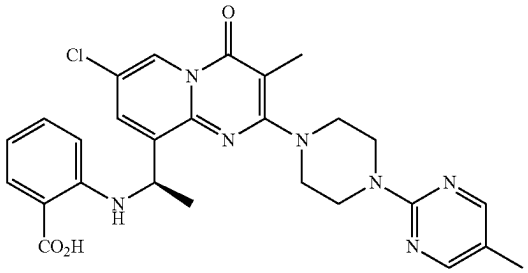
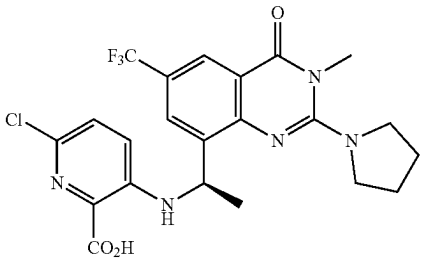
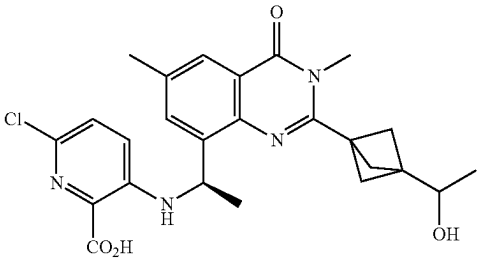
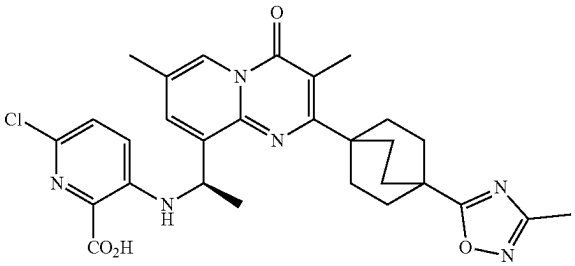
Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
568		478.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.55 (brs, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 5.50-5.48 (m, 1H), 5.47-5.27 (m, 2H), 4.13-4.00 (m, 2H), 3.98-3.77 (m, 2H), 3.46 (s, 3H), 2.31 (s, 3H), 1.61 (d, J = 6.4 Hz, 3H).
569		534.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.84 (brs, 1H), 8.75 (s, 1H), 8.26 (s, 2H), 7.83 (d, J = 6.8 Hz, 1H), 7.63 (s, 1H), 7.16-7.12 (m, 1H), 6.55-6.51 (m, 1H), 6.33 (d, J = 8.0 Hz, 1H), 5.26-5.24 (m, 1H), 3.86-3.84 (m, 4H), 3.58-3.56 (m, 4H), 2.15 (s, 3H), 2.10 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H).
570		496.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 13.02 (s, 1H), 8.55 (d, J = 6.4 Hz, 1H), 8.10 (d, J = 1.2 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 5.56-4.92 (m, 1H), 3.72-3.65 (m, 4H), 3.49 (s, 3H), 1.92 (d, J = 4.4 Hz, 4H), 1.66 (d, J = 6.6 Hz, 3H). 19F NMR (376 MHz, DMSO-d6, ppm): δ −60.31 (3F).
571		483.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.68 (brs, 1H), 7.84-7.76 (m, 1H), 7.59 (s, 1H), 7.37-7.21 (m, 1H), 7.15-7.01 (m, 1H), 5.55-5.36 (m, 1H), 4.70-4.36 (m, 1H), 3.75-3.66 (m, 1H), 3.62 (s, 3H), 2.37 (s, 3H), 2.25-2.06 (m, 6H), 1.67-1.58 (m, 3 H), 1.13-1.01 (m, 3H).
572		563.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 9.07 (s, 1H), 8.62 (s, 1H), 7.60 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 5.49-5.12 (m, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 2.24-2.16 (m, 6H), 2.08-1.99 (m, 6H), 1.62 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

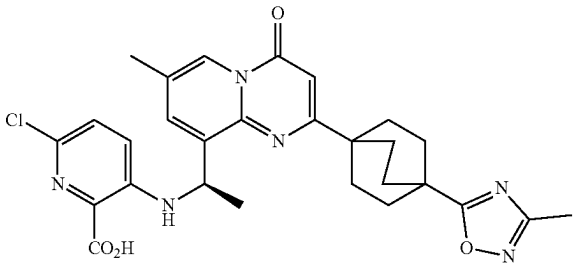
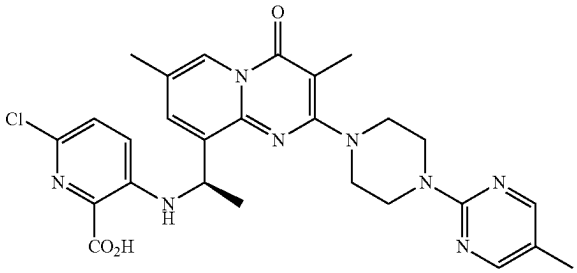
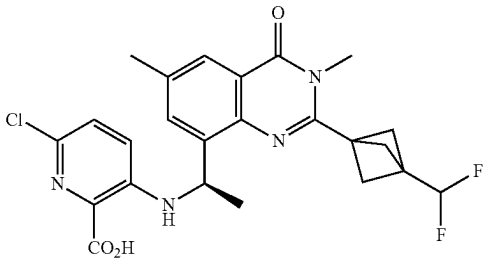
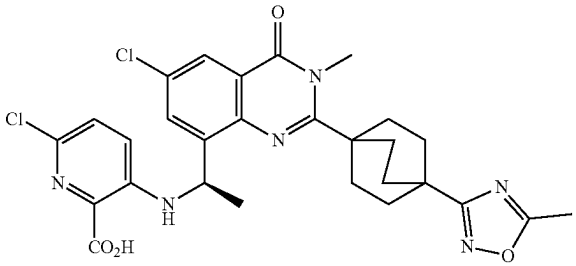
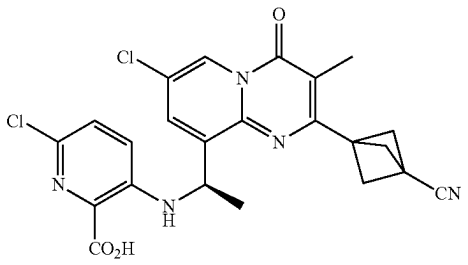
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
573		549.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.70 (s, 1H), 8.62 (s, 1H), 8.28 (s, 1H, FA), 7.63 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 7.2 Hz, 1H), 6.32 (s, 1H), 5.34-5.31 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 2.08-1.99 (m, 12H), 1.62 (d, J = 6.4 Hz, 3H).
574		549.4	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.95 (s, 1H), 8.59 (s, 1H), 8.26 (s, 2H), 7.59 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 5.28-5.21 (m, 1H), 3.85-3.83 (m, 4H), 3.52-3.48 (m, 4H), 2.27 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H).
575		489.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.57 (s, 1H), 7.82 (s, 1H), 7.64 (s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.34-6.05 (m, 1H), 5.40 (t, J = 6.8 Hz, 1H), 3.62 (s, 3H), 2.48-2.40 (m, 6H), 2.39 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −122.31 (2F).
576		583.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.76 (brs, 1H), 8.31 (s, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.08-7.02 (m, 1H), 6.71-6.61 (m, 1H), 5.52-5.30 (m, 1H), 3.72 (s, 3H), 2.56 (s, 3H), 2.24 (d, J = 8.0 Hz, 6H), 2.03-1.95 (m, 6H), 1.56 (d, J = 6.0 Hz, 3H).
577		484.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 13.00 (brs, 1H), 8.77 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H), 7.29 (s, 1H), 7.10 (s, 1H), 5.24 (t, J = 7.2 Hz, 1H), 2.83-2.72 (m, 6H), 2.21 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

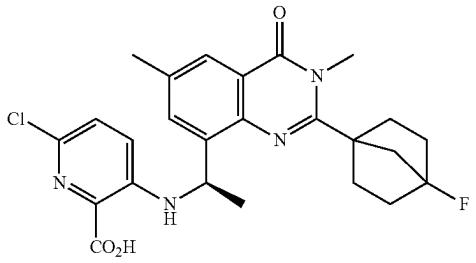
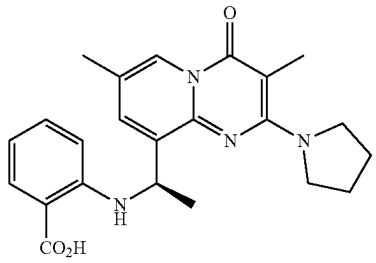
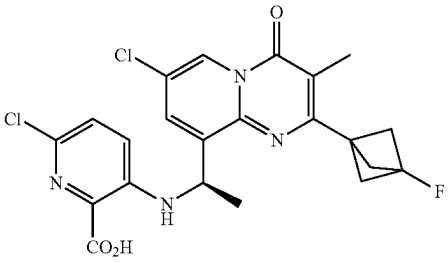
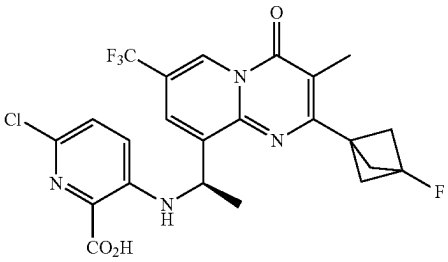
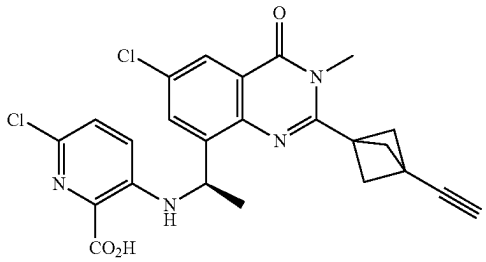
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
578		485.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.93 (brs, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 5.40-5.36 (m, 1H), 3.57 (s, 3H), 2.54 (s, 3H), 2.38-2.08 (m, 8H), 2.00-1.92 (m, 2H), 1.64 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −176.31 (s, 1F).
579		407.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.51 (s, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.21-7.18 (m, 1H), 6.54-6.50 (m, 1H), 6.32 (d, J = 8.4 Hz, 1H), 5.23-5.20 (m, 1H), 3.72-3.71 (m, 4H), 2.23 (s, 6H), 1.90-1.88 (m, 4H), 1.59 (d, J = 6.4 Hz, 3H).
580		477.2	^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 8.91 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 4.0 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 5.41-5.31 (m, 1H), 2.58 (s, 6H), 2.32 (s, 3H), 1.71 (d, J = 8.0 Hz, 3H); ^{19}F NMR (376 MHz, CDCl$_3$, ppm): δ −148.44 (1F).
581		511.4	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 9.14 (s, 1H), 7.78 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 5.42-5.32 (m, 1H), 2.61 (d, J = 2.4 Hz, 6H), 2.31 (s, 3H), 1.73 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −65.02 (3F), −149.81 (1F).
582		483.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.26 (brs, 1H), 7.96-7.85 (m, 1H), 7.80-7.65 (m, 1H), 7.32-7.06 (m, 1H), 6.97-6.78 (m, 1H), 5.44-5.24 (m, 1H), 3.59 (s, 3H), 3.21 (s, 1H), 2.71-2.54 (m, 6H), 1.61 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

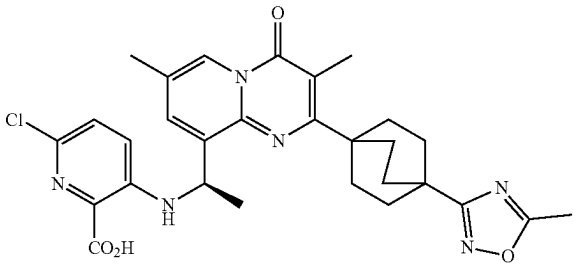
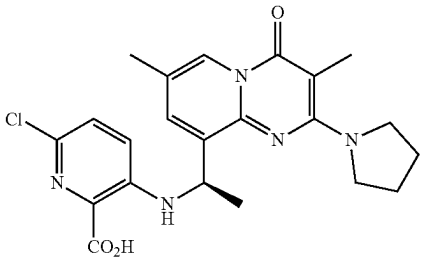
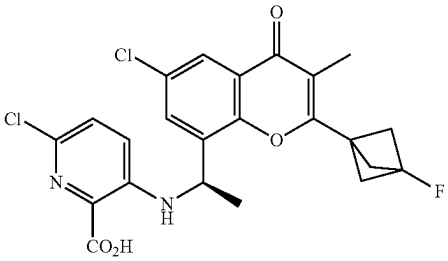
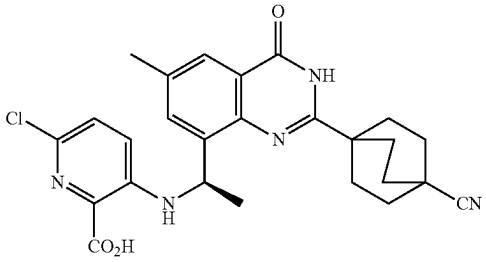
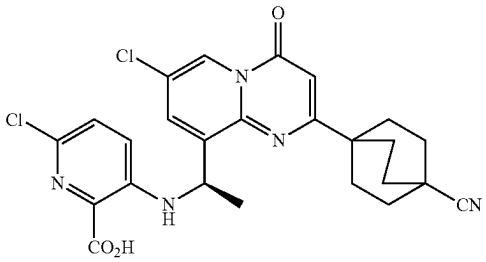
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
583		563.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.85 (s, 1H), 8.61 (s, 1H), 8.3 (s, 1H, FA), 7.50 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 5.41-5.21 (m, 1H), 2.55 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.22-2.13 (m, 6H), 2.02-1.91 (m, 6H), 1.62 (d, J = 6.4 Hz, 3H).
584		442.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.36 (s, 1H), 8.50 (s, 1H), 7.43 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.15-5.12 (m, 1H), 3.70-3.69 (m, 4H), 2.22-2.21 (m, 6H), 1.90-1.87 (m, 4H), 1.56 (d, J = 6.4 Hz, 3H).
585		477.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.55 (s, 1H), 7.85-7.84 (m, 1H), 7.74 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 5.12 (t, J = 6.4 Hz, 1H), 2.70-2.69 (m, 6H), 2.02 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −145.70 (1F).
586		492.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.77 (s, 1H), 7.55 (s, 1H), 7.30-7.17 (m, 1H), 7.03-6.90 (m, 1H), 5.44-5.34 (m, 1H), 2.34 (s, 3H), 2.17-1.90 (m, 12H), 1.57 (d, J = 6.4 Hz, 3H).
587		512.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.05 (d, J = 7.2 Hz, 1H), 8.80 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.40 (s, 1H), 5.31-5.18 (m, 1H), 2.07-1.88 (m, 12H), 1.57 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

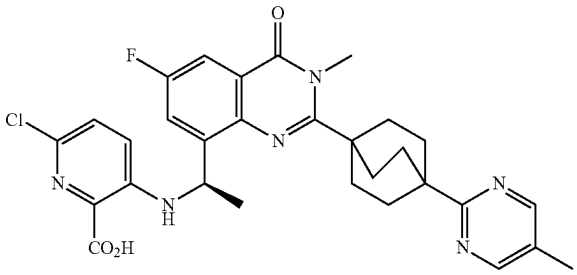
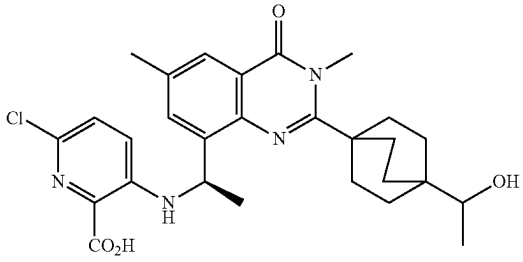
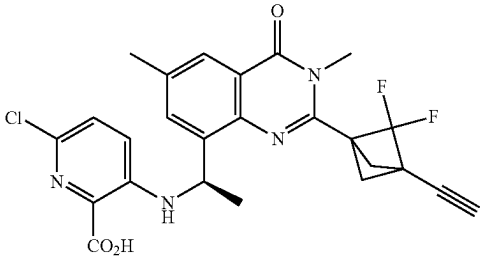
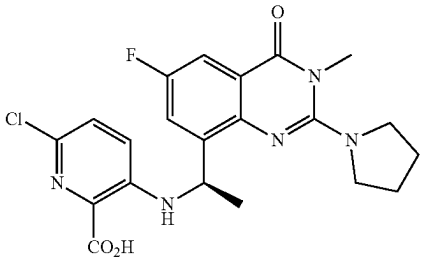
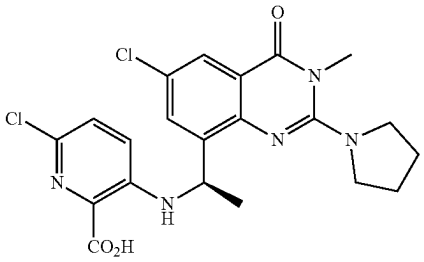
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
588		577.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.57 (s, 2H), 8.35 (s, 1H), 7.69-7.65 (m, 1H), 7.45 (dd, J = 9.6, 2.8 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 5.60 (q, J = 6.4 Hz, 1H), 3.83 (s, 3H), 2.41-2.33 (m, 6H), 2.30 (s, 3H), 2.20-2.11 (m, 6H), 1.65 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): δ −114.2 (1F).
589		525.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.84 (s, 1H), 7.55 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 9.2 Hz, 1H), 5.57 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.42 (q, J = 6.8 Hz, 1H), 2.37 (s, 3H), 2.70-2.16 (m, 6H), 1.72-1.53 (m, 9H), 1.11 (d, J = 6.4 Hz, 3H).
590		499.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.05-8.41 (m, 1H), 7.86-7.76 (m, 1H), 7.67-7.54 (m, 1H), 7.30-7.13 (m, 1H), 7.05-6.83 (m, 1H), 5.49-5.37 (m, 1H), 3.68-3.60 (m, 1H), 3.55 (s, 3H), 2.78-2.67 (m, 4H), 2.38 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −117.55 (1F).
591		446.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.58 (brs, 1H), 7.57-7.42 (m, 2H), 7.36-7.25 (m, 1H), 7.05-6.94 (m, 1H), 5.38-5.22 (m, 1H), 3.66-3.55 (m, 4H), 3.47 (s, 3H), 1.97-1.83 (m, 4H), 1.66-1.53 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −118.54 (1F).
592		462.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.70 (brs, 1H), 7.86-7.71 (m, 1H), 7.64-7.45 (m, 1H), 7.40-7.19 (m, 1H), 7.09-6.85 (m, 1H), 5.44-5.11 (m, 1H), 3.69-3.63 (m, 4H), 3.48 (s, 3H), 1.99-1.80 (m, 4H), 1.70-1.48 (m, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

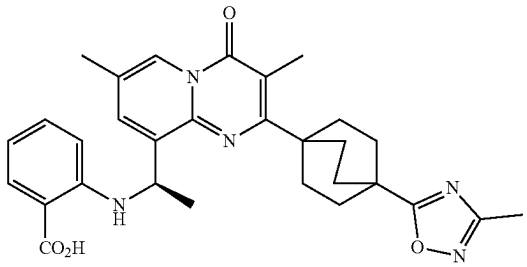
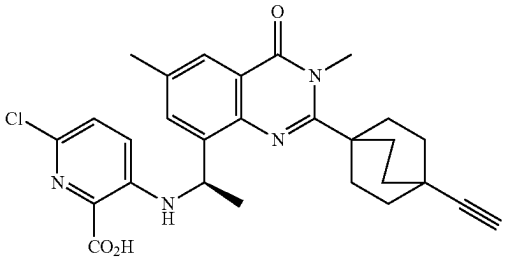
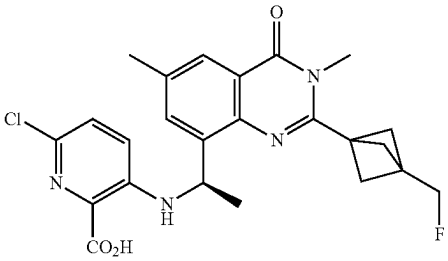
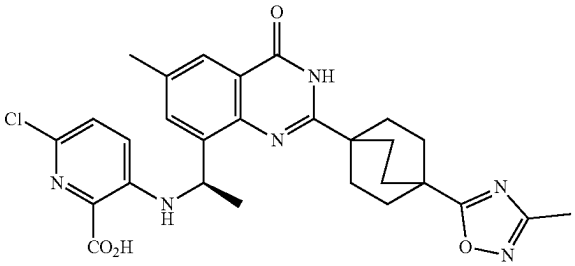
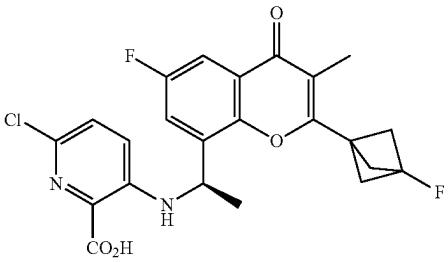
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
593		528.4	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.24 (s, 1H), 8.61 (s, 1H), 8.34 (s, 1H, FA), 7.85 (d, J = 7.2 Hz, 1H), 7.55 (s, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.48-6.43 (m, 1H), 6.18 (d, J = 8.0 Hz, 1H), 5.36 (s, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H), 2.22-2.15 (m, 6H), 2.09-1.99 (m, 6H), 1.57 (d, J = 6.4 Hz, 3H).
594		505.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.44 (brs, 1H), 7.79 (s, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.44-5.41 (m, 1H), 3.66 (s, 3H), 2.95 (s, 1H), 2.36 (s, 3H), 2.15-2.07 (m, 6H), 1.87-1.83 (m, 6H), 1.61 (d, J = 6.4 Hz, 3H).
595		471.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.60 (s, 1H), 7.81 (s, 1H), 7.62 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 5.40 (t, J = 6.8 Hz, 1H), 4.59 (s, 1H), 4.47 (s, 1H), 3.62 (s, 3H), 2.38-2.30 (m, 9H), 1.64 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −221.91 (1F).
596		549.2	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 7.87 (s, 1H), 7.60 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.07 d, J = 8.8 Hz, 1H), 5.60-5.50 (m, 1H), 2.40 (s, 3H), 2.34 (s, 3H), 2.25-2.09 (m, 12H), 1.69 (d, J = 6.8 Hz, 3H).
597		460.9	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.51 (s, 1H), 7.62-7.57 (m, 2H), 7.33 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 5.15-5.12 (m, 1H), 2.69 (d, J = 2.4 Hz, 6H), 2.02 (s, 3H), 1.65 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.25 (1F), −145.69 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

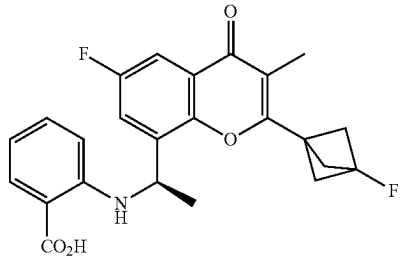
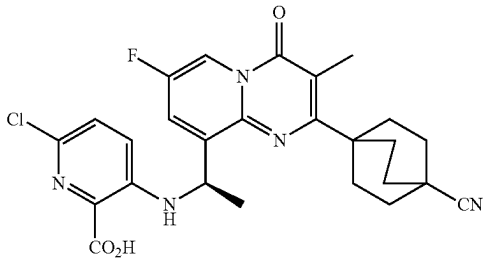
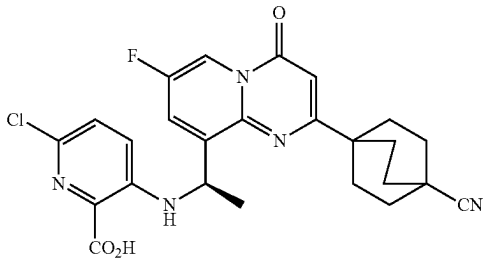
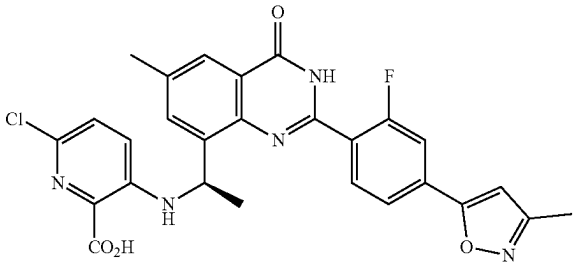
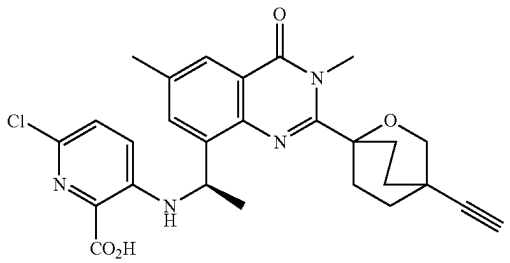
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
598		426.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.65 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.58-7.53 (m, 2H), 7.22-7.18 (m, 1H), 6.57-6.53 (m, 1H), 6.44 (d, J = 8.4 Hz, 1H), 5.13-5.10 (m, 1H), 2.69 (d, J = 2.4 Hz, 6H), 2.02 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −115.42 (1F), −145.68 (1F).
599		510.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.74 (s, 1H), 8.76-8.67 (m, 1H), 8.34 (s, 1H, FA), 7.62-7.60 (m, 1H), 7.01-6.91 (m, 1H), 6.62 (s, 1H), 5.34-5.18 (m, 1H), 2.34 (s, 3H), 2.17-2.06 (m, 6H), 2.03-2.00 (m, 6H), 1.59 (d, J = 6.4 Hz, 3H).
600		496.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.82 (s, 1H), 8.78 (s, 1H), 8.41 (s, 1H, FA), 7.74 (d, J = 5.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.68 (s, 1H), 6.38 (s, 1H), 5.29 (s, 1H), 2.08-1.96 (m, 6H), 1.94-1.92 (m, 6H), 1.59 (d, J = 6.4 Hz, 3H).
601		534.0	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.11 (t, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.83-7.77 (m, 2H), 7.67 (s, 1H), 7.14 (s, J = 8.8 Hz, 1H), 7.02 (s, J = 8.8 Hz, 1H), 6.87 (s, 1H), 5.65 (q, J = 6.4 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 1.67 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, MeOH-d$_4$, ppm): −115.3 (1F).
603		507.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.97 (brs, 1H), 8.48-8.35 (m, 1H), 7.86-7.75 (m, 1H), 7.63-7.53 (m, 1H), 7.37-7.29 (m, 1H), 7.07-6.97 (m, 1H), 5.46-5.31 (m, 1H), 4.02-3.90 (m, 2H), 3.74 (s, 3H), 3.22-3.15 (m, 1H), 2.49-2.24 (m, 6H), 2.19-1.95 (m, 5H), 1.61 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

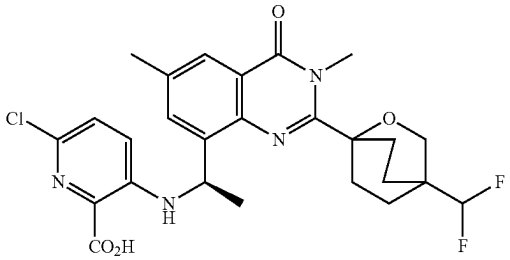
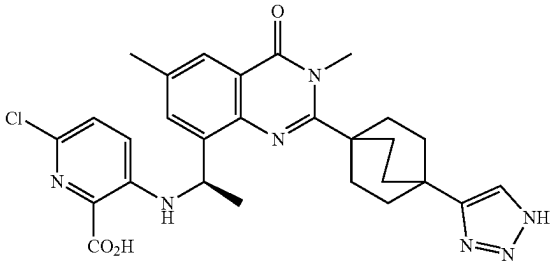
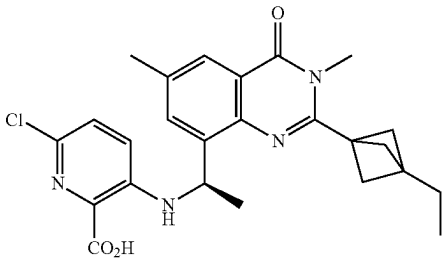
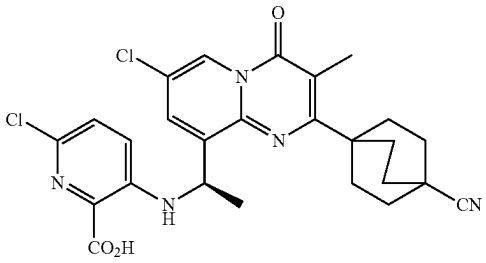
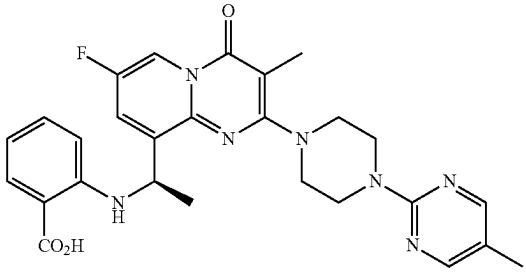
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
604		533.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.98 (brs, 1H), 8.50-8.48 (m, 1H), 7.88-7.78 (m, 1H), 7.66-7.57 (m, 1H), 7.39-7.26 (m, 1H), 7.11-6.99 (m, 1H), 6.13-5.75 (m, 1H), 5.45-5.30 (m, 1H), 3.97-3.86 (m, 2H), 3.75 (s, 3H), 2.50-2.27 (m, 6H), 2.20-2.10 (m, 1H), 1.94-1.76 (m, 4 H), 1.65-1.57 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −128.77 (2F).
605		548.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.66 (brs, 1H), 7.83-7.80 (m, 1H), 7.62-7.45 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 6.98-6.89 (m, 1H), 5.47-5.44 (m, 1H), 3.72 (s, 3H), 2.36 (s, 3H), 2.26-2.24 (m, 6H), 1.97-1.93 (m, 6H), 1.61 (d, J = 6.4 Hz, 3H).
606		467.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.03 (brs, 1H), 7.78 (s, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 5.46-5.36 (m, 1H), 3.61 (s, 3H), 3.45-3.36 (m, 1H), 2.35 (d, J = 12.8 Hz, 3H), 2.17 (q, J = 9.6 Hz, 6H), 1.69-1.56 (m, 3H), 1.55-1.47 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H).
607		526.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 10.03 (d, J = 6.8 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 5.26-5.13 (m, 1H), 2.35 (s, 3H), 2.17-1.95 (m, 12H), 1.58 (d, J = 6.4 Hz, 3H).
608		518.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.75-8.67 (m, 1H), 8.54 (s, 1H), 8.26 (s, 2H), 7.84-7.79 (m, 1H), 7.79-7.73 (m, 1H), 7.23-7.16 (m, 1H), 6.60-6.51 (m, 1H), 6.41-6.32 (m, 1H), 5.40-5.20 (m, 1H), 3.89-3.82 (m, 4H), 3.57-3.51 (m, 4H), 2.15 (s, 3H), 2.09 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −135.91 (1F).

TABLE 2-continued

Characterization of exemplary compounds.

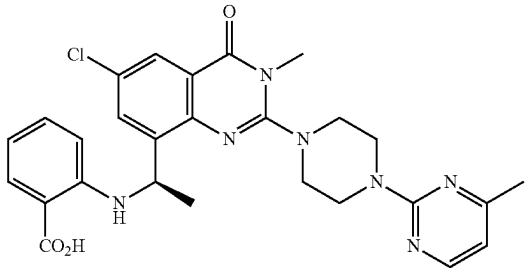
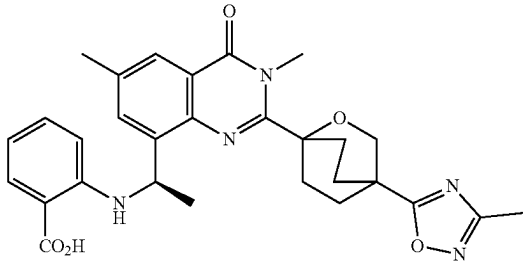
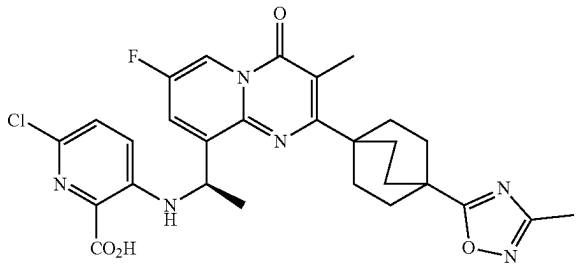
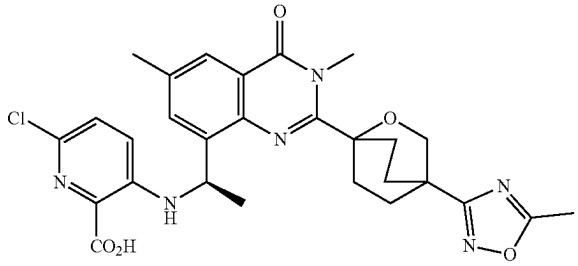
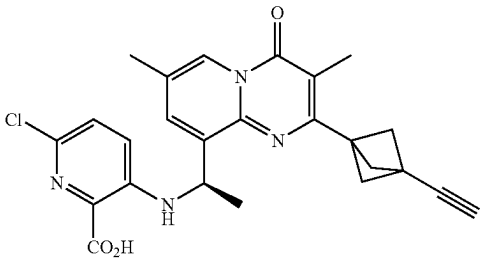
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
609		534.1	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.19 (d, J = 4.8 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.89 (dd, J = 1.6 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.13-7.05 (m, 1H), 6.54 (d, J = 5.2 Hz, 1H), 6.50 (t, J = 7.2 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 5.47 (q, J = 6.4 Hz, 1H), 4.08-3.97 (m, 4H), 3.66 (s, 3H), 3.45-3.37 (m, 4H), 2.34 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H).
610		530.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.90-8.44 (m, 1H), 7.85-7.75 (m, 2H), 7.60-7.52 (m, 1H), 7.18-7.05 (m, 1H), 6.53-6.43 (m, 1H), 6.42-6.32 (m, 1H), 5.51-5.35 (m, 1H), 4.27-4.19 (m, 2H), 3.78 (s, 3H), 2.68-2.54 (m, 2H), 2.45-2.19 (m, 12H), 1.56 (d, J = 6.8 Hz, 3H).
611		567.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.67 (s, 1H), 8.73-8.72 (m, 1H), 8.26 (s, 1H, FA), 7.63-7.62 (m, 1H), 7.05-7.03 (m, 1H), 6.67 (s, 1H), 5.45-5.25 (m, 1H), 2.39 (s, 3H), 2.32 (s, 3H), 2.19-2.17 (m, 6H), 2.05-2.03 (m, 6H), 1.61 (d, J = 6.4 Hz, 3H).
612		565.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.97 (brs, 1H), 8.49-8.38 (m, 1H), 7.86-7.81 (m, 1H), 7.64-7.58 (m, 1H), 7.37-7.31 (m, 1H), 7.10-7.02 (m, 1H), 5.45-5.32 (m, 1H), 4.20-4.12 (m, 2H), 3.78 (s, 3H), 2.68-2.52 (m, 5H), 2.47-2.40 (m, 1H), 2.39 (s, 3H), 2.29-2.12 (m, 5H), 1.63 (d, J = 6.8 Hz, 3H).
613		463.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.01-8.44 (m, 2H), 7.82-7.52 (m, 1H), 7.34-7.18 (m, 1H), 7.11-6.91 (m, 1H), 5.41-5.21 (m, 1H), 3.16 (s, 1H), 2.58-2.51 (m, 6H), 2.35-2.27 (m, 3H), 2.21 (s, 3H), 1.66 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

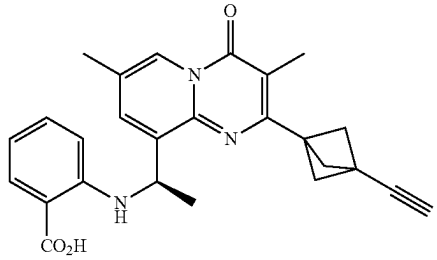
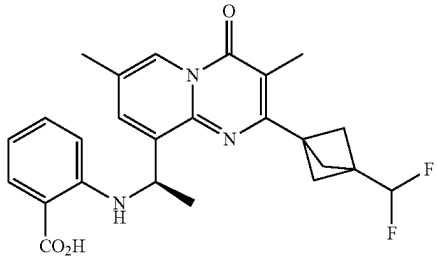
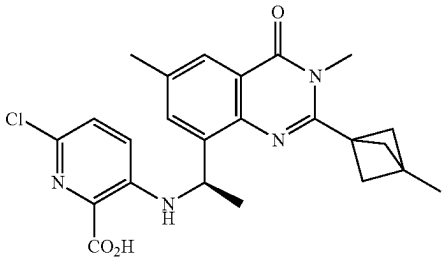
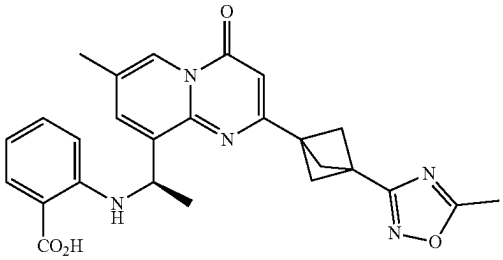
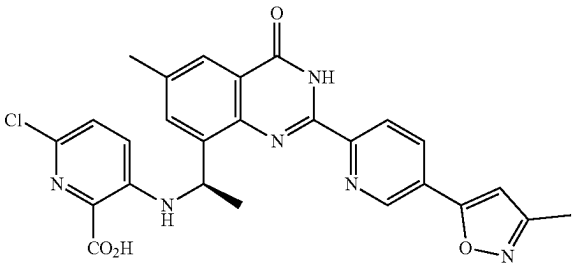
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
614		428.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.92-8.45 (m, 2H), 7.92-7.74 (m, 1H), 7.67-7.58 (m, 1H), 7.29-7.06 (m, 1H), 6.59-6.46 (m, 1H), 6.46-6.32 (m, 1H), 5.43-5.00 (m, 1H), 3.15 (s, 1H), 2.57-2.52 (m, 6H), 2.30 (s, 3H), 2.21 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
615		454.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.76-8.33 (m, 2H), 7.88-7.70 (m, 1H), 7.70-7.58 (m, 1H), 7.29-7.12 (m, 1H), 6.55-6.40 (m, 2H), 6.32-5.94 (m, 1H), 5.46-5.11 (m, 1H), 2.37-2.27 (m, 9H), 2.23 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −122.17 (2F).
616		453.0	^{1}H NMR (400 MHz, MeOH-d$_4$, ppm): δ 8.26 (s, 1H), 7.84 (s, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.97 (, J = 8.8 Hz, 1H), 5.56 (q, J = 6.8 Hz, 1H), 3.70 (s, 3H), 2.35 (s, 3H), 2.28-2.23 (m, 6H), 1.61 (d, J = 6.8 Hz, 3H), 1.29 (s, 3H).
617		471.2	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.72 (s, 1H), 8.62 (s, 1H), 7.82-7.79 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.54-6.47 (m, 2H), 6.37 (s, 1H), 5.36 (s, 1H), 2.58 (s, 3H), 2.51-2.42 (m, 6H), 2.34 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H).
618		517.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.03 (s, 1H), 9.21 (d, J = 1.2 Hz, 1H), 8.85 (s, 1H), 8.70 (d, J = 8.4 Hz, 1H), 8.47 (dd, J = 8.4, 1.6 Hz, 1H), 7.90 (s, 1H), 7.66 (s, 1H), 7.36-7.17 (m, 2H), 7.08 (t, J = 6.8 Hz, 1H), 5.73-5.38 (m, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).

TABLE 2-continued

Characterization of exemplary compounds.

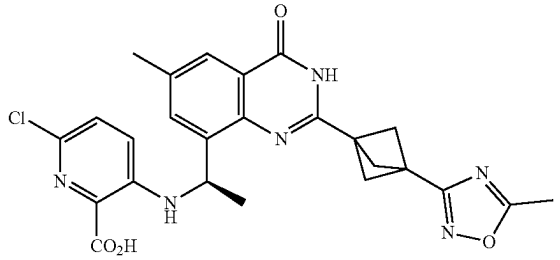
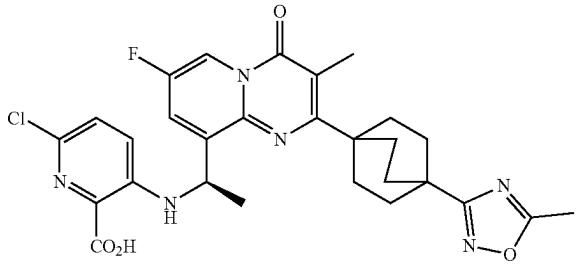
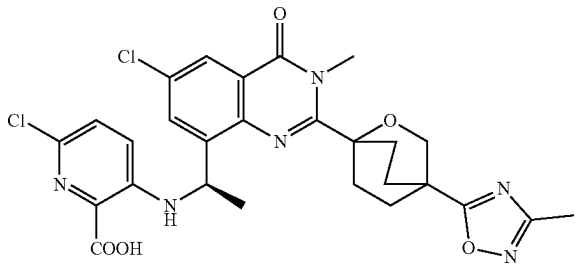
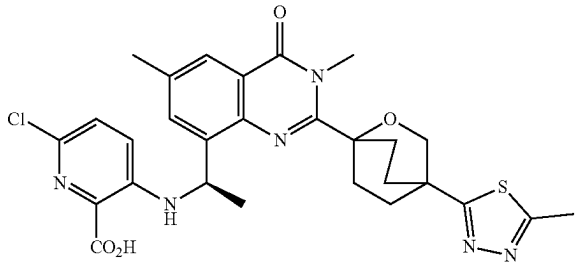
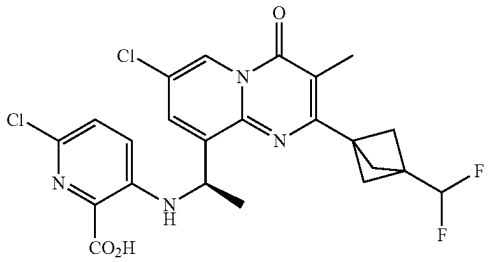
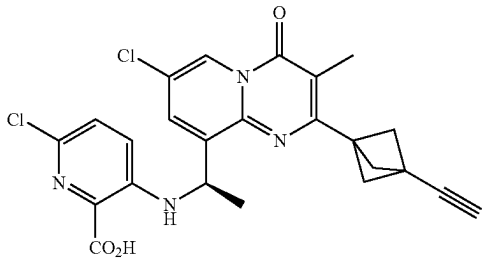
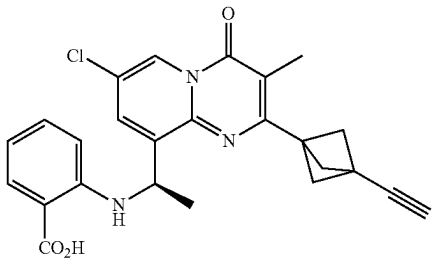
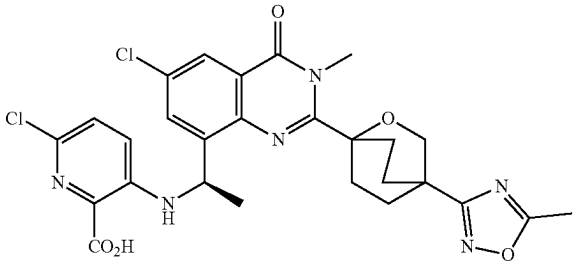
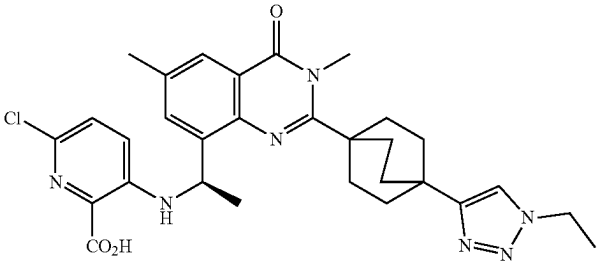
Compound	Structure	LCMS (ESI, m/z): [M + H]$^+$	^{1}H NMR & ^{19}F NMR
619		507.0	^{1}H NMR (400 MHz, MeOH-d$_4$) δ 7.89 (d, J = 1.2 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 5.54 (q, J = 6.4 Hz, 1H), 2.69-2.61 (m, 6H), 2.60 (s, 3H), 2.40 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).
620		567.2	As 1.0 FA salt. ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm) δ 9.62 (s, 1H), 8.73-8.72 (m, 1H), 8.27 (s, 1H, FA), 7.62 (d, J = 6.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 7.2 Hz, 1H), 5.41-5.17 (m, 1H), 2.56 (s, 3H), 2.39 (s, 3H), 2.21-2.14 (m, 6H), 2.02-1.92 (m, 6H), 1.61 (d, J = 6.4 Hz, 3H).
621		585.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 9.43 (s, 1H), 8.02-7.91 (m, 1H), 7.75-7.59 (m, 1H), 7.18-7.07 (m, 1H), 6.82-6.66 (m, 1H), 5.49-5.30 (m, 1H), 4.30-4.21 (m, 2H), 3.81 (s, 3H), 2.68-2.56 (m, 2H), 2.47-2.20 (m, 9H), 1.65-1.53 (m, 3H).
622		581.1	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 12.98 (s, 1H), 8.48-8.39 (m, 1H), 7.87-7.81 (m, 1H), 7.65-7.58 (m, 1H), 7.38-7.31 (m, 1H), 7.12-7.02 (m, 1H), 5.44-5.35 (m, 1H), 4.27-4.17 (m, 2H), 3.79 (s, 3H), 2.72 (s, 3H), 2.69-2.52 (m, 2H), 2.48-2.41 (m, 1 H), 2.39 (s, 3H), 2.34-2.18 (m, 5H), 1.68-1.57 (m, 3H).
623		489.0	^{1}H NMR (400 MHz, DMSO-d$_6$, ppm): δ 8.70-8.59 (m, 1H), 8.53-8.38 (m, 1H), 7.78-7.58 (m, 1H), 7.43-7.26 (m, 1H), 7.20-7.05 (m, 1H), 6.38-5.96 (m, 1H), 5.39-5.18 (m, 1H), 2.35-2.29 (m, 9H), 2.24 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d$_6$, ppm): δ −122.15 (2F).

TABLE 2-continued

Characterization of exemplary compounds.

Compound	Structure	LCMS (ESI, m/z): [M + H]+	1H NMR & 19F NMR
624		483.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.76 (d, J = 2.0 Hz, 1H), 7.85 (s, 1H), 7.28 (s, 1H), 7.07 (s, 1H), 5.24 (t, J = 7.2 Hz, 1H), 3.18 (s, 1H), 2.59-2.50 (m, 6H), 2.21 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).
625		448.2	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.76 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.15 (s, 1H), 6.52 (t, J = 7.2 Hz, 1H), 6.39 (s, 1H), 5.30-5.26 (m, 1H), 3.17 (s, 1H), 2.54 (d, J = 2.4 Hz, 6H), 2.22 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H).
626		584.9	1H NMR (400 MHz, DMSO-d6, ppm): δ 8.73 (s, 1H), 8.02-7.92 (m, 1H), 7.84-7.71 (m, 1H), 7.35-7.19 (m, 1H), 7.03-6.87 (m, 1H), 5.48-5.29 (m, 1H), 4.23-4.08 (m, 2H), 3.79 (s, 3H), 2.65-2.52 (m, 5H), 2.45-2.38 (m, 1H), 2.29-2.11 (m, 5H), 1.73-1.53 (m, 3H).
627		576.4	1H NMR (400 MHz, DMSO-d6, ppm): δ 7.88 (s, 1H), 7.78 (s, 1H), 7.51 (s, 1H), 7.12-7.10 (m, 1H), 6.78-6.76 (m, 1H), 5.45-5.42 (m, 1H), 4.35-4.29 (m, 2H), 3.72 (s, 3H), 2.34 (s, 3H), 2.25-2.23 (m, 6H), 1.97-1.93 (m, 6H), 1.56 (d, J = 6.4 Hz, 3H), 1.44-1.40 (m, 3H).

Biological Assay Example a: Cell Proliferation Assay in T47D and SK-BR-3 Cell Lines

1. Materials

[1204] Medium and reagents used in this study are listed in the following table.

Culture medium or reagent	Vendor	Cat#
96-well TC-treated Microplates	Corning	3610
Master plate	Greiner bio-one	651201

-continued

Culture medium or reagent	Vendor	Cat#
T25 flask	Thermo Fisher	156367
FBS	Excell Bio	FND500
0.25% Trypsin	GIBCO	25200-072
RPMI1640	GIBCO	11875-093
McCoy's 5A (Modified) Medium	GIBCO	12330031
PBS	GIBCO	C14190500BT
Pen/Strep	BI	03-031-1B
Insulin	BI	41-975-100

-continued

Culture medium or reagent	Vendor	Cat#
CellTiter-Glo ® Luminescent Cell Viability Assay	Promega	G7573

2. Experimental Methods and Procedures

[1205] The breast cancer cells T47D$^{PI3K\alpha_H1047R}$ and SK-BR-3 (obtained from ATCC) were cultured in a 37° C. incubator with 5% CO_2 and 100% relative humidity. The cells were routinely sub-cultured to maintain exponential growth. Each cell assay plate well was plated with 1500 cells in 100 μL suspension with culture media. Cells were incubated overnight before compounds were added to each well. Compounds were prepared as 10 mM stock solution in dimethyl sulfoxide (DMSO). Serial dilution was made in DMSO in a 200× stock plates. 0.5 μL of the 200× compound solution was added to each cell well of the cell assay plate. The final DMSO concentration was 0.5% in each well. High control wells were 0.5% DMSO with media added to the cells and low control wells are media only added the wells in the plate. The cell assay plate was incubated for 6 days. Cell viability assay was performed according to the Promega CellTiter-Glo Assay Kit.

3. Data Analysis

[1206] Inhibition rate (IR) of the tested compounds was determined by the following formula: IR (%)=(average High control−compound well)/(average High control−average Low control)*100%. Compound IC_{50} was calculated using non-linear regression equation: Y=Bottom+(Top-Bottom)/(1+10^((LogIC$_{50}$−X)*HillSlope)). X: Log of cpd concentration; Y: Inhibition rate (IR); Top and Bottom: Plateaus in same units as Y; logIC$_{50}$: same log units as X; HillSlope: Slope factor or Hill slope.

TABLE 3

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
1	>10000
2	278
3	311
4	3644
5	65.7
6	155
7	404
8	3416
9	5648
10	533.5
11	193.8
12	248.8
13	496.2
14	955.6
15	552.9
16	829.5
17	605.6
18	128.4
19	1479
20	1450
21	107.7

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
22	4931
23	9009
24	361.3
25	>10000
26	102.2
27	1507
28	606.9
29	126.4
30	160.3
31	115.8
32	1417
33	4034
34	248.6
35	1795
36	180.5
37	2690
38	243.3
39	2337
40	102.6
41	83.1
42	391.4
43	30.3
44	670.1
45	61.6
46	187.4
47	539.6
48	125.4
49	156.3
50	807.7
51	587.6
52	3641
53	128.6
54	460.0
55	317.2
56	89.9
57	272.9
58	59.5
60	1088
61	653.2
62	1289
63	257.9
64	132.4
65	68.0
66	54.1
67	304.0
68	61.7
69	89.1
70	59.4
71	97.1
72	335.3
73	319.5
74	4014
75	436.4
76	1538
77	632.4
78	230.8
79	230.6
80	312.7
81	462.6
82	93.1
83	352.9
84	70.1
85	1600
86	88.3
87	102.2
88	289.8
89	294.1
90	258.4
91	573.3

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
92	263.8
93	164.9
94	102.7
95	59.5
96	65.0
97	34.3
98	268
99	303.2
100	6221
101	2706
102	516
103	186.1
104	536.7
105	>10000
106	153.2
107	697.9
108	1326
109	371.4
110	59.7
111	110.1
112	158.7
113	122.9
114	111.8
115	1607
116	>10000
117	>10000
118	7904
119	408.9
120	796.3
121	765.5
122	1233
123	361.4
124	275.0
125	837
126	64.4
127	366
128	72.6
129	335.7
130	118.8
131	79.4
132	1049
133	900.9
134	943
135	693.8
136	2091
137	1301
138	912.6
139	152.7
140	2756
141	64.2
142	2146
143	66.1
144	71.0
145	76.2
146	123.6
147	>10000
148	478.5
149	>10000
150	439.1
151	171.2
152	3251
153	273.1
154	486.9
155	1260
156	744.1
157	454.3
158	341.7
159	1448
160	1267

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
161	750
162	153.8
163	440.6
164	284.6
165	61.5
166	162.9
167	2500
168	124.4
169	1202
170	938
171	5806
172	2656
173	1493
174	418.4
175	1038
176	153
177	1603
178	3093
179	>10000
180	1569
181	1188
182	1126
183	138.8
184	122.8
185	2175
186	5975
187	104.2
188	131.3
189	2387
190	130.7
191	62.3
192	80.7
193	280
194	177
195	4434
196	390.1
197	149.9
198	317.0
199	344.0
200	162.0
201	221.8
202	81.6
203	333.6
204	61.4
205	55.3
206	44.4
207	3624
208	230.0
209	85.1
210	61.2
211	65.2
212	34.0
213	296.0
214	234.5
215	91.9
216	107.5
217	80.9
218	148.2
219	133.9
220	37.4
221	77.6
222	558.0
223	73.3
224	3777
225	176.5
226	>10000
227	>10000
228	3232
229	8871

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
230	1871
231	80.1
232	36.9
233	270.7
234	78.7
235	1830
236	114.1
237	627.0
238	53.7
239	46.3
240	250.3
241	51.2
242	27.7
243	51.9
244	1008
245	199.2
246	182.2
247	200.5
248	46.0
249	82.8
250	73.6
251	267.1
252	51.4
253	37.1
254	283.7
255	219.5
256	466.6
257	298.1
258	464.6
259	52.4
260	700.0
261	69.1
262	289.0
263	535.0
264	700.0
265	419.0
266	443.0
267	625.0
268	266.2
269	152.8
270	149.2
271	201.5
272	66.8
273	39.6
274	242.9
275	91.1
276	296.2
277	440.9
278	229.5
279	102.0
280	460.2
281	146.7
282	128.5
283	142.6
284	203.5
285	77.9
286	340.6
287	358.6
288	427.0
289	132.7
290	31.4
291	224.2
292	38.8
293	134.2
294	56.7
295	45.8
296	65.8
297	145.1
298	36.0

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
299	38.9
300	58.1
301	58.4
302	588.0
303	79.4
304	71.2
305	40.4
306	635.0
307	168.2
308	58.0
309	60.9
310	77.9
311	63.4
312	219.3
313	1267
314	6887
315	92.6
316	297.9
317	352.9
318	1680
319	191.9
320	168.6
321	357.4
322	99.7
323	91.7
324	97.7
325	170.4
326	244.9
327	267.6
328	220.0
329	63.8
330	4733
331	96.0
332	151.3
333	212.5
334	353.9
335	130.8
336	52.9
337	336.1
338	301.9
339	265.8
340	484.8
341	864.1
342	378.0
343	72.6
344	371.0
345	389.9
346	136.0
347	67.4
348	313.0
349	118.1
350	94.9
351	150.7
352	127.8
353	199.8
354	452.7
355	7968
356	223.9
357	142.8
358	100.6
359	115.4
360	146.5
361	107.4
362	105.8
363	77.0
364	134.1
365	94.4
366	402.4
367	104.1

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
368	113.1
369	209.5
370	87.2
371	118.5
372	70.7
373	1476
374	115.1
375	275.6
376	148.6
377	59.2
378	742.0
379	565.3
380	228.1
381	87.2
382	311.3
383	180.9
384	956.0
385	95.3
386	299.0
387	368.1
388	101.4
389	1072
390	548.4
391	174.1
392	79.4
393	323.4
394	351.6
395	66.7
396	161.0
397	87.3
398	99.5
399	127.8
400	84.4
401	102.2
402	74.5
403	175.7
404	53.9
405	498.2
406	136.7
407	652.6
408	436.3
409	145.8
410	250.9
411	128.1
412	410.4
413	326.0
414	88.7
415	1340
416	55.4
417	69.4
418	176.1
419	133.2
420	83.9
421	36.6
422	62.2
423	1161
424	80.7
425	146.9
426	66.0
427	42.1
428	239.1
429	80.9
430	60.2
431	56.2
432	628.8
433	38.1
434	97.1
435	76.3
436	294.7

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
437	173.0
438	36.4
439	138.4
440	74.7
441	72.2
442	75.6
443	76.9
444	99.8
445	175.7
446	93.5
447	189.9
448	81.1
449	58.6
450	94.5
451	108.4
452	68.7
453	42.6
454	45.8
455	246.8
456	76.1
457	86.5
458	66.0
459	120.0
460	67.1
461	73.7
462	113.3
463	488.3
464	71.0
465	94.7
466	88.5
467	42.8
468	58.3
469	37.9
470	45.7
471	48.2
472	132.0
473	49.4
474	104.8
475	132.1
476	40.3
477	128.2
478	419.8
479	54.5
480	41.8
481	74.5
482	57.0
483	108.6
484	59.7
485	71.3
486	201.5
487	180.5
488	293.0
489	182.6
490	94.5
491	81.1
492	48.2
493	86.3
494	161.2
495	97.5
496	71.3
497	369.6
498	141.9
499	43.7
500	92.6
501	65.6
502	54.3
503	30.9
504	5940
505	563.3

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
506	705.8
507	162.1
508	227.8
509	64.3
510	125.8
511	78.8
512	80.2
513	131.4
514	33.6
515	152.5
516	67.0
517	79.4
518	565.4
519	210.2
520	168.8
521	95.2
522	62.2
523	70.4
524	57.6
525	141.9
526	66.6
527	64.7
528	53.5
529	70.1
530	103.7
531	218.8
532	96.0
533	101.9
534	149.1
535	123.8
536	105.6
537	60.1
538	84.8
539	71.0
540	155.3
541	446.5
542	91.4
543	96.8
544	140.0
545	58.6
546	50.2
547	888.6
548	487.3
549	66.6
550	118.9
551	62.9
552	62.6
553	83.8
554	168.7
555	70.5
556	249.8
557	178.0
558	80.6
559	175.2
560	1115
561	170.9
562	166.1
563	356.9
564	65.9
565	57.3
566	72.9
567	55.1
568	91.5
569	86.0
570	180.5
571	117.3
572	70.1
573	71.7
574	76.6

TABLE 3-continued

Inhibition of Cancer Cell Growth of Representative Compounds in T47D$^{PI3K\alpha_H1047R}$ cells (IC_{50})

Compound#	T47D (H1047R) CTG IC_{50} (nM)
575	67.4
576	111.2
577	64.2
578	82.9
579	104.9
580	661.5
581	159.5
582	68.3
583	108.3
584	129.3
585	103.7
586	361.7
587	152.4
588	72.8
589	59.6
590	66.6
591	104.3
592	108.2
593	89.9
594	121.0
595	59.1
596	149.2
597	56.1
598	74.2
599	74.2
600	254.7
601	273.1
602	45.1
603	106.2
604	106.0
605	147.9
606	166.2
607	90.9
608	50.3
609	242.5
610	115.0
611	65.7
612	120.7
613	82.2
614	96.9
615	85.1
616	97.9
617	362.4
618	213.9
619	302.9
620	70.5
621	115.5
622	67.1
623	107.6

TABLE 4

Inhibition of Cancer Cell Growth of Representative Compounds in SK-BR-3$^{wt/wt}$ cells (IC_{50})

Compound#	SK-BR-3 (wt-PI3KCA) CTG IC_{50} (nM)
2	8287
3	6453
5	4931
6	7763
7	7491
11	3096

TABLE 4-continued

Inhibition of Cancer Cell Growth of Representative Compounds in SK-BR-3$^{wt/wt}$ cells (IC_{50})

Compound#	SK-BR-3 (wt-PI3KCA) CTG IC_{50} (nM)
12	3031
16	844
17	>10000
18	2042
19	5625
20	7217
21	2757
22	>10000
23	>10000
24	>10000
25	>10000
26	>10000
27	>10000
28	>10000
29	>10000
30	4764
31	>10000
32	>10000
33	>10000
34	>10000
35	>10000
36	4839
37	>10000
38	>10000
39	4175
40	5934
41	2932
42	>10000
43	3666
44	2936
45	2294
46	4380
47	3728
48	4412
49	>10000
50	8101
51	>10000
52	8472
53	3086
54	9163
55	8240
56	3634
57	>10000
58	5762
60	9819
61	>10000
62	8981
65	4168
67	7723
70	2712
71	3253
72	4603
81	>10000
84	3848
86	5906
87	5167
91	>10000
95	>10000
96	4099
108	>10000
113	3678
114	3310
123	>10000
124	4799
125	2578
133	>10000
135	>10000
137	>10000
138	>10000

TABLE 4-continued

Inhibition of Cancer Cell Growth of Representative Compounds in SK-BR-3$^{wt/wt}$ cells (IC_{50})

Compound#	SK-BR-3 (wt-PI3KCA) CTG IC_{50} (nM)
157	>10000
158	>10000
176	>10000
177	>10000
188	4809
189	>10000
193	>10000
197	>10000
199	>10000
203	3494
204	2617
206	1885
218	>10000
219	5399
220	2134
221	2673
222	>10000
223	4062
231	5057
232	4252
235	4682
237	5852
241	2032
242	1089
244	4612
245	6507
246	4979
247	5028
250	3509
251	5798
254	>10000

Biological Assay Example B: Human Microsomal Clearance Assay

[1207] This study aimed to assess the metabolic stability of a compound in human liver microsomes using a microsomal clearance assay.

[1208] A mixture containing 100 mM potassium phosphate, pH 7.4, 0.5 mg/mL liver microsomes, 2 mM NADPH, and 1 μM compound were prepared and added to 96-well plate. The plates were then incubated at 37° C. for different time points (0, 5, 15, 30, 45 minutes) and the reaction was stopped with acetonitrile solution containing an internal standard. The samples were then analyzed by LC/MS/MS to determine how much of the compound remained at each time point. The elimination rate constant and half-life were calculated from the data as follows: Elimination rate constant (k)=−slope; Half-life (t1/2)=0.693/k.

[1209] The in vitro intrinsic clearance, CLint, was calculated from the t1/2 as follows: CLint=(0.693/t1/2)×(1/(microsomal protein concentration (0.5 mg/mL)))×Physiological Scaling Factor.

TABLE 5

In vitro intrinsic clearance values of representative compounds.

Compound #	Clint (mL/min/kg)	T½ (min)	Compound #	Clint (mL/min/kg)	T½ (min)
6	10.1	173	492	6.40	271
130	15.1	115	539	8.02	217

TABLE 5-continued

In vitro intrinsic clearance values of representative compounds.

Compound #	Clint (mL/min/kg)	T½ (min)	Compound #	Clint (mL/min/kg)	T½ (min)
309	6.62	263	577	1.27	1367
422	8.4	207	575	5.03	346
448	0.68	2556	502	2.39	728
480	1.29	1349	590	3.84	452
555	9.67	180	552	4.18	416
503	2.62	663	Cmpd A	13.2	132

Note:

(Cmpd A is (R)-2-((1-(2-(4,4-difluoropiperidin-1-yl)-6-fluoro-3-methyl-4-oxo-4H-chromen-8-yl)ethyl)amino)benzoic acid).

Biological Assay Example C: Human Plasma Protein Binding Assay

[1210] The plasma protein binding of compounds in human plasma was determined using a dialysis method. The dialysis membrane strips were prepared by soaking them in ultra-pure water for about 1 hr at room temperature, followed by separation and soaking in ethanol:water (20:80 v:v) for about 20 min, and a final rinse with ultra-pure water. Prior to use, the membranes were rinsed and soaked for another 20 min in ultra-pure water.

[1211] The blank plasma samples were thawed, centrifuged and verified its pH values. Only the plasma with pH between 7.0-8.0 was used in the experiment. The final concentration of compound in the spiked plasma is 1 μM, with final DMSO≤10%. All samples were prepared in triplicates. The time zero (T**0**) samples was used for determining the recovery of the compound of interest after dialysis. It was prepared in the same way as other dialysis samples except it was stored at 2-8° C. before LC-MS/MS analysis.

[1212] The other spiked plasma samples were loaded onto the dialysis device and incubated at and 37±1° C. with 5% CO_2 for 6 hr. At the end of the dialysis, aliquots of samples from the plasma and buffer sides of the dialysis device were taken and processed for LC-MS/MS analysis. Detailed sample processing methods are described in the appendix (xx).

[1213] The % Unbound, % Bound, and % Recovery of the compounds were calculated from the peak area ratios of the analyte and internal standard in the plasma and buffer samples as shown in the following equations:

$$\%\ \text{Unbound} = 100 \times F/T$$

$$\%\ \text{Bound} = 100 - \%\ \text{Unbound}$$

$$\%\ \text{Recovery} = 100 * (F + T)/T0$$

[1214] where [F] is the peak area ratio of analyte/internal standard on the buffer (receiver) side of the membrane; [T] is the peak area ratio of analyte/internal standard on the plasma (donor) side of the membrane; [T**0**] is the peak area ratio of analyte/internal standard in the plasma sample at time zero.

TABLE 6

Human plasma protein binding values of representative compounds.

Compound #	% Unbound	Compound #	% Unbound
212	3.0	549	2.6
335	4.0	243	2.6
523	3.3	435	2.4
381	3.1	527	2.3
323	4.7	524	2.2
502	2.7	529	2.1
526	2.1	461	2.1

Biological Assay Example D: Rat PK Assay

[1215] This study measured pharmacokinetic profiles of compounds following a single oral dose in male SD rats. Each tested compound was prepared at 0.3 mg/ml in the formulation of 100% PEG^{400}, and administered at a dose of 10 mg/kg to 3 male rats with body weight ~220 g (Vital River Laboratory Animal Technology Co., Ltd). Blood samples (0.2 mL) were collected at 0.083, 0.25, 0.5, 1, 2, 4, 6 and 24 h after compound administration.

[1216] The collected blood samples were centrifuged to prepare plasma samples, which were then frozen at −70° C. until analysis. The plasma samples were mixed with ACN solution containing internal standards and vortexed for 5 min. The supernatant of the mixture obtained by centrifuging at 14000 rpm at 4° C. for 10 min were injected to LC-MS/MS for plasma concentration determination.

[1217] The pharmacokinetic parameters were calculated using standard noncompartmental methods with Phoenix WinNonLin Professional Version 8.1. The calculated parameters included terminal half-life (T1/2), area under the concentration-time curve (AUC), Tmax, Cmax, and other parameters.

TABLE 7

Rat PK data of representative compounds.

Compound #	Rat PO (5 mpk) F %	Rat PO (5 mpk) C_{max} (uM)	Rat PO (5 mpk) AUC last (uM · hr)
275	33	3.0	13
296	54	4.5	14
343	54	4.7	15
350	54	6.0	8.2
422	51	3.3	7.9
480	35	3.9	8.3
537	71	6.6	8.0
492	69	11	14
516	50	1.5	5.6
539	38	4.9	5.4
567	34	4.5	6.2
555	75	12	36

Biological Assay Example E: In Vivo Efficacy Studies in Human Lung Cancer Tumor Xenograft Model NCI-H1048

[1218] All animal experiments were performed in accordance with the standard operating procedures for animal study and handling.

[1219] The NCI-H1048 human lung cancer cells were maintained in vitro as monolayer cultured in DMEM: F12 medium (supplemented with 5% fetal bovine serum, 0.005

mg/mL insulin, 0.01 mg/mL Transferrin, 30 nM Sodium selenite, 10 nM Hydrocortisone; 10 nM beta-estradiol; 2 mM L-glutamine). All cells were grown at 37° C. in an atmosphere of 5% CO_2 in the incubator. The cells were sub-cultured twice weekly by trypsin-EDTA treatment. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[1220] For in vivo efficacy studies in NCI-H1048 tumor xenograft model, 6-8 weeks old female immune-deficient NCG mice (GemPharmatech Co., Ltd, Nanjing, China) were used for inoculation. Each mouse was inoculated subcutaneously at the flank with 10×10^6 tumor cells in 0.2 mL of PBS with Matrigel (1:1 PBS: Matrigel). Mice were treated orally twice per day (PO, BID) with compound 422 at 15 mg/kg, 50 mg/kg, compound 296 at 15 mg/kg, compound 309 at 15 mg/kg or vehicle control.

[1221] Tumor volume was calculated by measuring two perpendicular diameters using the following formula: $(L\times W^2)/2$ in which L and W refer to the length and width tumor diameter, respectively.

[1222] Exemplary compounds have been tested in this model and were found to inhibit tumor growth (see FIG. **1**).

Biological Assay Example F: In Vivo Efficacy Studies in Human Tumor Xenograft Model CAL33

[1223] All animal experiments were performed in accordance with the standard operating procedures for animal study and handling.

[1224] The CAL33 human oral and pharyngeal cancer cells were cultured in DMEM medium (supplemented with 10% fetal bovine serum). All cells were grown at 37° C. in an atmosphere of 5% CO_2 in the incubator. The cells were sub-cultured twice weekly by trypsin-EDTA treatment. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[1225] For in vivo efficacy studies in CAL33 tumor xenograft model, 6-8 weeks old female athymic BALB/c nude mice (Beijing Vital River Laboratory Animal Technology Co., Ltd.) were subcutaneously inoculated at the flank with 5.0×10^6 CAL33 cells (suspended in sterile Ca- and Mg-free PBS, mixed 1:1 by volume with Matrigel). Mice were randomized for efficacy studies when tumor reached the size of 100-200 mm^3. Mice were treated orally twice per day (PO, BID) with compound 275 at 100 mg/kg or vehicle control. Tumor volume was calculated by measuring two perpendicular diameters using the following formula: $(L\times W^2)/2$ in which L and W refer to the length and width tumor diameter, respectively.

[1226] Exemplary compound has been tested in this model and were found to inhibit tumor growth (see FIG. **2**).

[1227] The Summary and Abstract sections may set forth one or more but not all exemplary embodiments of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.

[1228] The present invention has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[1229] With respect to aspects of the invention described as a genus, all individual species are individually considered separate aspects of the invention. If aspects of the invention are described as "comprising" a feature, embodiments also are contemplated "consisting of" or "consisting essentially of" the feature.

[1230] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the ordinary skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the ordinarily skilled artisan in light of the teachings and guidance.

[1231] The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments.

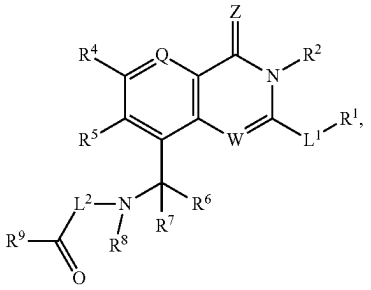
[1232] All of the various aspects, embodiments, and options described herein can be combined in any and all variations.

[1233] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent that any meaning or definition of a term in this document conflicts with any meaning or definition of the same term in a document incorporated by reference, the meaning or definition assigned to that term in this document shall govern. This application specifically incorporates herein the following two applications: International Application No. PCT/CN2022/088724, filed Apr. 24, 2022, and PCT/CN2022/118054, filed Sep. 9, 2022, the content of each of which is incorporated herein by reference in its entirety for all purposes.

What is claimed is:

1. A compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof:

Formula I



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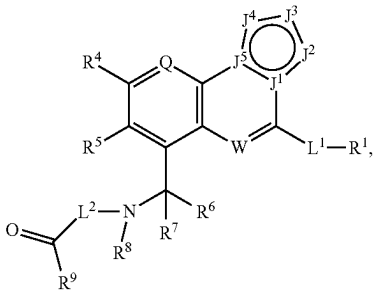
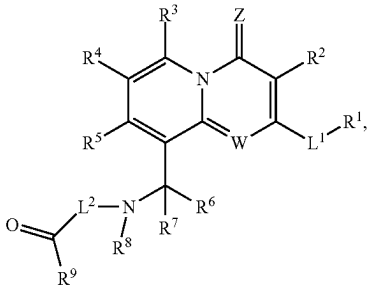
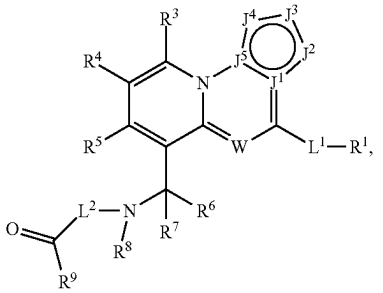
Formula II



Formula III



Formula IV



wherein:

W is CR^{10} or N, wherein R^{10} is hydrogen, deuterium, halogen, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or C_{1-4} alkoxy optionally substituted with 1-3 fluorine;

Q is Nor CR^3;

Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy;

J^1, J^2, J^3, J^4, and J^5 together form an optionally substituted 5- or 6-membered ring having 2 or 3 ring heteroatoms, preferably, 2 or 3 ring nitrogen atoms, preferably, an optionally substituted 5-membered heteroaryl wherein J^4 is N, and J^5 is C or N;

L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

R^1 is a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

R^2, R^3, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1; preferably, in Formula I, R^2 is not halogen, CN, OH, or OG^1;

R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2;

R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

L^2 is optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$;

wherein:

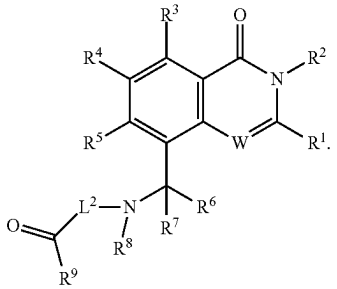
G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

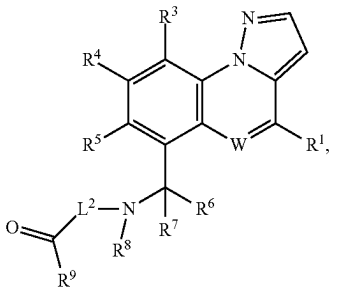
2. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, having a structure according to Formula I-1:

Formula I-1

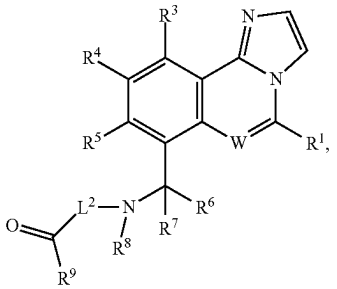


3. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, having a structure according to Formula II-1, II-2, or II-3:

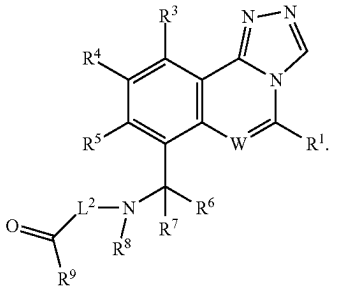
Formula II-1



Formula II-2

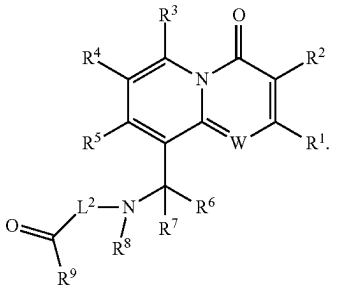


Formula II-3



4. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, having a structure according to Formula III-1:

Formula III-1



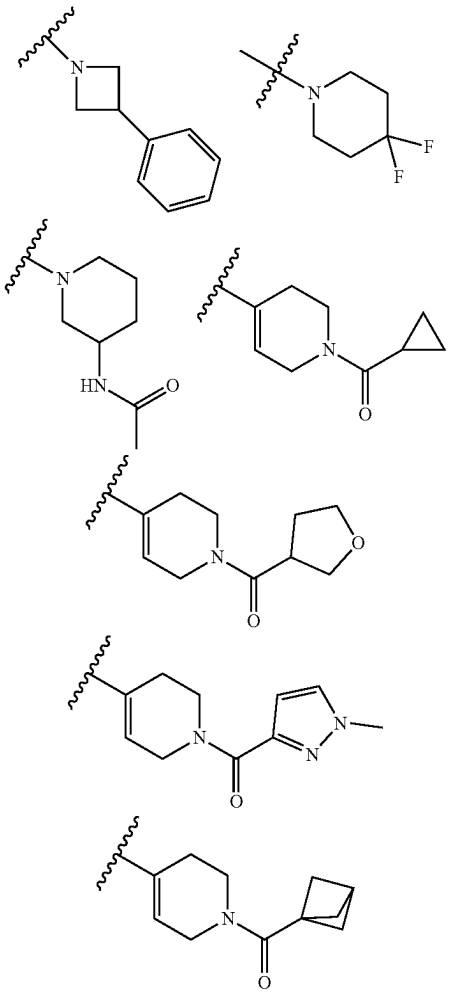
5. The compound of any one of claims **1-4**, or a pharmaceutically acceptable salt thereof, wherein W is N.

6. The compound of any one of claims **1-4**, or a pharmaceutically acceptable salt thereof, wherein W is CH.

7. The compound of any one of claims **1-6**, or a pharmaceutically acceptable salt thereof, wherein R^1 is defined:

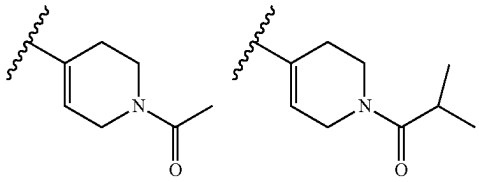
(1) according to Embodiment B7,
(2) according to Embodiment B8,
(3) according to Embodiment B9,
(4) according to Embodiment B10,
(5) according to Embodiment B11,
(6) according to Embodiment B12,
(7) according to Embodiment B14,
(8) according to Embodiment B15,
(9) according to Embodiment B17,
(10) according to Embodiment B18,
(11) according to Embodiment B20, or
(12) according to Embodiment B21.

8. The compound of any one of claims **1-6**, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from



or

R^1 is selected from



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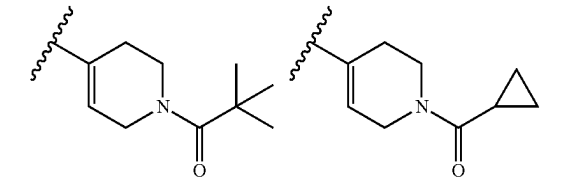

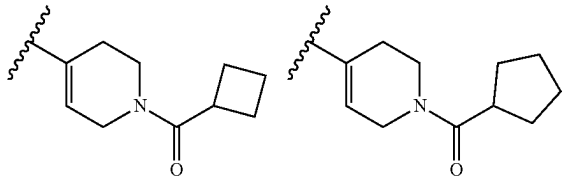

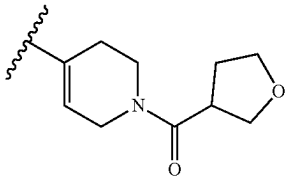

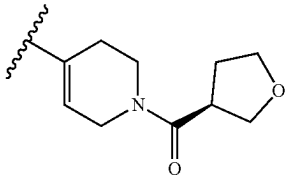

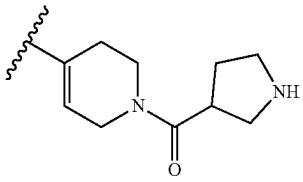

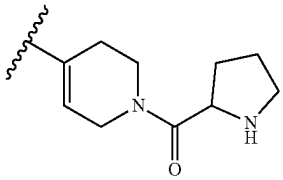

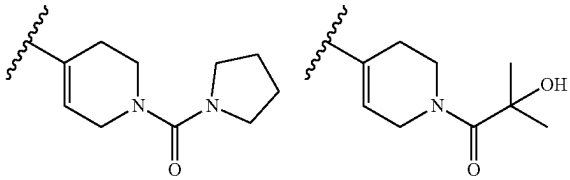

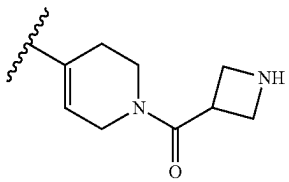

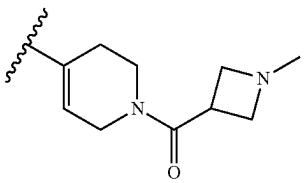

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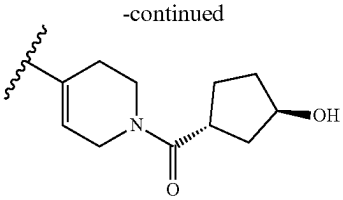

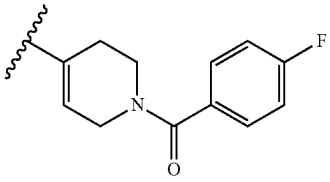

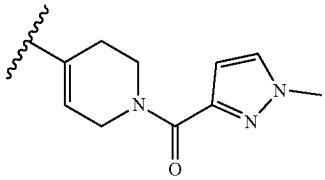

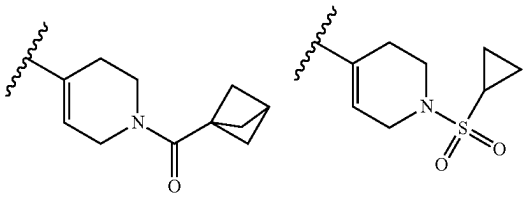

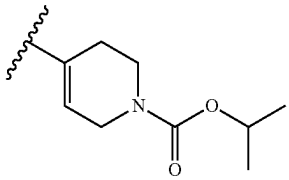

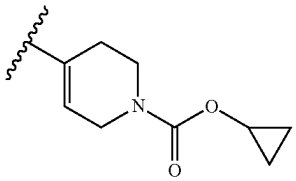

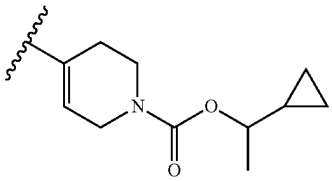

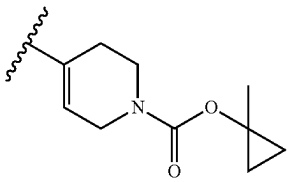

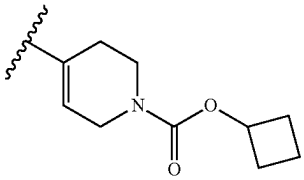

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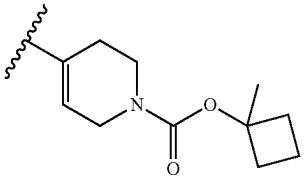

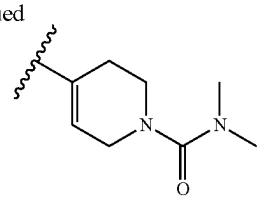

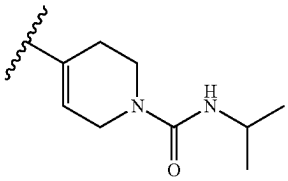

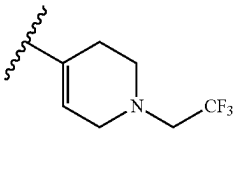

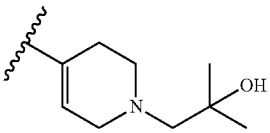

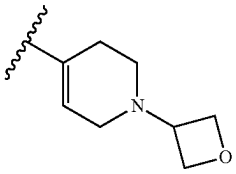

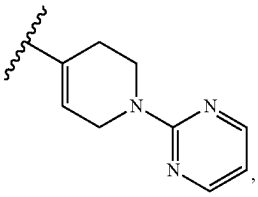

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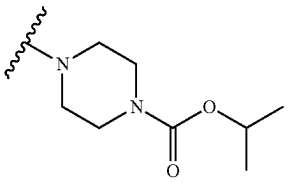
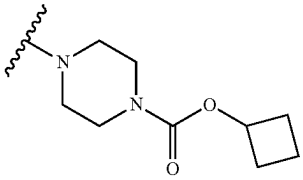
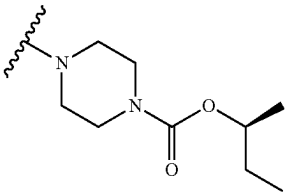
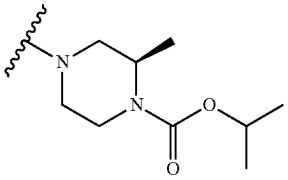
R^1 is selected from









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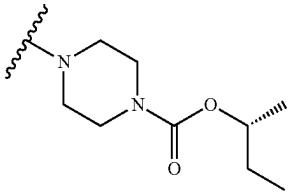

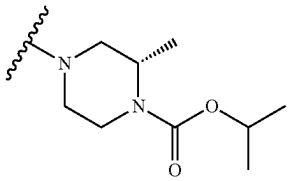

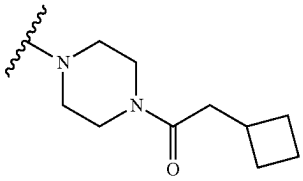

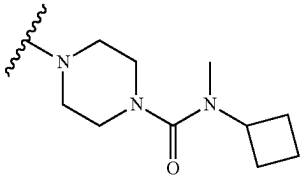

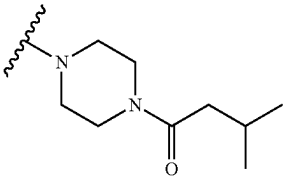

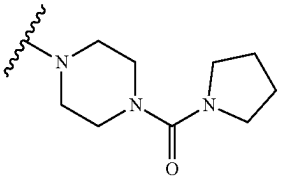

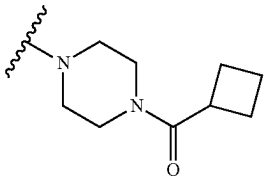

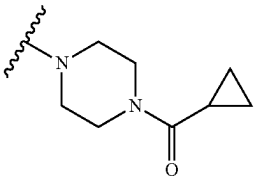

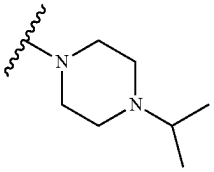

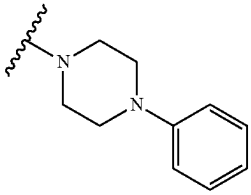

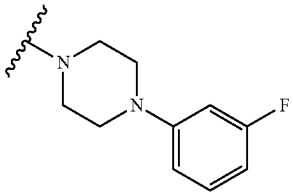

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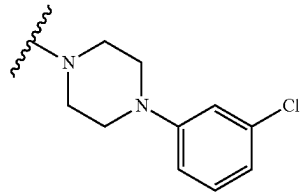

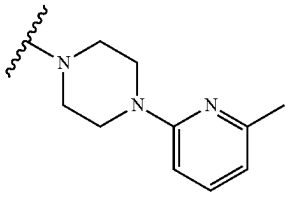

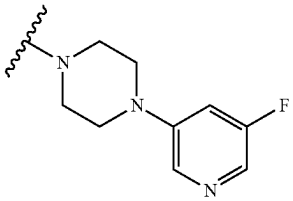

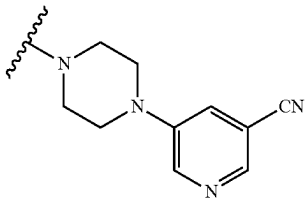

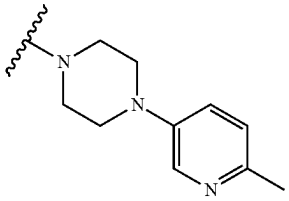

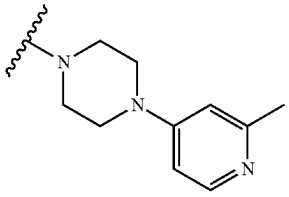

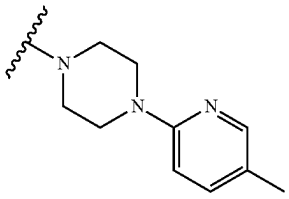

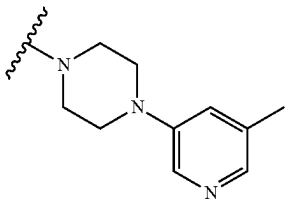

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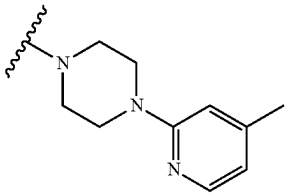

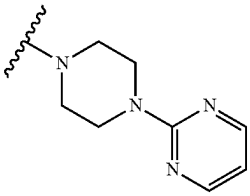

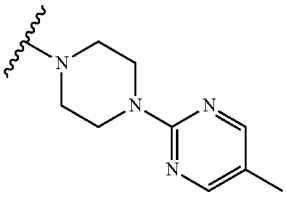

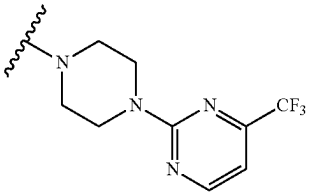

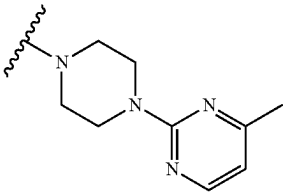

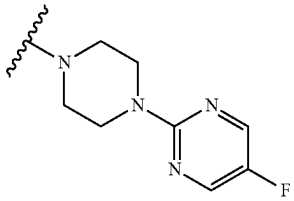

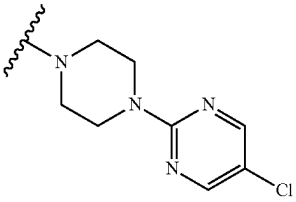

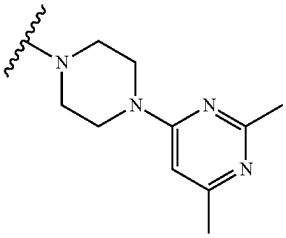

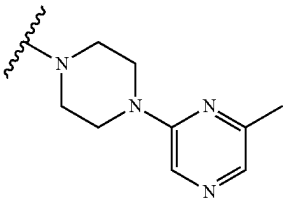

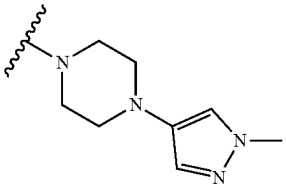

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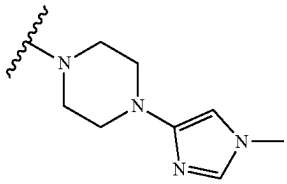

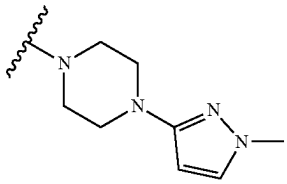

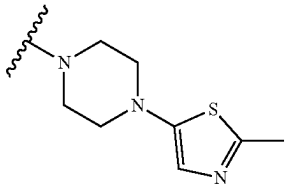

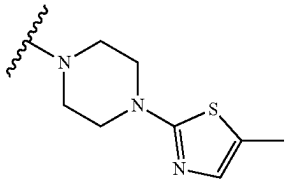

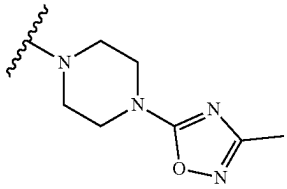

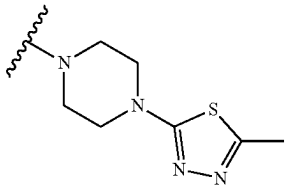

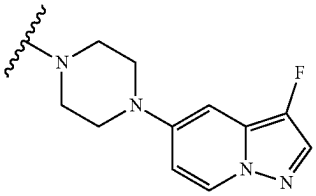

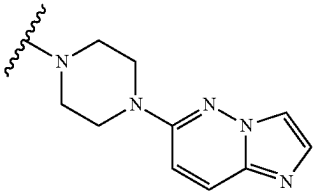

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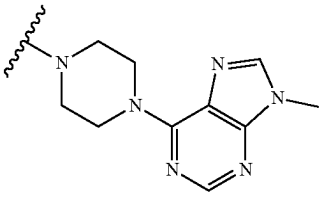

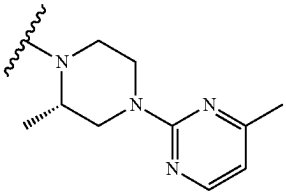

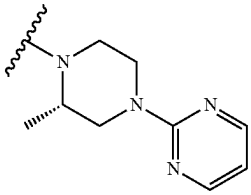

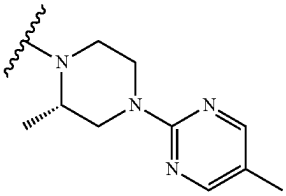

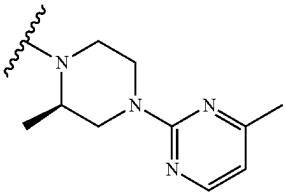

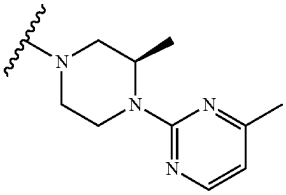

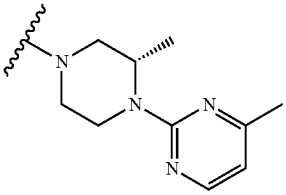

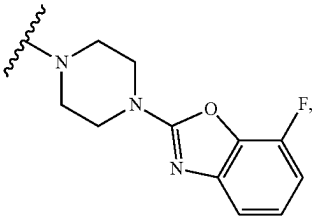

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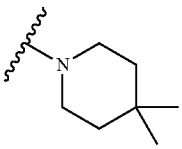

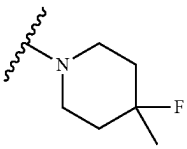

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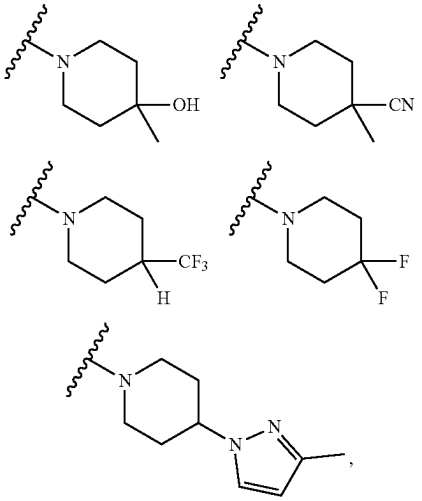

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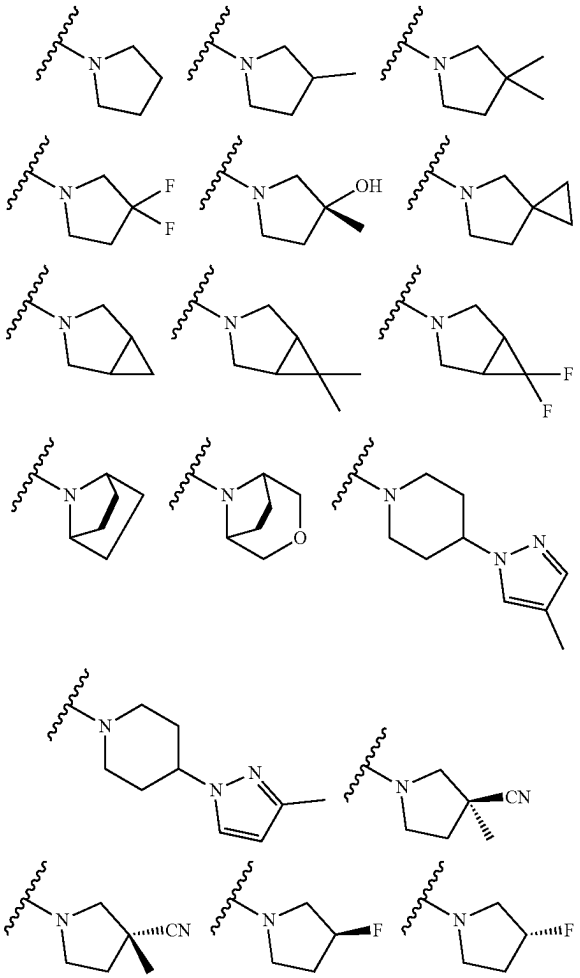

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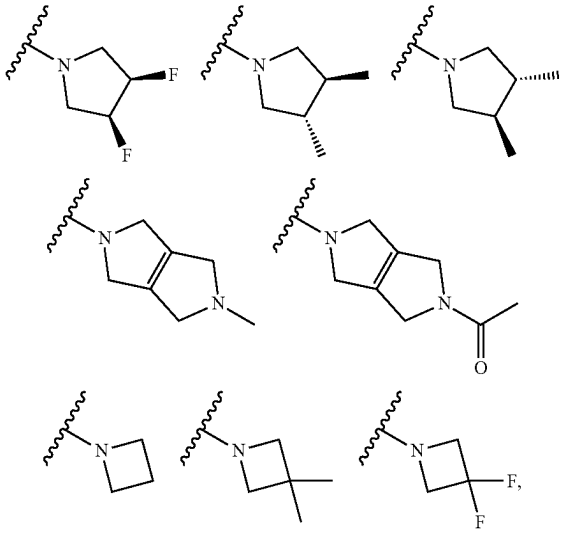

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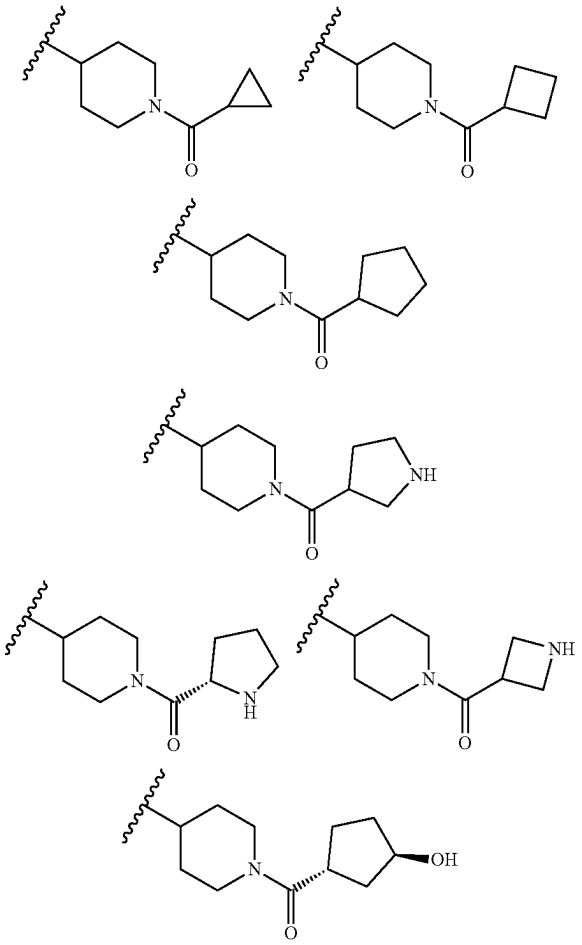

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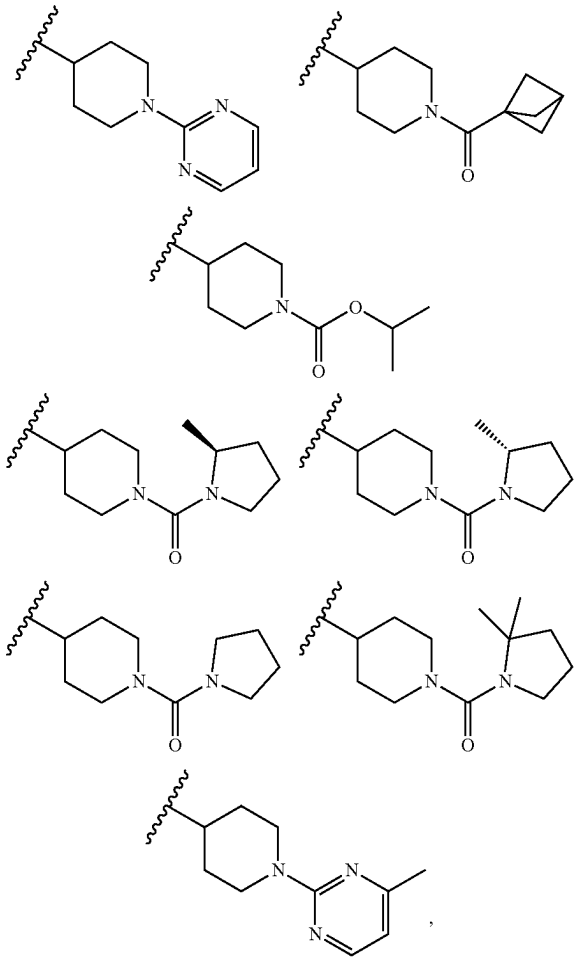

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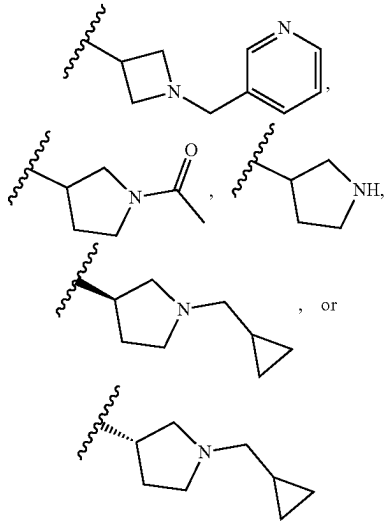

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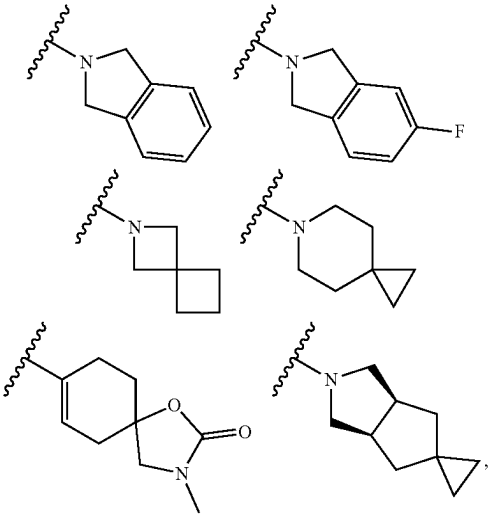

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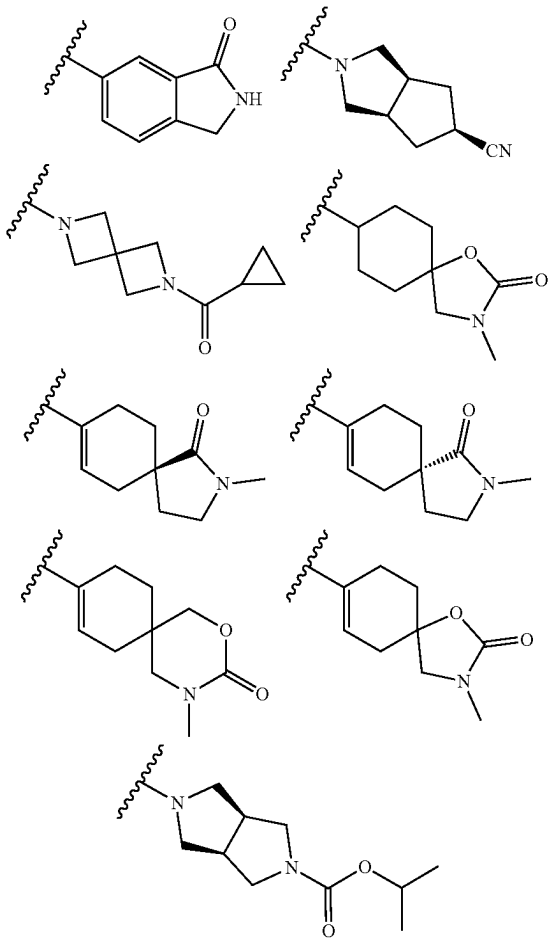

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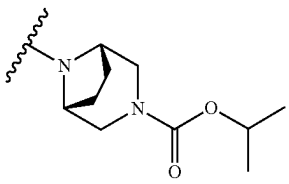

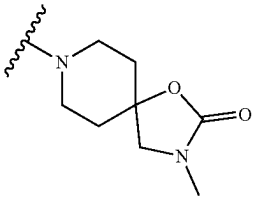

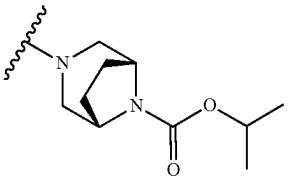

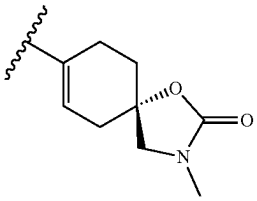

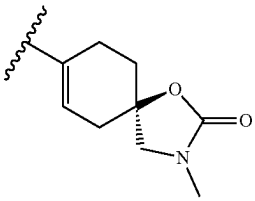

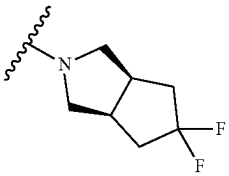

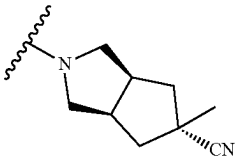

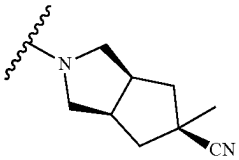

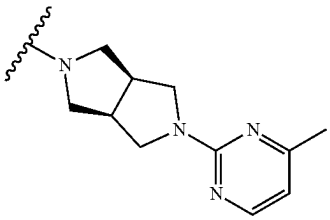

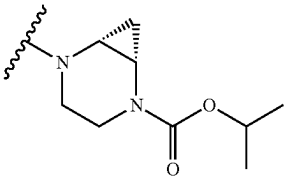

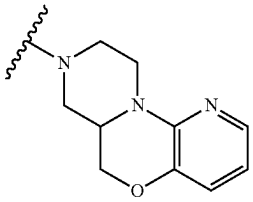

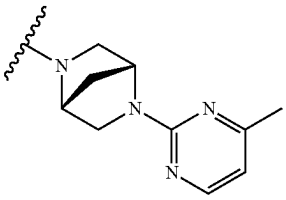

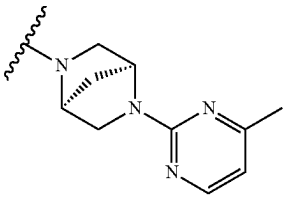

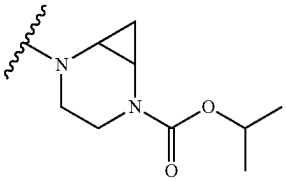

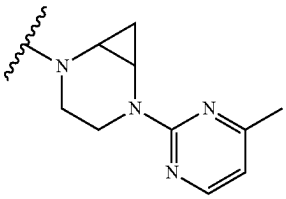

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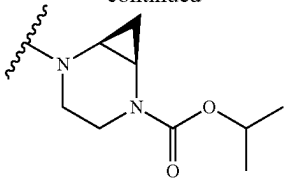

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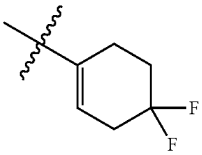

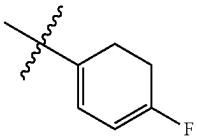

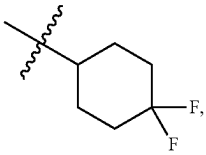

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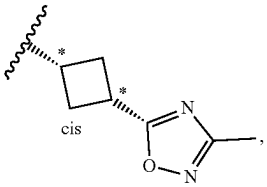

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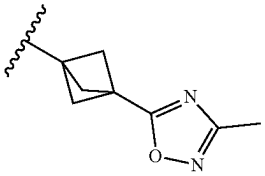

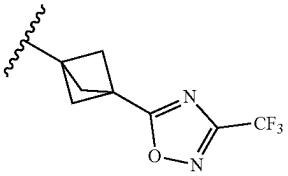

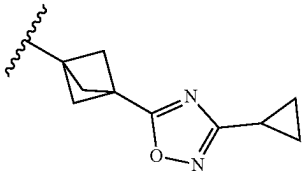

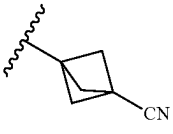

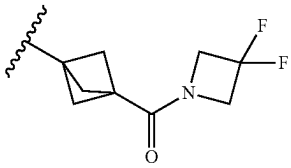

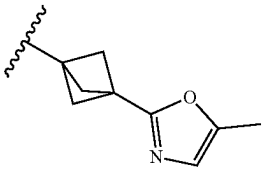

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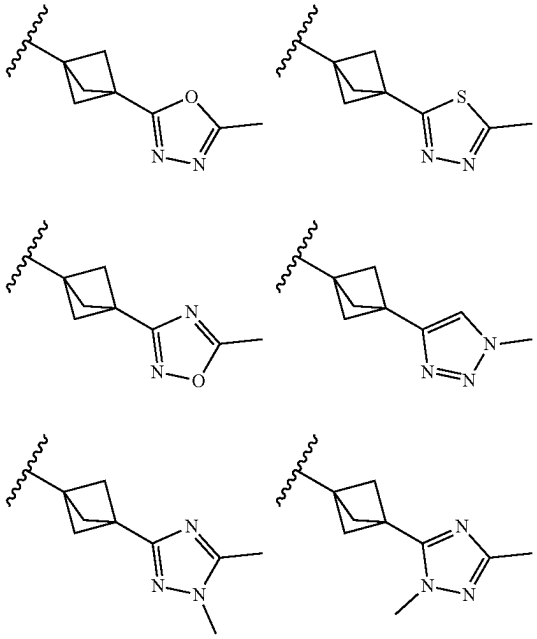

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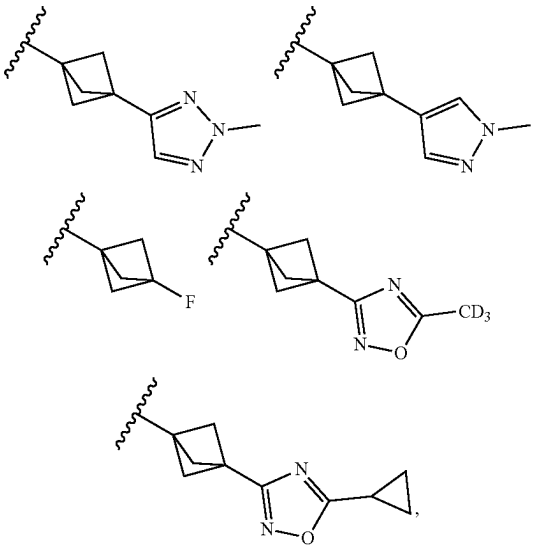

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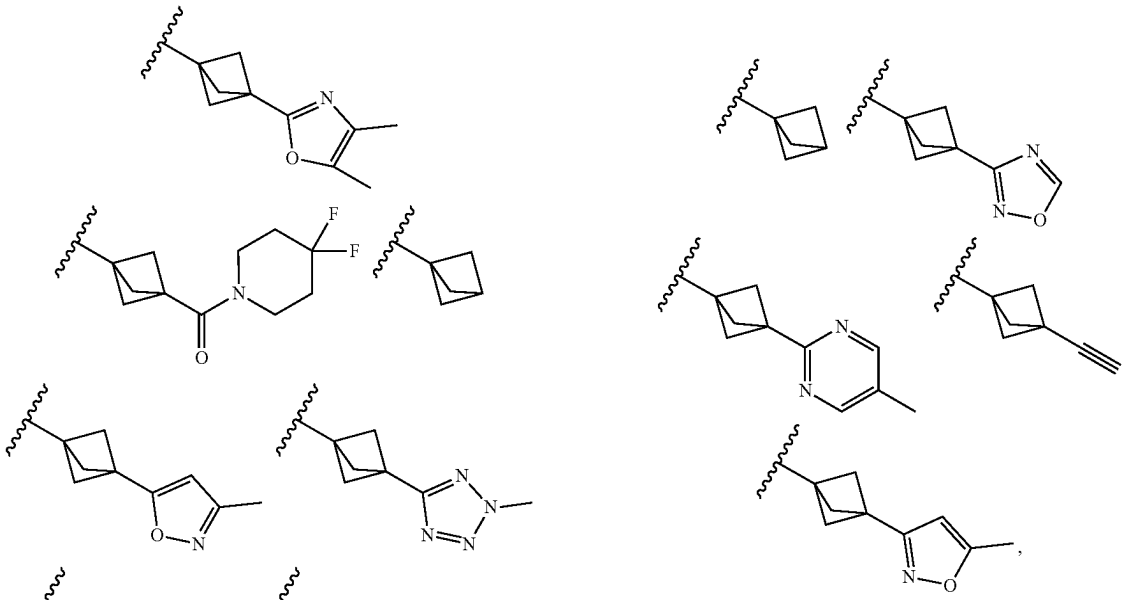

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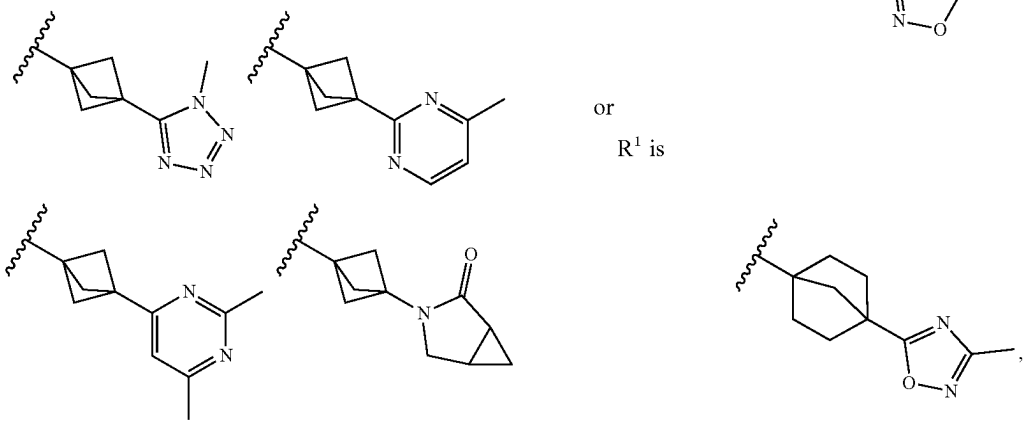

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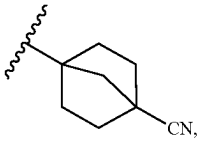

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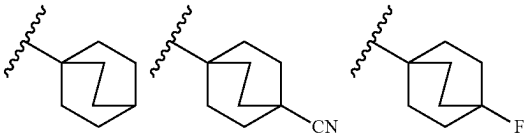

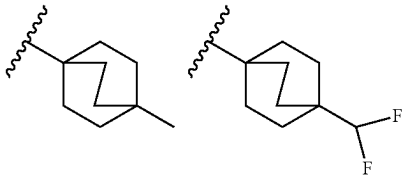

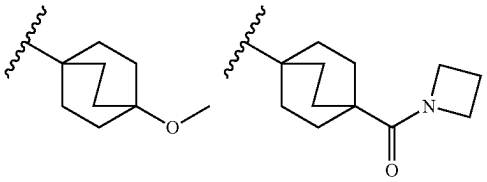

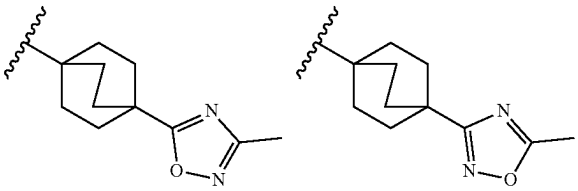

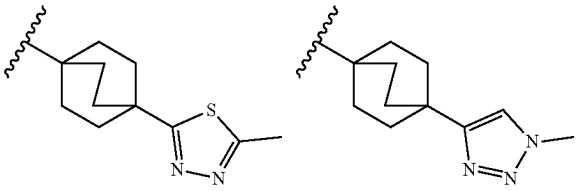

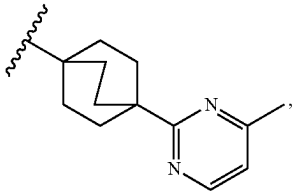

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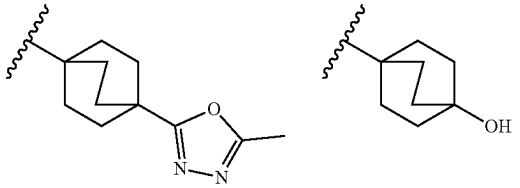

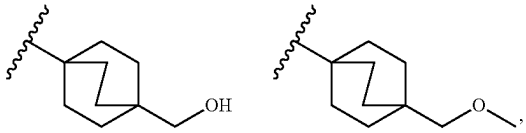

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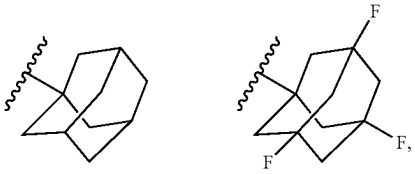

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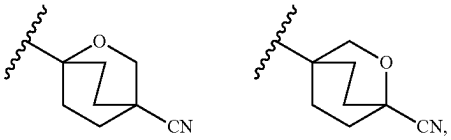

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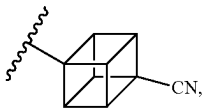

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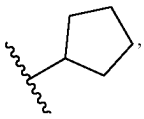

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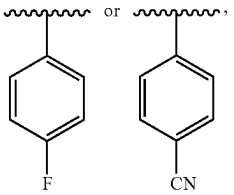

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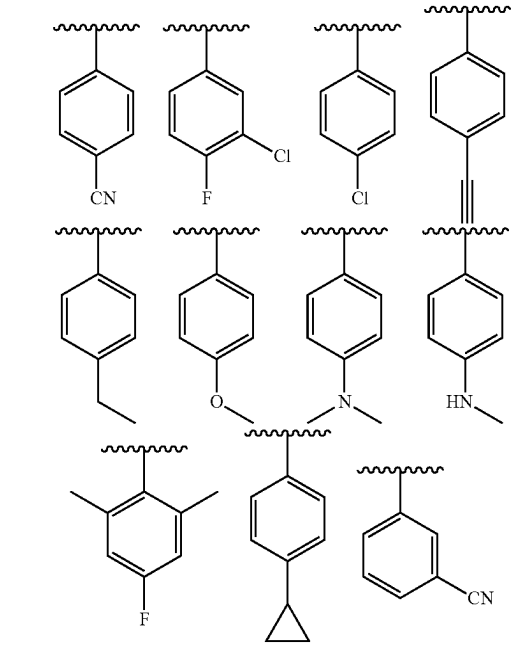

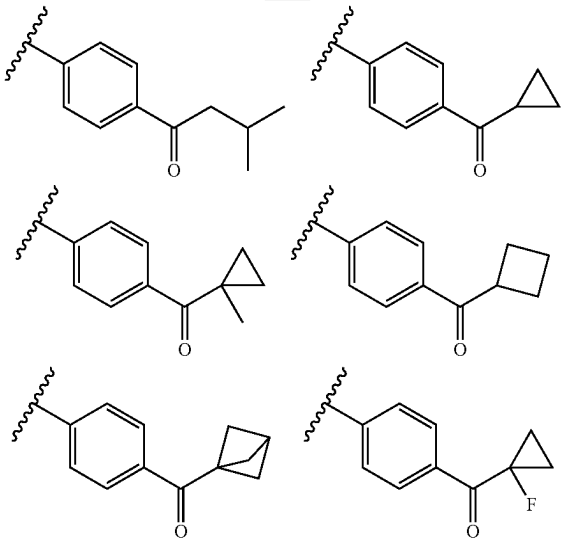

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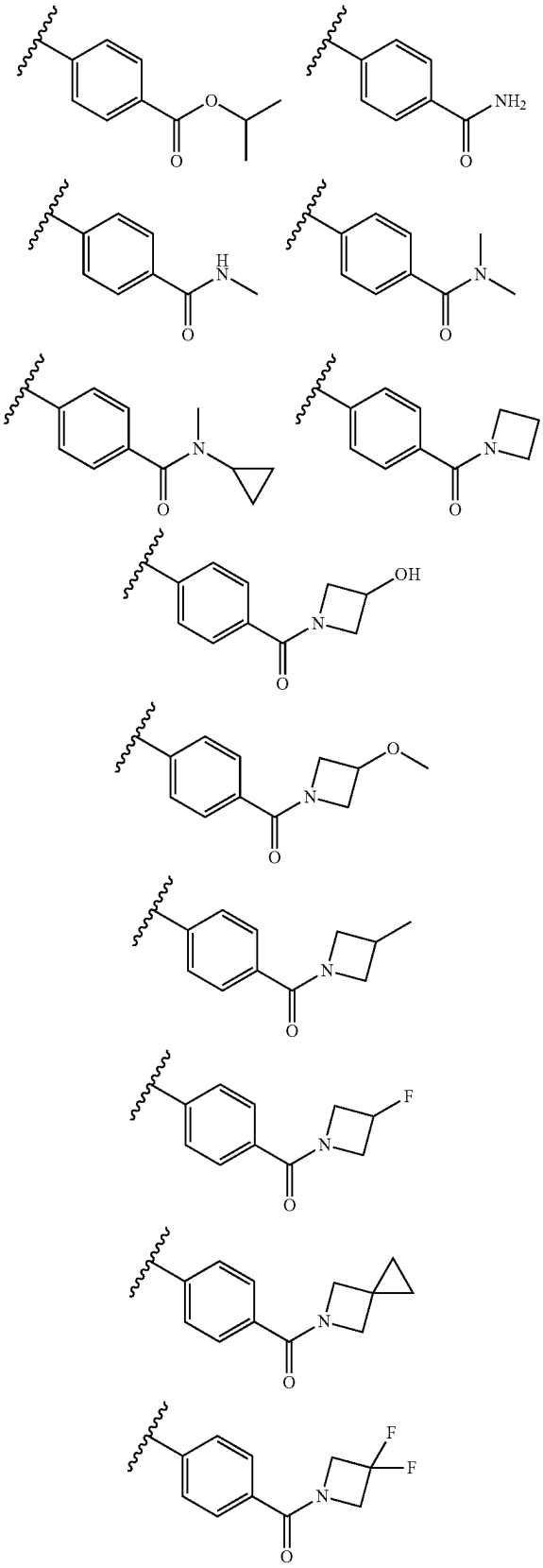

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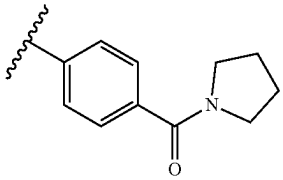

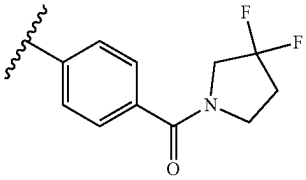

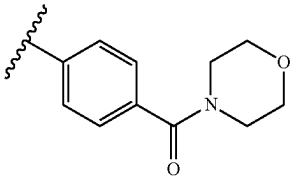

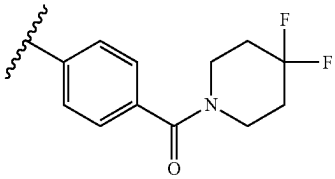

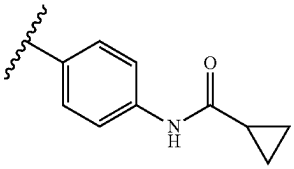

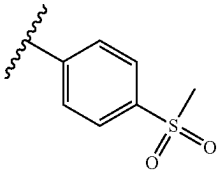

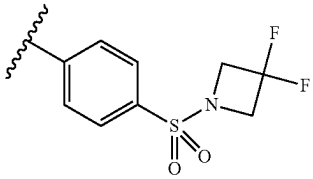

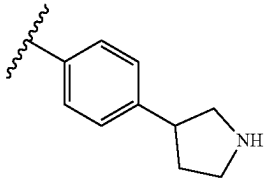

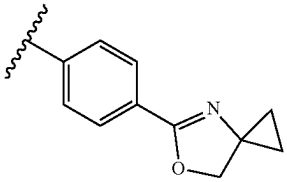

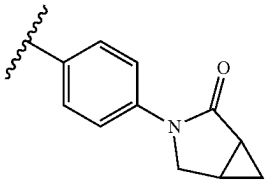

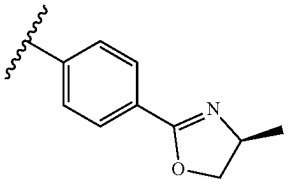

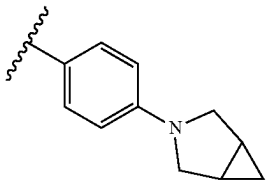

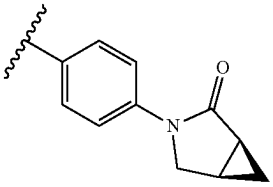

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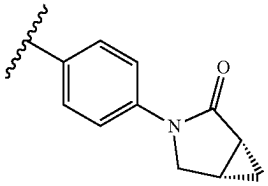

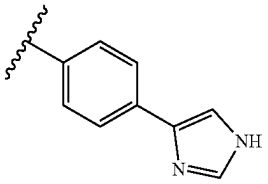

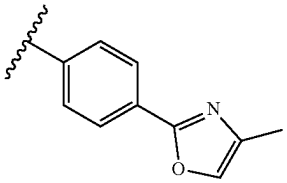

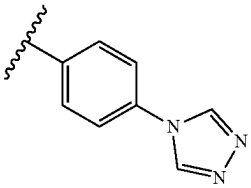

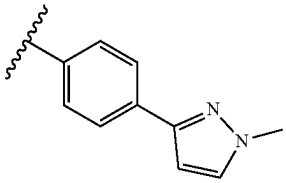

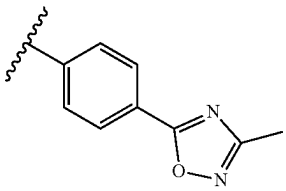

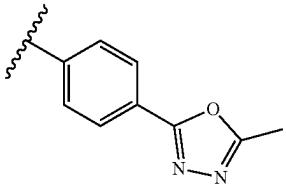

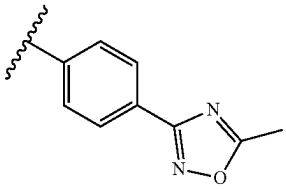

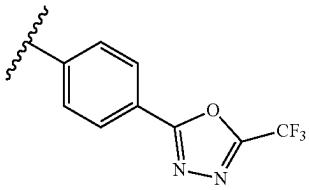

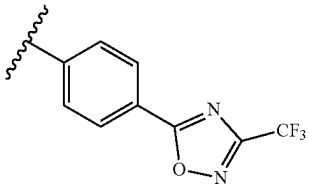

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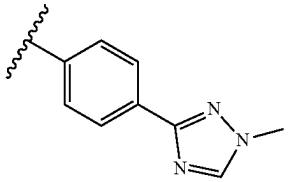

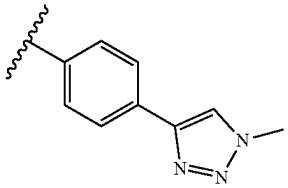

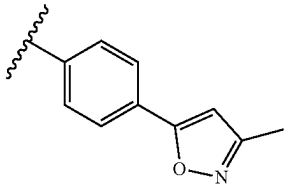

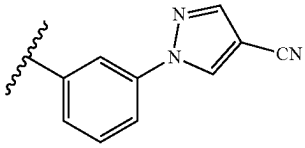

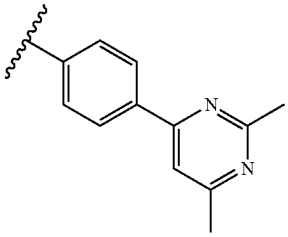

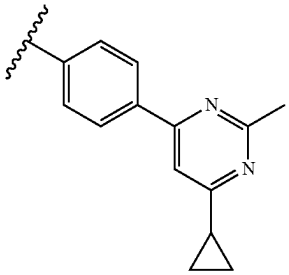

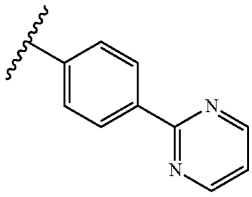

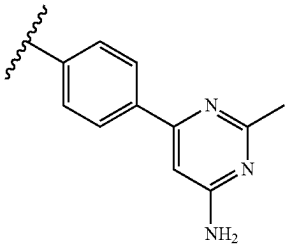

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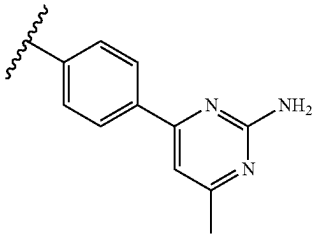

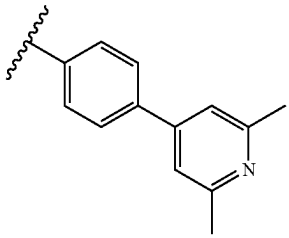

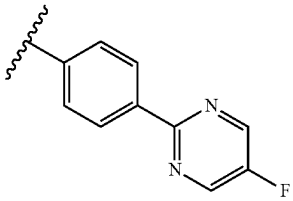

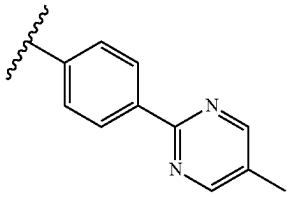

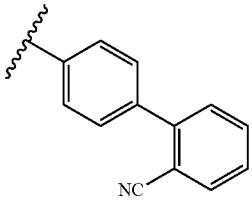

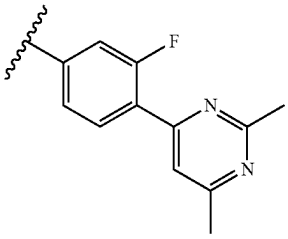

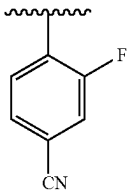

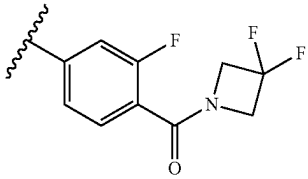

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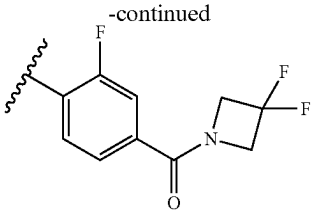

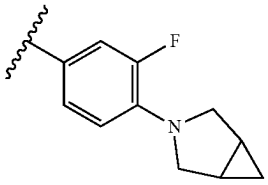

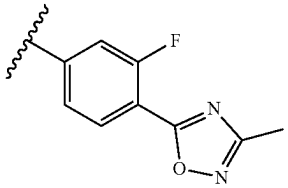

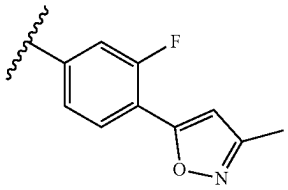

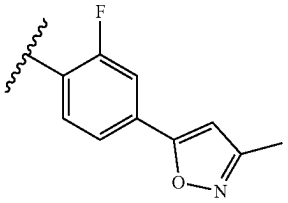

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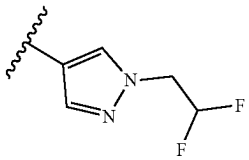

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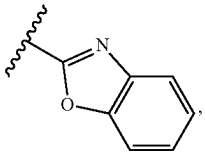

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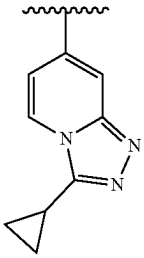

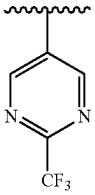

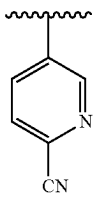

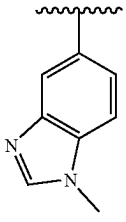

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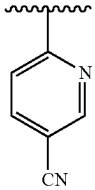

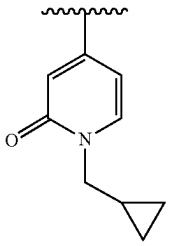

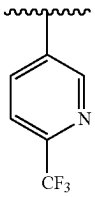

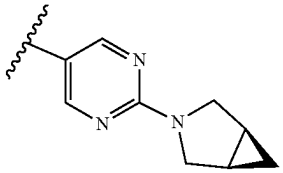

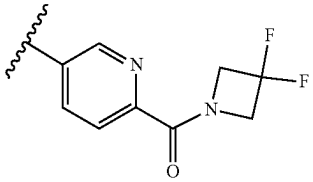

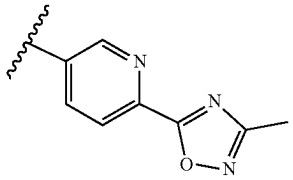

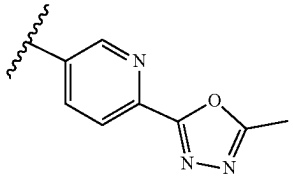

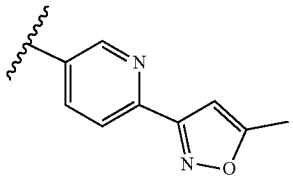

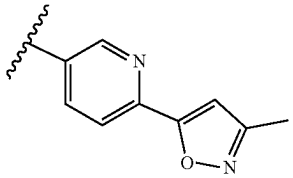

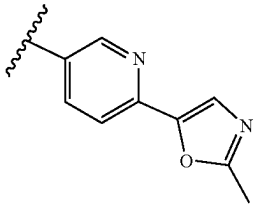

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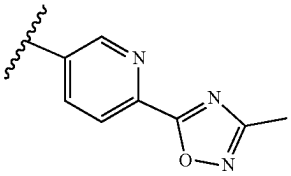

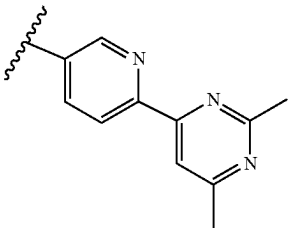

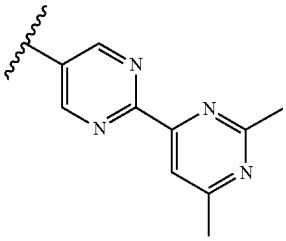

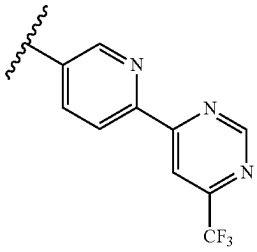

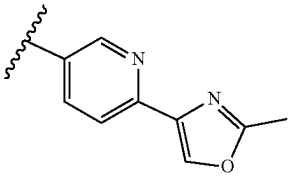

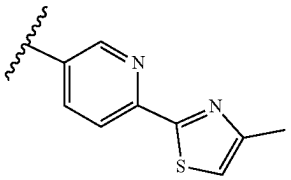

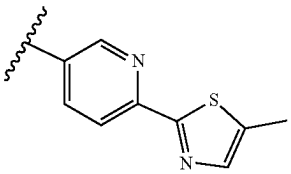

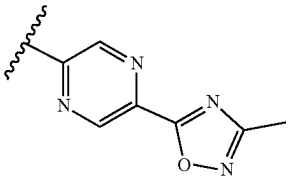

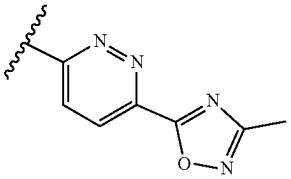

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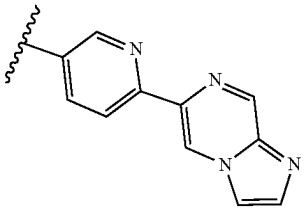
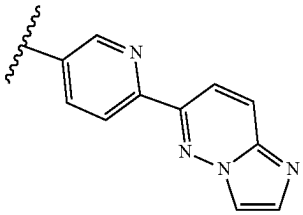
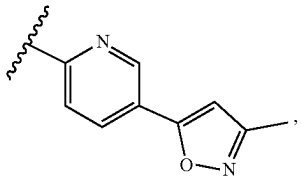
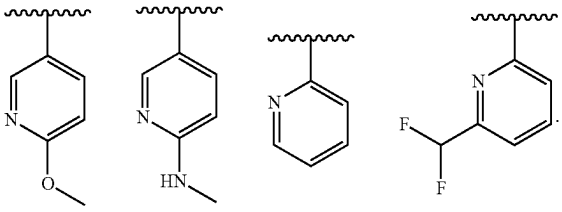






or

or R^8 is selected from



9. The compound of Formula I-1 according to claim **2**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a bridged 5-12 membered ring structure, which is optionally substituted, wherein the bridged ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S.

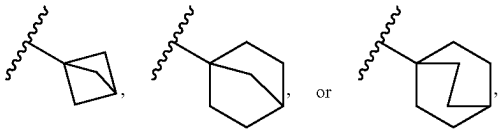
10. The compound of claim **9**, or a pharmaceutically acceptable salt thereof, wherein W is N.

11. The compound of claim **9**, or a pharmaceutically acceptable salt thereof, wherein W is CH.

12. The compound of any of claims **9-11**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5-12 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted.

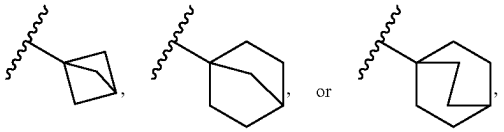
13. The compound of claim **12**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5-8 membered bridged bicyclic carbocyclic ring structure, which is optionally substituted.

14. The compound of claim **13**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



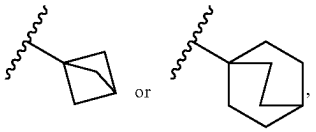
each of which is optionally substituted.

15. The compound of claim **14**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



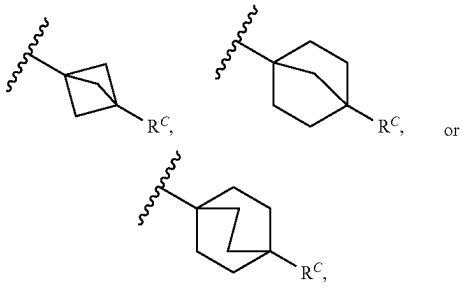
each of which is optionally substituted with 1-3 substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

16. The compound of claim **14**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



each of which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—$C(O)G^5$, or $C(O)G^5$, wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

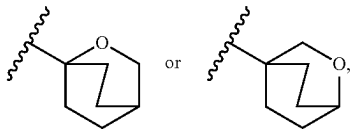
17. The compound of claim **14**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



wherein R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

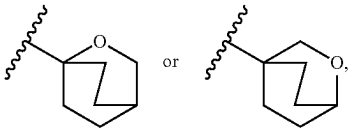
18. The compound of any of claims **9-11**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5-12 membered (preferably, 7-10 membered, e.g., 7 or 8 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one ring heteroatom which is a ring oxygen.

19. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



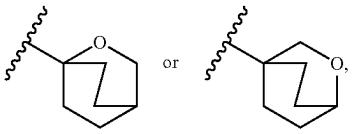
each of which is optionally substituted.

20. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



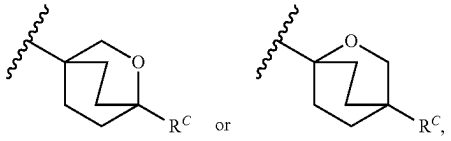
each of which is optionally substituted with 1-3 substituents each independently selected from deuterium, halogen, OH, NH_2, COOH, $CONH_2$, CN, G^4, OG^4, $OC(O)G^4$, NHG^4, NG^4G^4, NH—$C(O)G^4$, $C(O)G^4$, $C(O)OG^4$, $C(O)NHG^4$, $C(O)NG^4G^4$, $OC(O)NHG^4$, $OC(O)NG^4G^4$, $NHC(O)NHG^4$, or $N(G^4)C(O)NG^4G^4$, wherein G^4 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^A, wherein G^A at each occurrence is independently deuterium, halogen, CN, OH, C-4 alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

21. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^1 is



each of which is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, NH_2, CN, G^5, OG^5, NH—$C(O)G^5$, or $C(O)G^5$, wherein G^5 at each occurrence is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc.), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^B, wherein G^B at each occurrence is independently deuterium, F, Cl, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

22. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^1 is

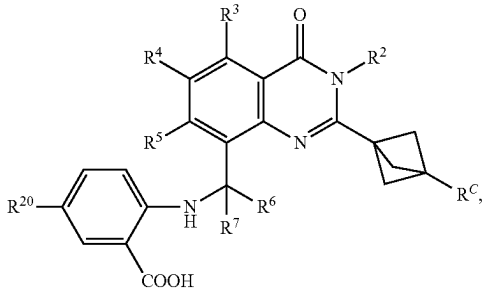


wherein R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

23. The compound of any of claims **9-11**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5-12 membered (preferably, 8-10 membered) bridged bicyclic heterocyclic ring structure, which is optionally substituted, wherein the bridged bicyclic heterocyclic ring structure has one or two ring heteroatoms independently selected from S, O, and N.

24. The compound of claim **9**, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-1-a-2-b, I-1-a-2-c, I-1-a-2-e, I-1-a-2-f, I-1-a-3-b, I-1-a-3-c, I-1-a-3-e, or I-1-a-3-f:

Formula I-1-a-2-b



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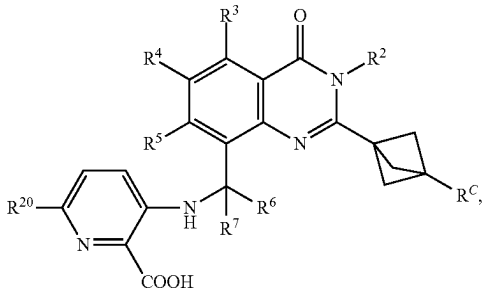
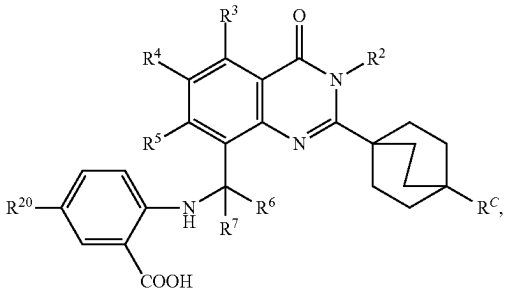
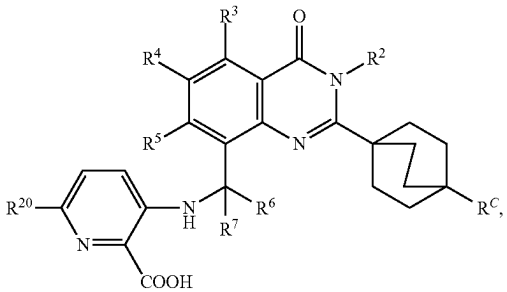
Formula I-1-a-3-b



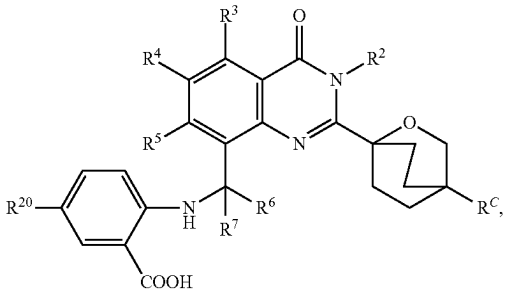
Formula I-1-a-2-c



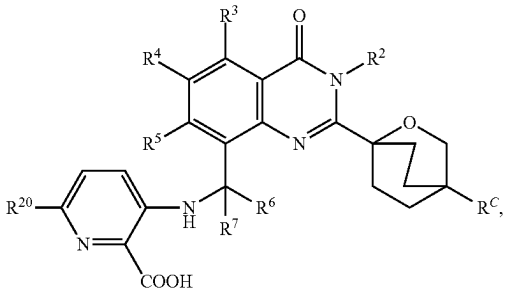
Formula I-1-a-3-c



Formula I-1-a-2-e



Formula I-1-a-3-e



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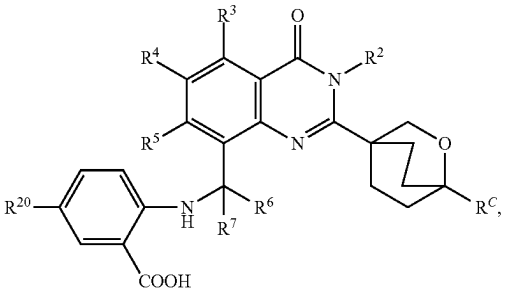
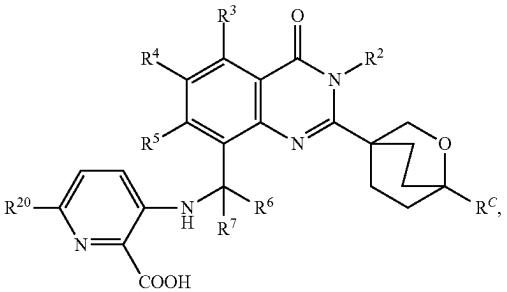
Formula I-1-a-2-f



Formula I-1-a-3-f



wherein:

R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F; and

R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as —(C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substi-

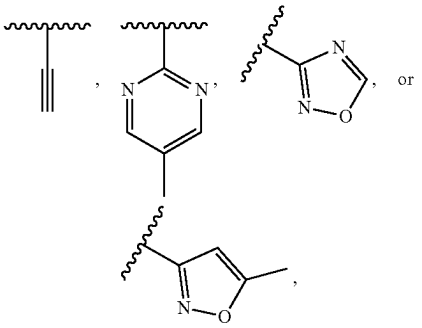
tuted with one or more substituents independently F, CN, OH, methoxy, or methyl.

25. The compound of claim **24**, or a pharmaceutically acceptable salt thereof, wherein R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3.

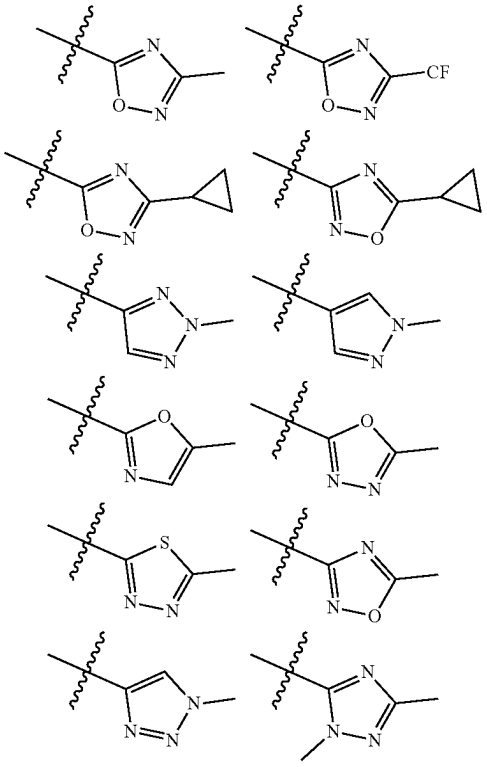
26. The compound of claim **24** or **25**, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3, or R^C is OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, or CH_2OCH_3.

27. The compound of claim **24** or **25**, or a pharmaceutically acceptable salt thereof, wherein

R^C is



or R^C is selected from:



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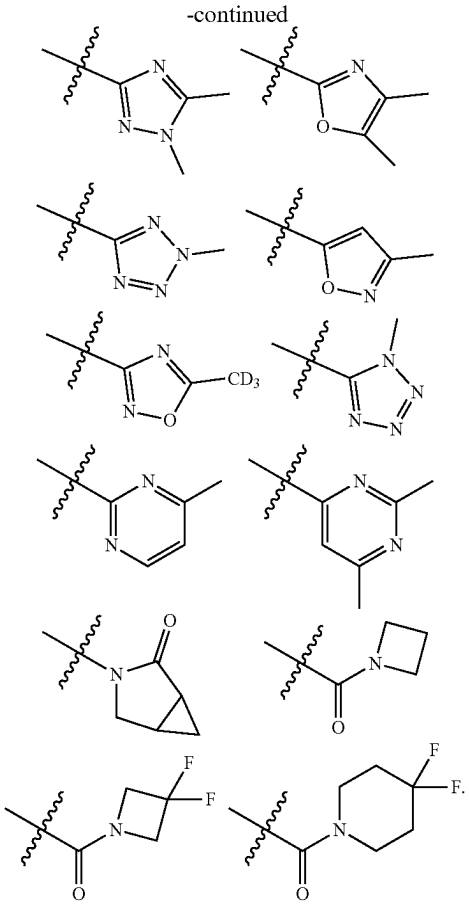
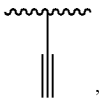
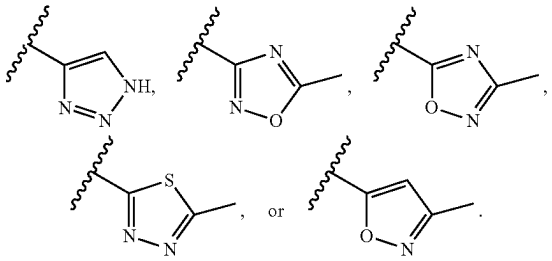


28. The compound of claim **24** or **25**, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, CN,



CHF_2, or a 5-membered heteroaryl, such as an oxadiazole, optionally substituted with methyl, CD_3, CF_3, or cyclopropyl, e.g.,



29. The compound of Formula III-1 according to claim **4**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a bridged 5-12 membered ring structure, which is optionally

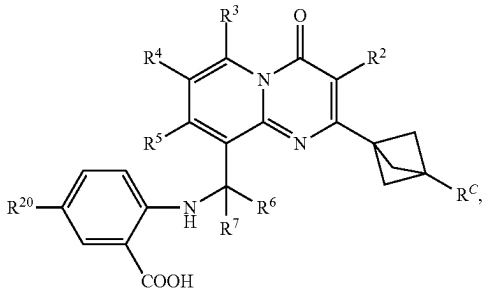
substituted, wherein the bridged ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S.

30. The compound of claim **29**, or a pharmaceutically acceptable salt thereof, wherein W is N.

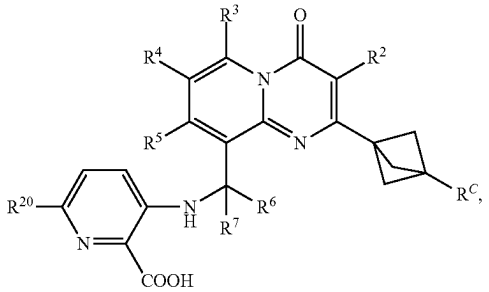
31. The compound of claim **29** or **30**, or a pharmaceutically acceptable salt thereof, wherein R^1 in Formula III-1 is any of the definition of R^1 defined in claims **12-23** in connection with Formula I-1.

32. The compound of claim **29**, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to III-1-a-2-b, III-1-a-2-c, III-1-a-2-e, III-1-a-2-f, III-1-b-2-b, III-1-b-2-c, III-1-b-2-e, or III-1-b-2-f:

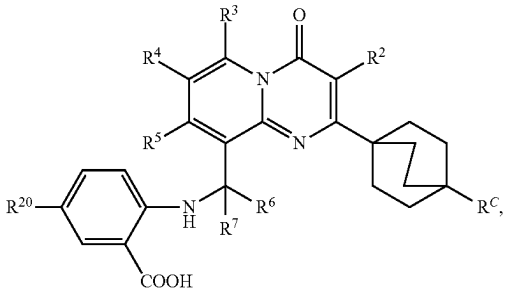
Formula III-1-a-2-b



Formula III-1-b-2-b



Formula III-1-a-2-c



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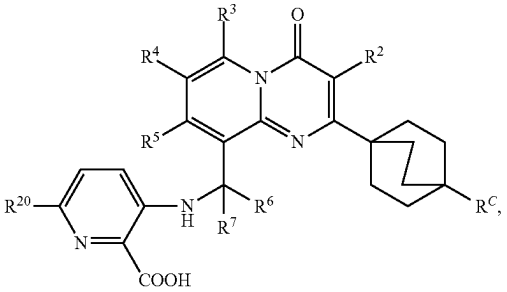
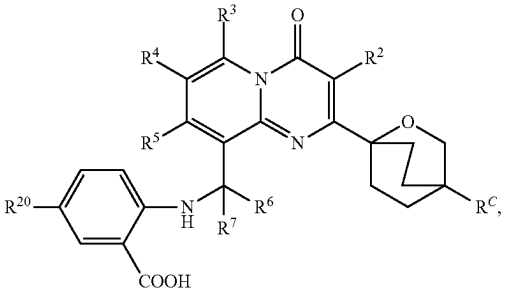
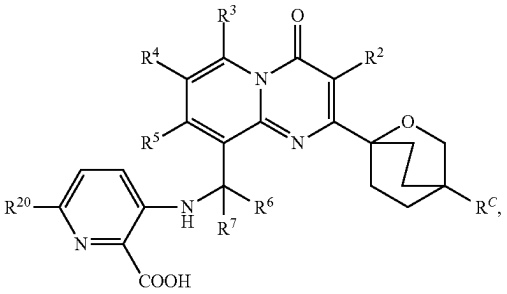
Formula III-1-b-2-c



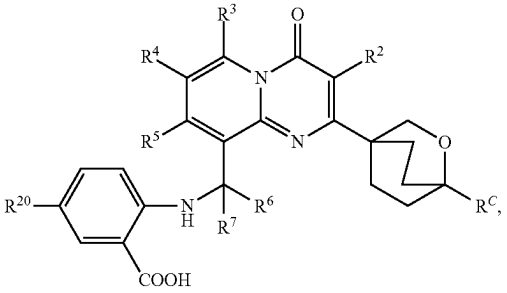
Formula III-1-a-2-e



Formula III-1-b-2-e



Formula III-1-a-2-f



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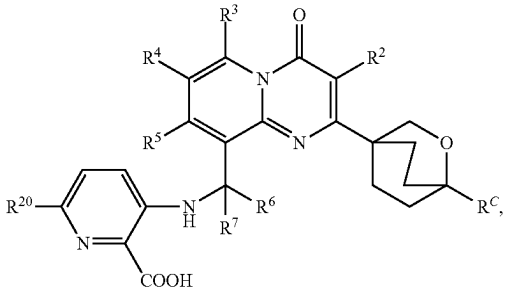
Formula III-1-b-2-f



wherein:

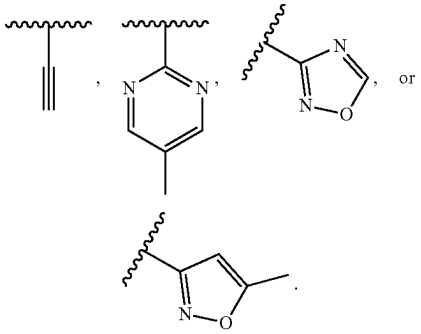
R^{20} is hydrogen, halogen, CN, OH, COOH, Ge, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F; and

R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}$, $C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as (C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

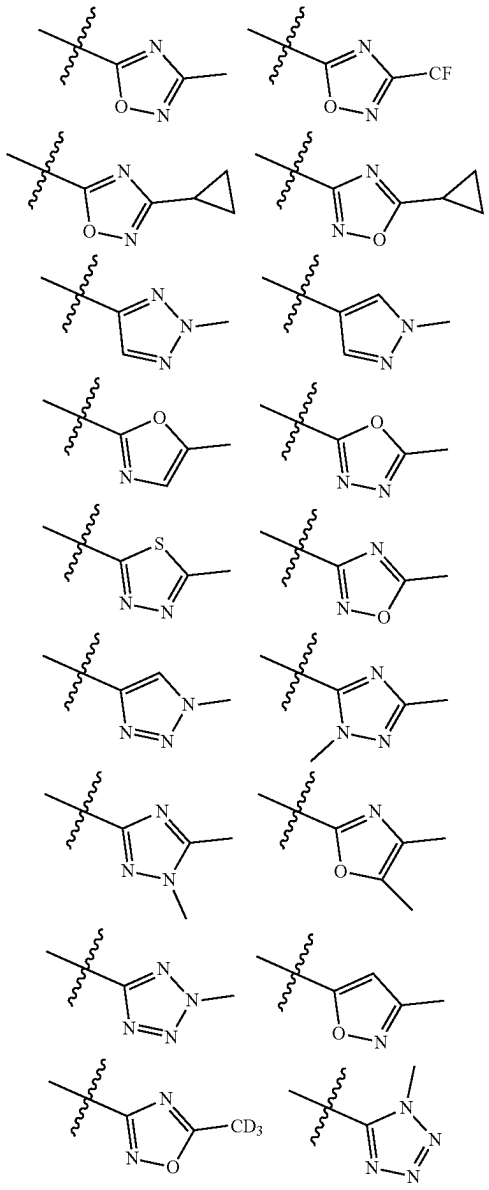
33. The compound of claim **32**, or a pharmaceutically acceptable salt thereof, wherein R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3.

34. The compound of claim **32** or **33**, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3, or R^C is OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, or CH_2OCH_3.

35. The compound of claim **32** or **33**, or a pharmaceutically acceptable salt thereof, wherein R^C is



or R^C is selected from:



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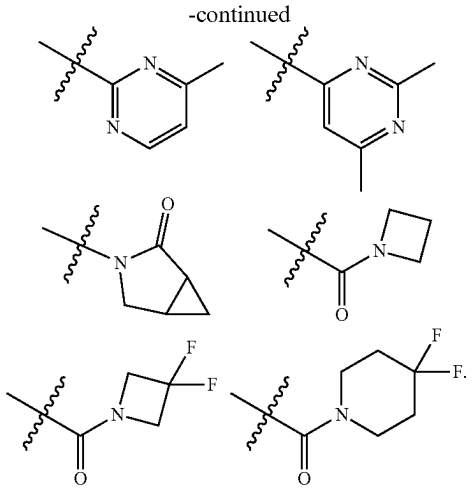
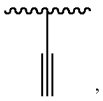
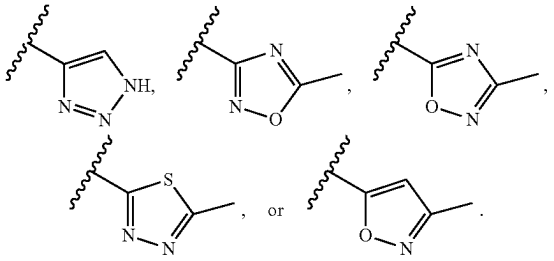


36. The compound of claim **32** or **33**, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, CN,



CHF_2, or a 5-membered heteroaryl, such as an oxadiazole, optionally substituted with methyl, CD_3, CF_3, or cyclopropyl, e.g.,



37. The compound of any one of claims **1-2** and **4-36**, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

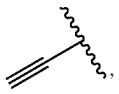
38. The compound of claim **37**, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl, or R^2 is CD_3 or CF_3.

39. The compound of any one of claims **1-38**, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

40. The compound of claim **39**, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

41. The compound of any one of claims **1-40**, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C-4 alkyl optionally substituted with 1-3F.

42. The compound of any one of claims **1-40**, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl, or R^4 is F, Cl, Br, or



or R^4 is CD_3 or CF_3.

43. The compound of any one of claims **1-42**, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, CN, OH, G^6, or OG^1, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

44. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

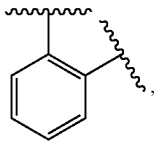
45. The compound of any one of claims **1-44**, or a pharmaceutically acceptable salt thereof, wherein both R^6 and R^7 are hydrogen.

46. The compound of any one of claims **1-44**, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is C_{1-4} alkyl, which is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, or C_{1-4} alkoxy optionally substituted with 1-3F.

47. The compound of any one of claims **1-44**, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is methyl.

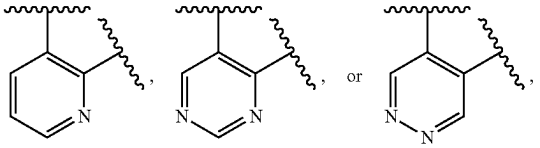
48. The compound of any one of claims **1-47**, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

49. The compound of any one of claims **1-48**, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted phenylene, such as



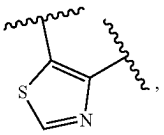
which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

50. The compound of any one of claims **1-48**, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 6-membered heteroarylene, such as



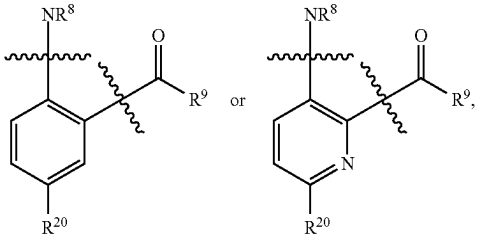
each of which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

51. The compound of any one of claims **1-48**, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 5-membered heteroarylene, such as

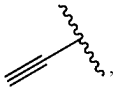


which is optionally substituted with halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

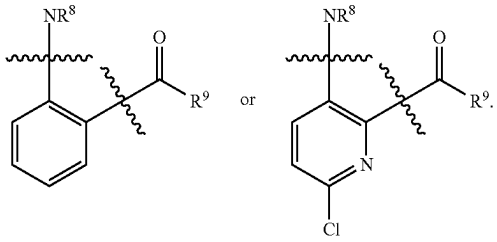
52. The compound of any one of claims **1-48**, or a pharmaceutically acceptable salt thereof, wherein L^2 is (NR^8 and $C(O)R^9$ are shown to show direction of attachment to the remainder of the molecule):



wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, preferably, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3 F, such as CHF_2 or CF_3, or R^{20} is



preferably, L^2 is

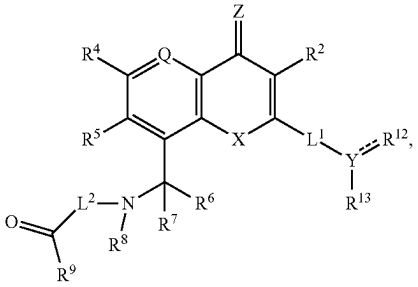


53. The compound of any one of claims **1-52**, or a pharmaceutically acceptable salt thereof, wherein R^9 is OH.

54. The compound of any one of claims **1-53**, or a pharmaceutically acceptable salt thereof, wherein as applicable, the variables of the compound is as defined in any of Embodiments B40-48.

55. A compound of Formula V, or a pharmaceutically acceptable salt thereof,

Formula V



wherein:

X is O, NR^{14}, or S, wherein R^{14} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine;

Q is N or CR^3, wherein R^3 is hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

R^2, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

wherein G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2, wherein G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_2-6 alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl);

R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

L^2 is optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene);

R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$, wherein G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure;

wherein:

(1) Z is NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; or

(2) Z is O, and R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; provided that (a) Y is C when the bond between Y and R^{12} is a double bond; (b) Y is CR^1S, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; or (c) Y is C or N, when Y is included in a a heteroaryl, such as a 5-membered heteroaryl;

(3) Z is O or NR^1, wherein R^1 is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; R^2 and R^{12}, together with the intervening atoms, are joined together to form a ring structure, wherein (a) Y is N; (b) Y is C when the bond between Y and R^{12} is a double bond; or (c) Y is CR^{15}, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and R^{13} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms; or

(4) Z is O or NR^{11}, wherein R^{11} is hydrogen, OH, CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-4} alkoxy; L^1 is defined above but not null; and

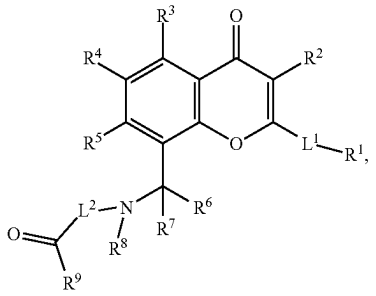
(i) R^{12}, R^{13}, and Y are joined together to form a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S; or

(ii) R^2 and R^{12}, together with the intervening atoms, are joined together to form a ring structure, wherein (a) Y is N; (b) Y is C when the bond between Y and R^{12} is a double bond; or (c) Y is CR's, when the bond between Y and R^{12} is a single bond, wherein R^{15} is hydrogen, deuterium, OH, halogen, CN, C_{1-4} alkyl optionally substituted with 1-3 fluorine, or optionally substituted C_{1-4} alkoxy; and R^{13} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms.

56. The compound of claim **55**, or a pharmaceutically acceptable salt thereof, as defined in Embodiments B50-79 herein.

57. A compound of Formula VII, or a pharmaceutically acceptable salt thereof,

Formula VII



wherein:

L^1 is null, O, C(O), S, S(O), SO_2, NR^{101}, an optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms, wherein R^{101} is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

R^1 is a 3-12 membered ring structure, which is optionally substituted, wherein the 3-12 membered ring structure is selected from a monocyclic non-aromatic ring, monocyclic aromatic ring, and a polycyclic structure, wherein each of the rings in the polycyclic structure is independently aromatic or non-aromatic, and wherein the 3-12 membered ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S;

R^2, R^3, R^4, and R^5 are each independently hydrogen, deuterium, halogen, CN, OH, G^1, or OG^1;

R^6 and R^7 are each independently hydrogen, deuterium, CN, or G^2;

R^8 is hydrogen or C_{1-4} alkyl optionally substituted with 1-3 fluorine, or a nitrogen protecting group;

R^9 is OH, NH_2, OG^3, NHG^3, NG^3G^3, or $NHSO_2G^3$;

L^2 is optionally substituted 5-10 membered ring, preferably, optionally substituted phenylene or optionally substituted heteroarylene (e.g., 5 or 6 membered heteroarylene or a bicyclic heteroarylene); and

wherein:

G^1 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-10 membered ring structure having 0-4 ring heteroatoms;

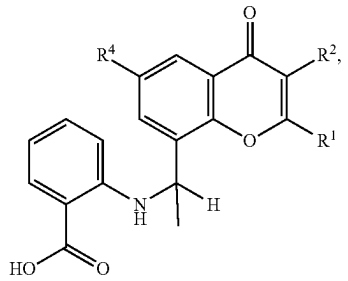
G^2 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-6 membered ring having 0-3 ring heteroatoms (e.g., cyclopropyl); and

G^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or an optionally substituted 3-8 membered non-aromatic ring structure having 0-4 ring heteroatoms, or NG^3G^3 represents an optionally substituted nitrogen containing 4-8 membered non-aromatic ring structure.

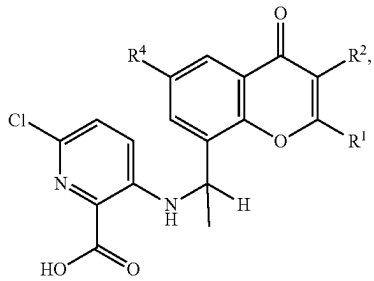
58. The compound of claim **57**, or a pharmaceutically acceptable salt thereof, wherein R^8 is a bridged 5-12 membered ring structure, which is optionally substituted, wherein the bridged ring structure optionally contains 1-4 ring heteroatoms independently selected from O, N, and S.

59. The compound of claim **57** or **58**, or a pharmaceutically acceptable salt thereof, having a structure according to Formula VII-1 or VII-2:

Formula VII-1



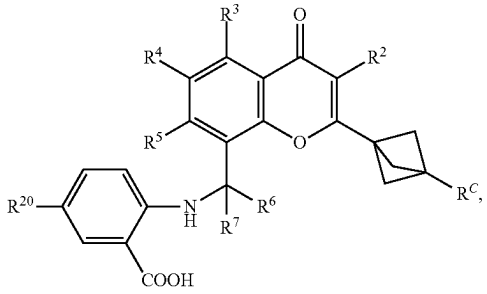
Formula VII-2



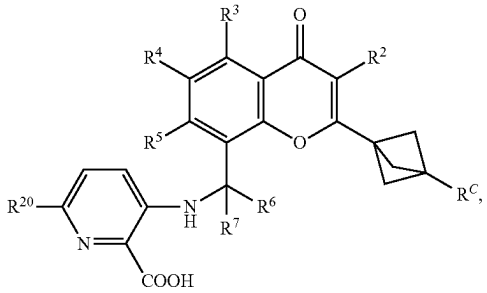
60. The compound of claim **58** or **59**, or a pharmaceutically acceptable salt thereof, wherein R^1 in Formula VII, VII-1, or VII-2 is any of the definition of R^1 defined in claims **12-23** in connection with Formula I-1.

61. The compound of claim **57** or **58**, or a pharmaceutically acceptable salt thereof, having a structure according to Formula VII-3-a, VII-3-b, VII-4-a, VII-4-b, VII-5-a, VII-5-b, VII-6-a, or VII-6-b:

Formula VII-3-a



Formula VII-3-b



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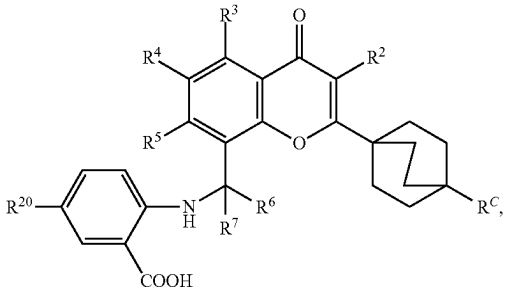
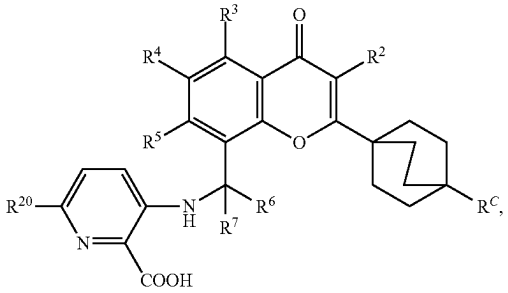
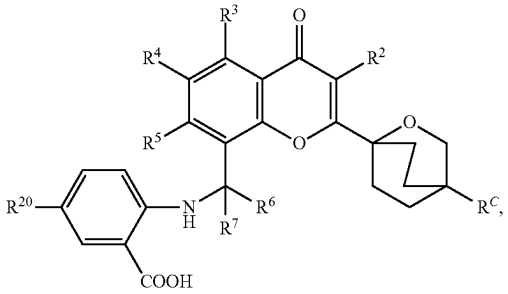
Formula VII-4-a



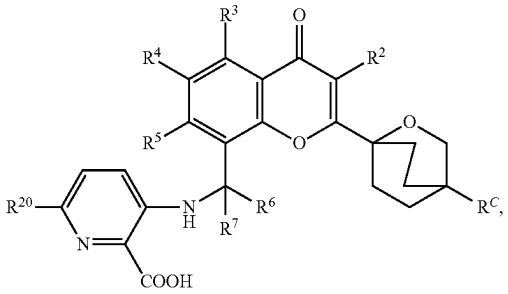
Formula VII-4-b



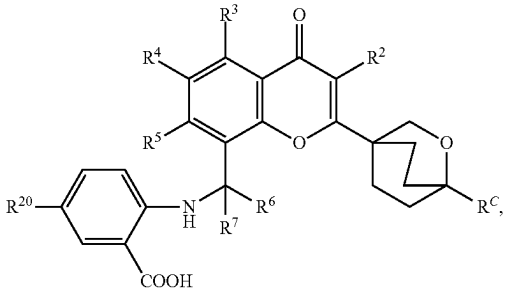
Formula VII-5-a



Formula VII-5-b



Formula VII-6-a



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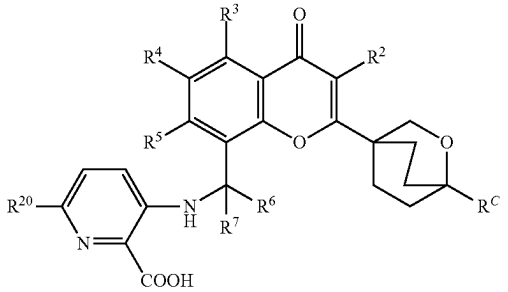
Formula VII-6-b



wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3 F; and

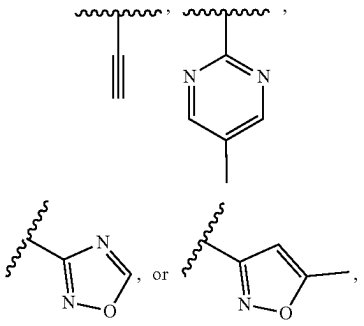
R^C is hydrogen, halogen, CN, COOH, $CONH_2$, G^{4A}, $C(O)G^{4A}$, $C(O)OG^{4A}$, $C(O)NHG^{4A}C(O)NG^{4A}G^{4A}$, SO_2G^{4A}, SO_2NHG^{4A}, or $SO_2NG^{4A}G^{4A}$, wherein G^{4A} at each occurrence is independently (i) C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl; (ii) a 3-12 membered ring, such as 3-7 membered ring or a bicyclic heteroaryl, e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrazolyl, imidazolyl, oxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,3,4-triazolyl), tetrazolyl, pyrimidinyl, phenyl, 9H-purinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, benzo[d]oxazolyl, etc., (iii) —(C_{1-4} alkylene)-3-12 membered ring such as (C_{1-4} alkylene)-3-7 membered ring, or (iv) —(C_{1-4} heteroalkylene)-3-12 membered ring such as —(C_{1-4} heteroalkylene)-3-7 membered ring, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3-12 membered ring (e.g., 3-7 membered ring or a bicyclic heteroaryl) is optionally substituted with one or more (e.g., 1, 2, or 3) G^{A1}, wherein G^{A1} at each occurrence is independently deuterium, halogen, CN, OH, NH_2, C_{1-4} heteroalkyl optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, or a 3-5 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, azetidinyl, etc.) which is optionally substituted with one or more substituents independently F, CN, OH, methoxy, or methyl.

62. The compound of claim **61**, or a pharmaceutically acceptable salt thereof, wherein R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3F, such as CHF_2 or CF_3.

63. The compound of claim **61** or **62**, or a pharmaceutically acceptable salt thereof, where R^C is H, F, Cl, CN, COOH, CH_3, OCH_3, CHF_2, or CF_3, or

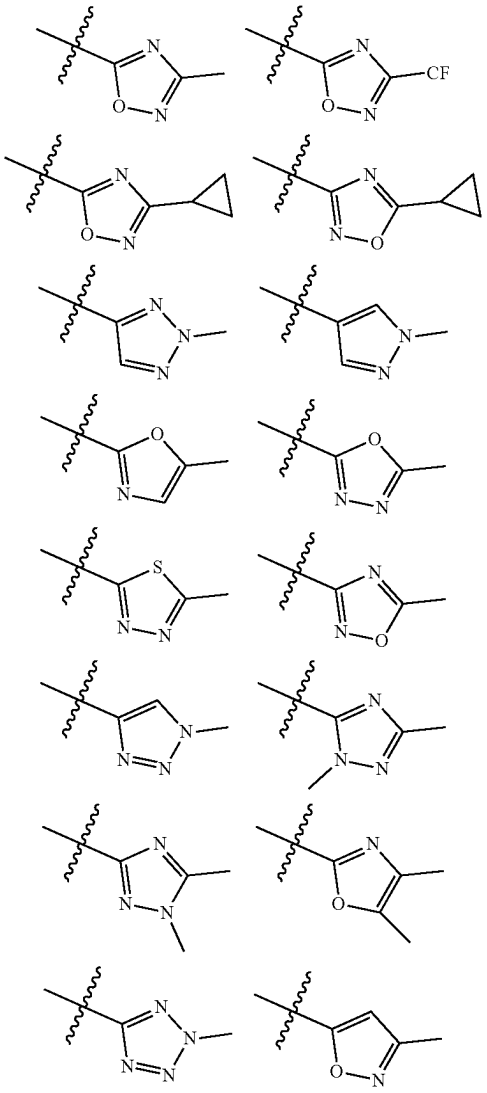
R^C is OH, NH_2, CH_2OH, $CH(OH)CH_3$, CH_2CH_3, CH_2F, or CH_2OCH_3, or

R^C is



or

R^C is selected from:



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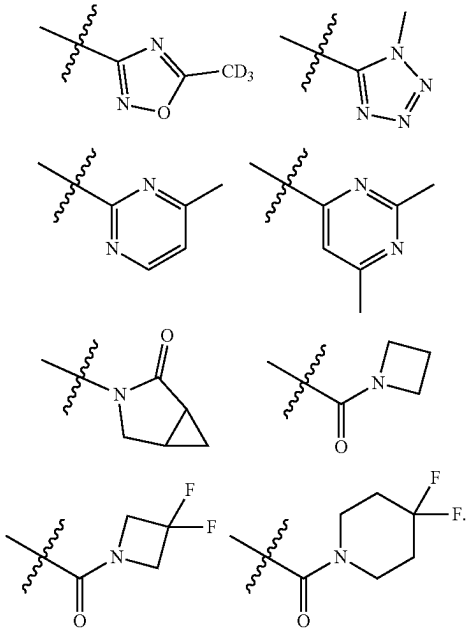
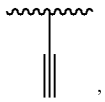
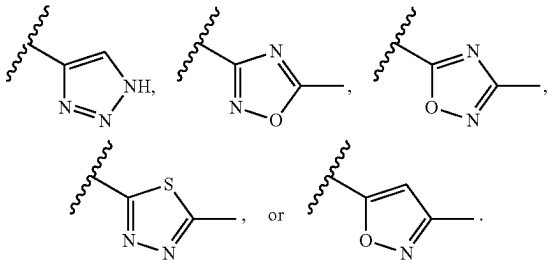


64. The compound of claim **61** or **62**, or a pharmaceutically acceptable salt thereof, wherein R^C is H, F, CN,



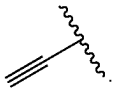
CHF_2, or a 5-membered heteroaryl, such as an oxadiazole, optionally substituted with methyl, CD_3, CF_3, or cyclopropyl, e.g.,



65. The compound of any one of claims **57-64**, or a pharmaceutically acceptable salt thereof, where R^2 is hydrogen, C_{1-4} alkyl, or 3- or 4-membered ring, wherein the C_{1-4} alkyl or 3- or 4-membered ring is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_1-4 alkyl optionally substituted with 1-3F.

66. The compound of any one of claims **57-64**, or a pharmaceutically acceptable salt thereof,

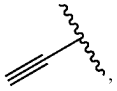
where R^2 is H, F, Cl, CH_3, CF_3, or CD_3, or



67. The compound of any one of claims **57-66**, or a pharmaceutically acceptable salt thereof, where R^4 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

68. The compound of any one of claims **57-66**, or a pharmaceutically acceptable salt thereof,

where R^4 is F, Cl, Br, methyl, CF_3, or



or R^4 is CD_3.

69. The compound of any one of claims **57-68**, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, CN, OH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

70. The compound of claim **69**, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

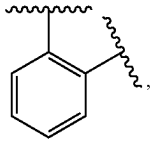
71. The compound of any one of claims **57-70**, or a pharmaceutically acceptable salt thereof, wherein both R^6 and R^7 are hydrogen.

72. The compound of any one of claims **57-70**, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is C_{1-4} alkyl, which is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, or C_{1-4} alkoxy optionally substituted with 1-3F.

73. The compound of any one of claims **57-70**, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is hydrogen or deuterium, and the other of R^6 and R^7 is methyl.

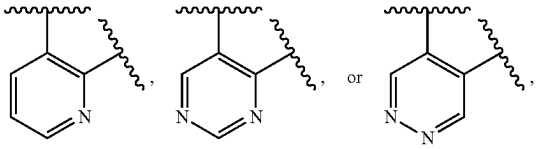
74. The compound of any one of claims **57-73**, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

75. The compound of any one of claims **57-74**, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted phenylene, such as



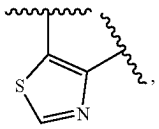
which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

76. The compound of any one of claims **57-74**, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 6-membered heteroarylene, such as



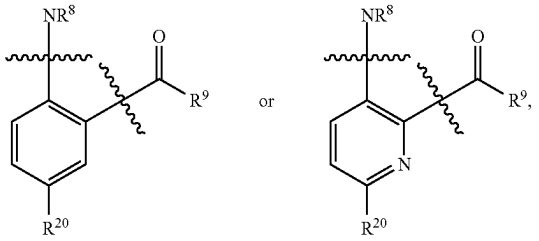
each of which is optionally substituted with one or more substituents each independently halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F.

77. The compound of any one of claims **57-74**, or a pharmaceutically acceptable salt thereof, wherein L^2 is an optionally substituted 5-membered heteroarylene, such as

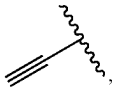


which is optionally substituted with halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_1-4 alkyl optionally substituted with 1-3F.

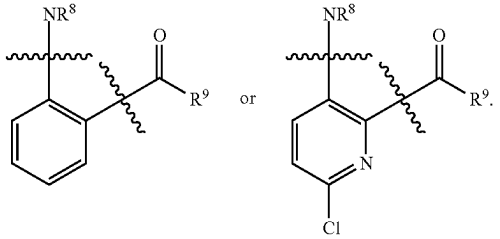
78. The compound of any one of claims **57-74**, or a pharmaceutically acceptable salt thereof, wherein L^2 is (NR^8 and $C(O)R^9$ are shown to show direction of attachment to the remainder of the molecule):



wherein R^{20} is hydrogen, halogen, CN, OH, COOH, G^6, or OG^6, wherein G^6 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or a 3- or 4-membered ring (e.g., cyclopropyl), wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, or 3- or 4-membered ring (e.g., cyclopropyl) is optionally substituted with one or more such as 1-3 substituents each independently deuterium, F, CN, OH, C_{1-4} alkoxy optionally substituted with 1-3F, or C_{1-4} alkyl optionally substituted with 1-3F, preferably, R^{20} is hydrogen, F, Cl, or C_{1-4} alkyl optionally substituted with 1-3 F, such as CHF_2 or CF_3, or R^{20} is



preferably, L^2 is



79. The compound of any one of claims **57-78**, or a pharmaceutically acceptable salt thereof, wherein R^9 is OH.

80. The compound of any one of claims **57-79**, or a pharmaceutically acceptable salt thereof, wherein L^1 is absent.

81. A compound selected from the compounds shown in Examples section or any of the compounds shown in Table A herein, or a pharmaceutically acceptable salt thereof.

82. A pharmaceutical composition comprising the compound according to any one of claims **1-81**, or a pharmaceutically acceptable salt thereof.

83. A method of treating a disease or disorder associated with modulation of phosphoinositide 3-kinase (PI3K), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims **1-81** or a pharmaceutical composition of claim **82**.

84. The method of claim **83**, wherein the PI3K is PI3Ka.

85. The method of claim **83** or **84**, wherein the PI3K associated with the disease or disorder has a H1047R mutation.

86. The method of any one of claims **83-85**, wherein the disease or disorder is a cancer.

87. The method of claim **86**, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

88. The method of any one of claims **83-85**, wherein the disease or disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

89. A method of inhibiting phosphoinositide 3-kinase (PI3K), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims **1-81** or a pharmaceutical composition of claim **82**.

90. A method of treating cancer, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims **1-81** or a pharmaceutical composition of claim **82**.

91. The method of claim **90**, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

92. A method of treating a disorder selected from CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3CA-related overgrowth syndrome (PROS), the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims **1-81** or a pharmaceutical composition of claim **82**.

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