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(54) **SMALL MOLECULE INHIBITORS OF NAV1.8 SODIUM CHANNELS FOR PAIN RELIEF**

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(57) **ABSTRACT**

The present invention is directed to novel compounds that inhibit Nav1.8 sodium channels, methods of making, and methods of using thereof. The present disclosure is further directed to administering the disclosed compounds as therapeutic solutions for chronic pain, primary pain, idiopathic pain, gastrointestinal pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer-related pain, idiopathic pain, postoperative pain, visceral pain, multiple sclerosis, Summer-Marr-Tuff syndrome, incontinence, pathological cough, or arrhythmia to a subject in need thereof.

SMALL MOLECULE INHIBITORS OF NAV1.8 SODIUM CHANNELS FOR PAIN RELIEF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application No. 63/551,843 titled "NAV1.8 SODIUM CHANNEL BLOCKER COMPOUNDS FOR PAIN TREATMENT", filed on Feb. 9, 2024, the entire contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] This invention is centered on the development and synthesis of novel compounds that inhibit Nav1.8 sodium channels. These compounds exhibit potential for treating different forms of pain, such as acute, chronic, and neuropathic pain.

BACKGROUND OF THE INVENTION

[0003] Chronic pain remains one of the most pressing unmet medical challenges today. In the United States alone, around 50 million people are affected by chronic pain. Traditional pain relief methods often rely on opioids, which are associated with significant risks and adverse effects. To mitigate these issues, the focus in pain management is shifting towards therapeutic targets that address the fundamental mechanisms of pain signaling. This strategy aims to create future pain medications with improved safety and tolerability.

[0004] Voltage-gated ion channels (VGICs) are crucial transmembrane proteins responsible for enabling cellular electrical signaling. Among these, Nav channels are essential for generating sodium currents that trigger and propagate action potentials in nerves and muscle fibers. Nav1.8, predominantly found in the peripheral nervous system, is one of the nine sodium channel subtypes (Nav1.1-Nav1.9) and has been validated as a promising target for pain relief. Targeting Nav1.8 offers the potential for effective pain treatment with fewer central nervous system and cardiac side effects.

[0005] Over the years, various inhibitors of the Nav1.8 channel have been identified. Abbott's compound A-803467, for instance, demonstrated limited oral bioavailability, which led to the discontinuation of its preclinical trials. Pfizer's compounds, PF-04531083 and PF-06305591, were subjected to multiple clinical trials but failed to produce favorable outcomes. Vertex Pharmaceuticals' VX-150 completed Phase II clinical trials for conditions such as acute pain post-bunionectomy, osteoarthritis, and small fiber neuropathy. While VX-150 confirmed the potential of Nav1.8 as a pain relief target, its moderate potency at high doses and side effects, like headaches, hindered further development.

[0006] Minghui Pharmaceutical advanced the field by incorporating a bicyclic aromatic amide group into the benzamide scaffold, initially derived from VX-150, to create novel Nav1.8 inhibitors. Additionally, a cyclization strategy was employed, utilizing an aryl amine pharmacophore derived from the benzamide and a nicotinamide core developed by Merck Sharp & Dohme Corp, to discover Nav1.8-selective inhibitors. Furthermore, cycloalkyl 3-oxopiperazine carboxamides were introduced as new Nav1.8 inhibitors. Wuhan humanwell, Latigo Biotherapeutics, Grunenthal, and Guangzhou Fermion also developed Nav1.8 small molecule inhibitors after this.

[0007] Recently, Vertex's VX-548 demonstrated significant analgesic efficacy in Phase Ill clinical trials for patients undergoing abdominoplasty and bunionectomy. Administered orally with an initial dose of 100 mg followed by 50 mg every 12 hours, VX-548 exhibited mild to moderate side effects without severe adverse reactions. This led to its FDA designation as a breakthrough therapy for moderate-to-severe acute pain.

[0008] Following the promising results of VX-548, several pharmaceutical companies, including Huilun Pharmaceutical and Hengrui, have developed Nav1.8 inhibitor compounds inspired by VX-548.

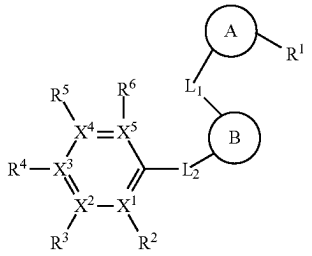
[0009] In this patent, our research focuses on designing and synthesizing a new series of compounds aimed at potentially serving as selective inhibitors of Nav1.8. This effort aims to contribute to innovation in the field of pain research.

[0010] The compound of this invention possesses a novel structure, demonstrating potent Nav1.8 channel inhibitory activity in in vitro tests. It is suitable for the preparation of medications aimed at treating and/or preventing diseases and conditions associated with the Nav1.8 channel. Specifically, these include chronic pain, primary pain, idiopathic pain, gastrointestinal pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer-associated pain, postoperative pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or arrhythmia.

SUMMARY OF THE INVENTION

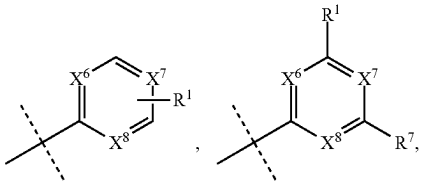
[0011] The present disclosure is directed to a compound comprising formula (I), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated derivatives, metabolites, or prodrugs:

I



wherein:

[0012] ring A is selected from the group consisting of



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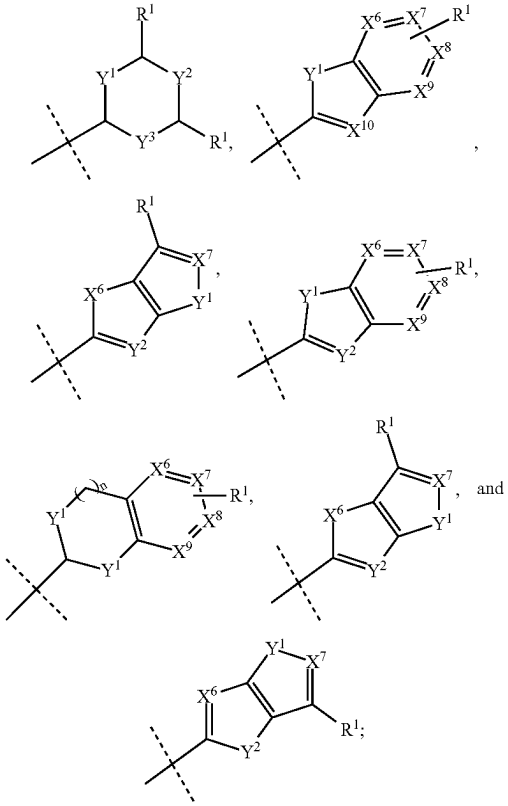
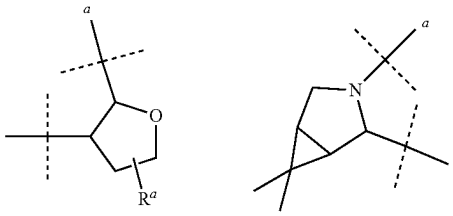


[0013] the A ring is optionally substituted with 0 to 5 independent R^1 groups;

[0014] B ring is selected from the group consisting of 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl; wherein heteroatoms in the 3-8 membered heterocyclic alkyl and the 5 or 8 membered heteroaryl are N, O, or S; wherein number of the heteroatoms in the 3-8 membered heterocyclic alkyl and the 5 or 8 membered heteroaryl is 1, 2, 3, or 4; wherein the 3-8 membered cycloalkyl, the 3-8 membered heterocyclic alkyl, and the 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 Ra groups comprising hydrogen, deuterium, halogen, hydroxyl, cyano, amino, C_1-C_6 alkyl, C_1-C_6 thioalkyl, C_3-C_6 cycloalkyl, halogenated C_1-C_6 alkyl, 3-6 membered heterocyclic alkyl; wherein the 3-8 membered cycloalkyl, the 3-8 membered heterocyclic alkyl, and the 5 or 8 membered heteroaryl comprise any one of:



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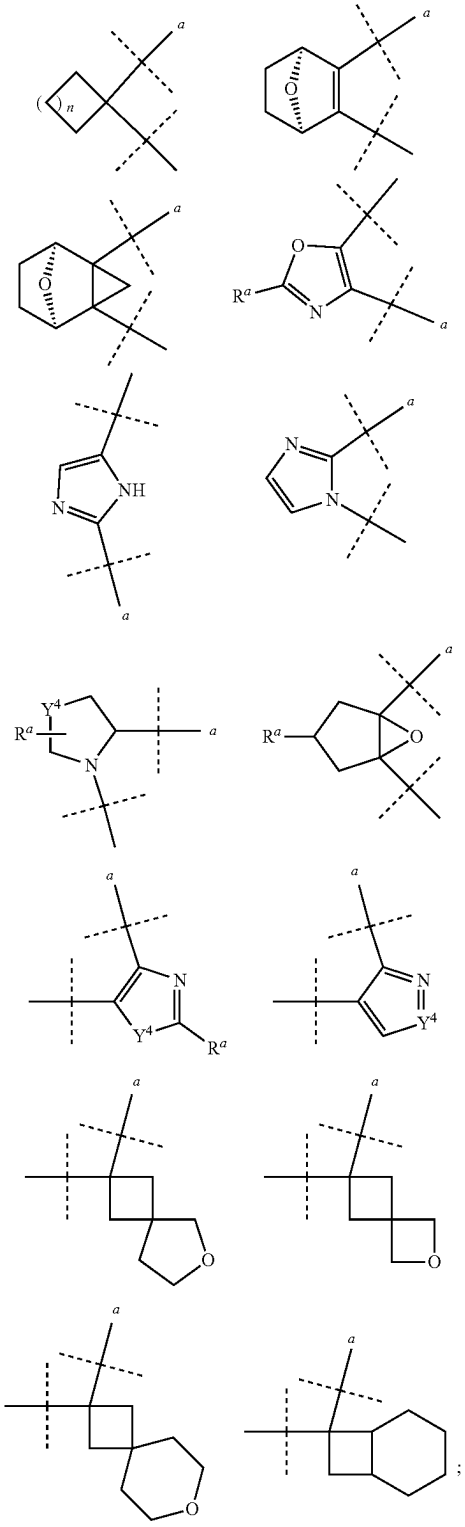
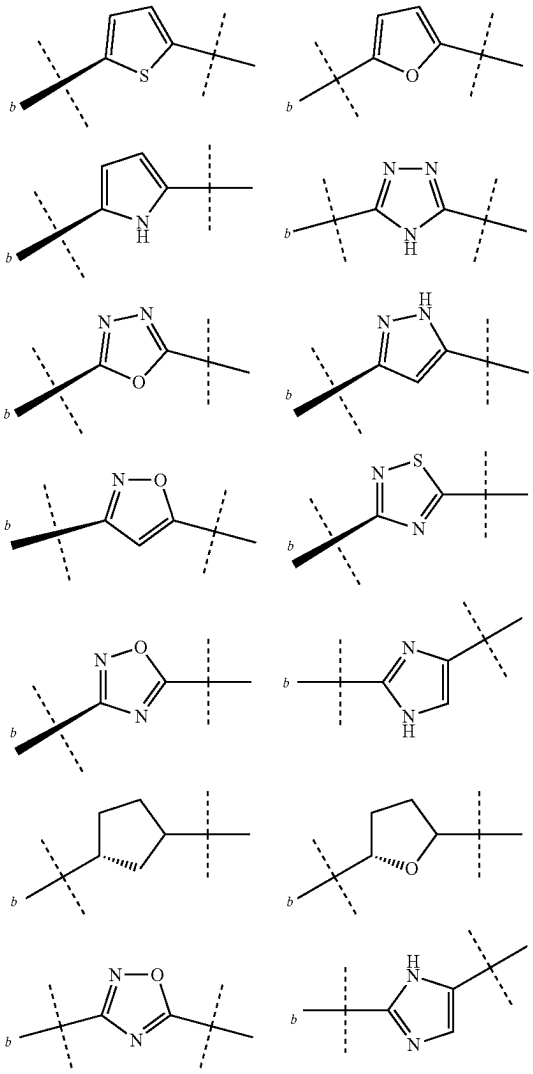


and wherein a-end is connected to L_1;

[0015] L_1 and L_2 are each independently a single bond, —$CONR^b$—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl;

wherein the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents; wherein the substituents are each independently deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, or C3-C6 cycloalkyl; Rb is hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl-3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, and —S(O)2C3-C6 cycloalkyl; wherein the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocyclic alkyl are substituted with 0 to 3 substituents; wherein the substituents are deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl; wherein the 3-8 membered heterocyclic alkyl and the 5 or 8 membered heteroaryl are each independently any one of:



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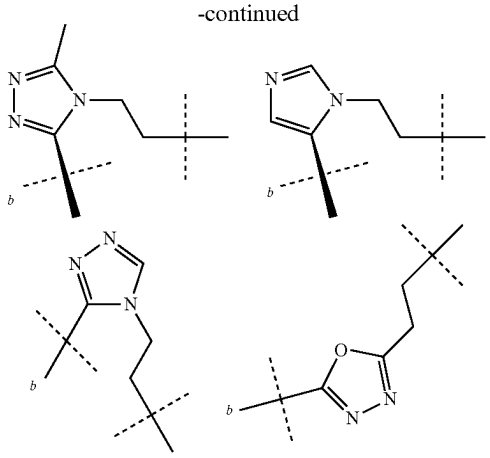


and wherein b-end is connected to the B ring;

[0016] R^1 and R^7 are each independently hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —NHCOR^c, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —NHCOR^cNHR^d, —C(O)OR^c, 3-8 membered heterocyclic alkyl, 5 or 6 membered heteroaryl; wherein the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 substituents; wherein the substituents are deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or CO(C1-C6 alkyl);

[0017] or any two adjacent R^1 or R^7 and the atoms to which they are connected form a five-membered ring; and

[0018] any two ortho-positioned R^1 (or R^7) and the atoms to which they are connected form a heterocyclic alkenyl;

[0019] R^c and R^d are each independently hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)O(C1-C6 alkyl)OC(O)(C1-C6) alkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, or 5 or 8 membered heteroaryl; wherein the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 substituents; wherein the substituents are deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl; Re is selected from C1-C6 alkyl, C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl. R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, where the C1-C6 alkyl, C2-C6

alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, C1-C3 alkyl;

[0020] X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently O, S, N, CH, or N-oxide derivatives;

[0021] Y^1, Y^2, Y^3, and Y^4 are each independently CH_2, NH, O, or S; and

[0022] n=0, 1, 2, 3.

[0023] In some aspects, disclosed herein is a pharmaceutical composition, which includes a therapeutically effective amount of the aforementioned compound, its tautomeric isomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, prodrugs, and pharmaceutically acceptable pharmaceutical carriers, diluents, or excipients.

[0024] In some aspects, disclosed herein is a method for synthesizing the compound.

[0025] In some aspects, disclosed herein is a method for inhibiting voltage-gated sodium channels or preventing and/or treating diseases associated with voltage-gated sodium channels, which includes the step of administering to a subject the compound of Formula I as described in Aspect 1, its tautomeric isomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, prodrugs, or the pharmaceutical composition as described in Aspect 2. The voltage-gated sodium channels include Nav1.1-Nav1.9, Nav1.5, Nav1.8, and Nav1.9, with Nav1.8 being preferred. The diseases related to voltage-gated sodium channels are pain-related diseases, including chronic pain, primary pain, idiopathic pain, gastrointestinal pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer-related pain, idiopathic pain, postoperative pain, visceral pain, multiple sclerosis, Shy-Drager syndrome, incontinence, pathological cough, or arrhythmias.

[0026] In some aspects, disclosed herein is the use of the aforementioned compound, its tautomeric isomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, prodrugs, or the pharmaceutical composition in the preparation of a drug for inhibiting voltage-gated sodium channels. The voltage-gated sodium channels include Nav1.1-Nav1.9, Nav1.5, Nav1.8, and Nav1.9, with Nav1.8 being preferred. The drug can be used to treat, alleviate, or prevent pain, and the diseases include chronic pain, primary pain, idiopathic pain, gastrointestinal pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer-related pain, idiopathic pain, postoperative pain, visceral pain, multiple sclerosis, Shy-Drager syndrome, incontinence, pathological cough, or arrhythmias.

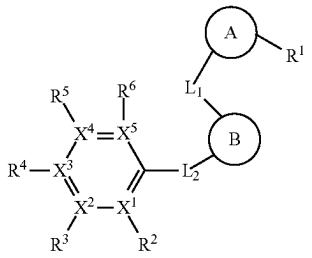
DETAILED DESCRIPTION

[0027] The following is an overview of the subject matter of this invention's detailed description. This overview is not intended to limit the scope of protection of the claims.

[0028] The purpose of the present invention is to introduce Nav1.8 inhibitors suitable for developing drugs for pain treatment, where the pain treatment includes various types of pain, such as chronic pain, acute pain, idiopathic pain, neuropathic pain, inflammatory pain, musculoskeletal pain, cancer pain, visceral pain, postoperative pain.

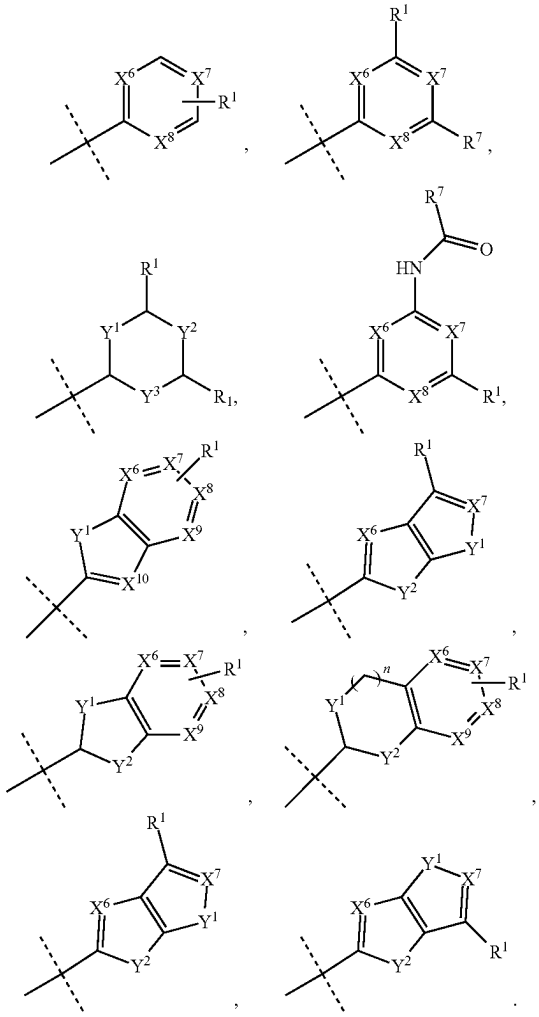
[0029] In a first aspect, the invention provides a compound as shown in formula (I), or its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated forms, metabolites, or prodrugs.

I



[0030] wherein,

[0031] Ring A selected from

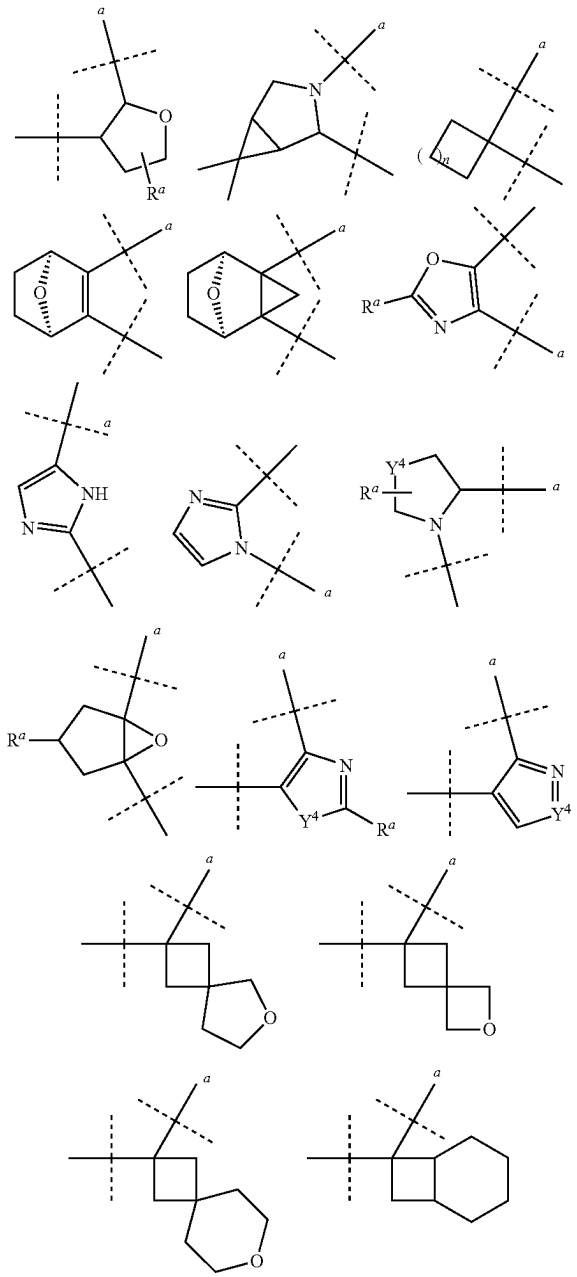


[0032] The A ring is optionally substituted with 0-5 independently selected R^1 groups.

[0033] The B ring is selected from 3-8 membered cycloalkyls, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups, where the heteroatoms or heteroa-

tom groups in the 3-8 membered heterocycloalkyls and 5 or 8 membered heteroaromatic groups are selected from N, O, and S, with the number of heteroatoms or heteroatom groups being 1-4. The 3-8 membered cycloalkyls, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 Ra groups: hydrogen, deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogenated C1-C6 alkyl, or 3-6 membered heterocycloalkyls.

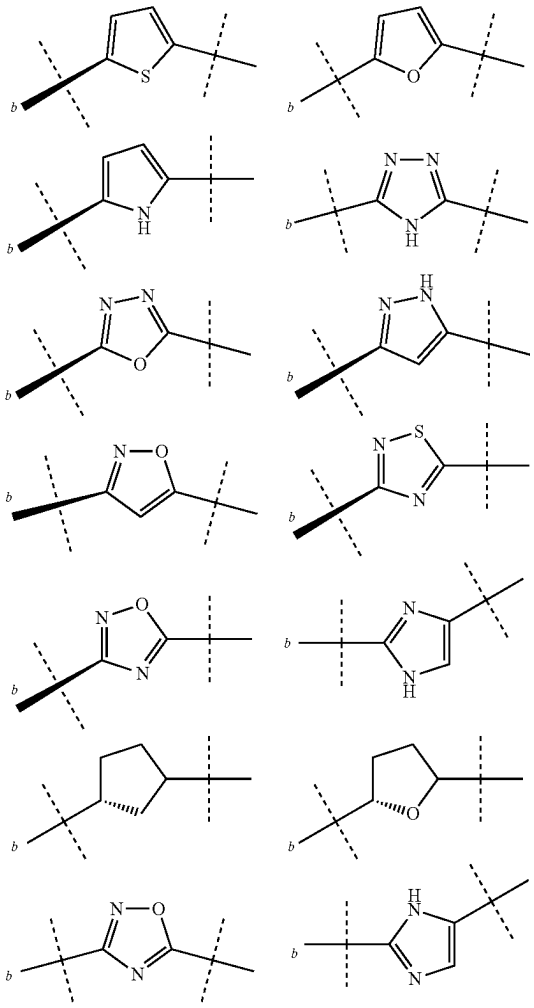
[0034] The 3-8 membered cycloalkyls, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups include, but are not limited to, the following (where the a-terminal and L_1 are connected).



[0035] L_1 and L_2 are selected from a single bond, —$CONR^b$—, —CO—, —NHCONH—, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups. The 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkyl groups, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl groups.

[0036] R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, C1-C6 alkyl 3-8 membered heterocycloalkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —$S(O)_2$C1-C6 alkyl, and —$S(O)_2$C3-C6 cycloalkyl. The C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocycloalkyl groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0037] The 3-8 membered heterocycloalkyl and 5 or 8 membered heteroaromatic groups include, but are not limited to, the following (where the b-terminal is connected to the B ring).



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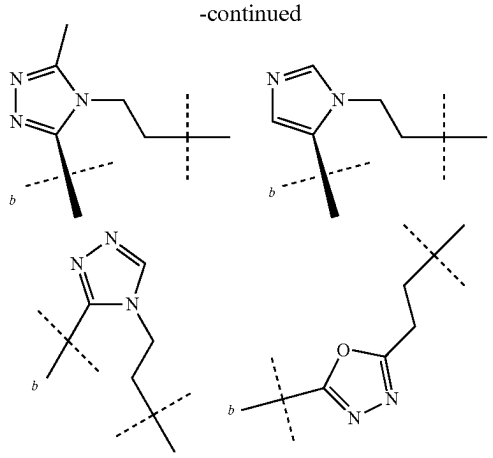


[0038] R^1 and R^7 are each independently selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^c-NHR^d, —C(O)OR^c, 3-8 membered heterocycloalkyl, 5 or 6 membered heteroaromatic groups. The C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 additional substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or CO(C1-C6 alkyl).

[0039] Alternatively, two adjacent R^1 (or R^7) groups and the atoms they are connected to may form a five-membered ring, and two non-adjacent R^1 (or R^7) groups and the atoms they are connected to may form a heterocyclic alkene group.

[0040] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl), OC(O)(C1-C6 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0 to 3 substituents, which may be deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

[0041] R^e is selected from C1-C6 alkyl and C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl.

[0042] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogens, —CONH^2, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups. The C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, or C1-C3 alkyl groups.

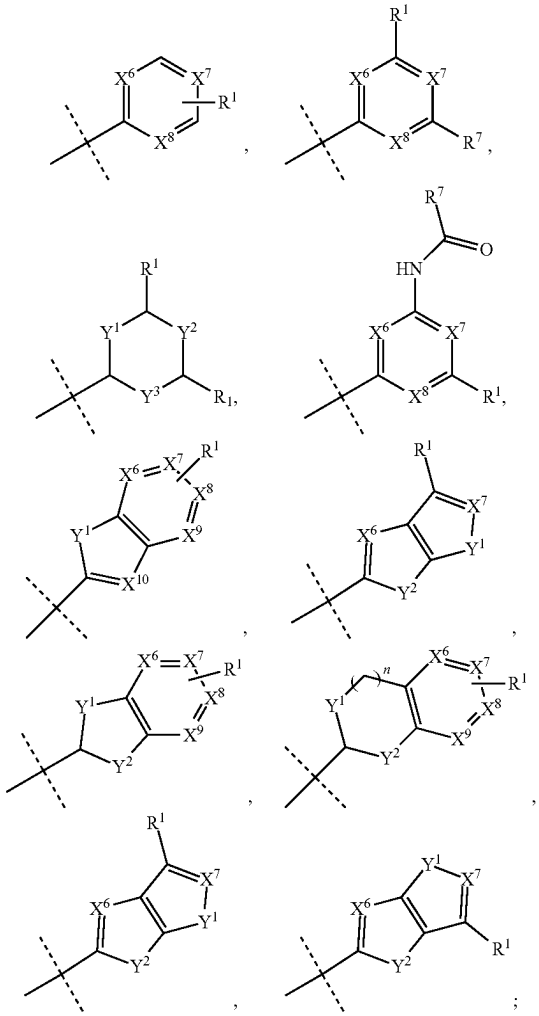
[0043] X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives.

[0044] Y^1, Y^2, Y^3, and Y^4 are each independently selected from CH_2, NH, O, or S.

[0045] n=0, 1, 2, or 3.

[0046] More specifically, in some embodiments, the invention provides a compound as shown in formula (I), along with its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated forms, metabolites, or prodrugs.

[0047] A ring selected from

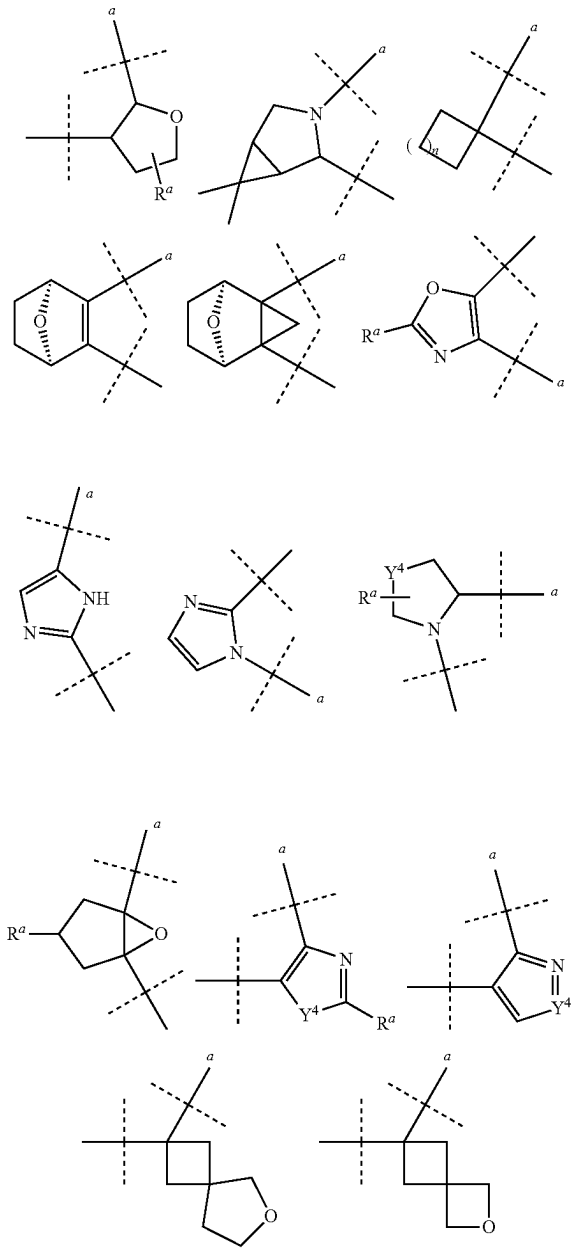


[0048] The A ring is optionally substituted with 0-5 independently selected R^1 groups.

[0049] The B ring is selected from 3-8 membered cycloalkyls, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups, where the heteroatoms or heteroa-

tom groups in the 3-8 membered heterocycloalkyls and 5 or 8 membered heteroaromatic groups are selected from N, O, and S, with the number of heteroatoms or heteroatom groups being 1-4. The 3-8 membered cycloalkyls, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 Ra groups: hydrogen, deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogenated C1-C6 alkyl, or 3-6 membered heterocycloalkyls.

[0050] The 3-8 membered cycloalkyls, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups include, but are not limited to, the following (where the a-terminal is connected to L_1),



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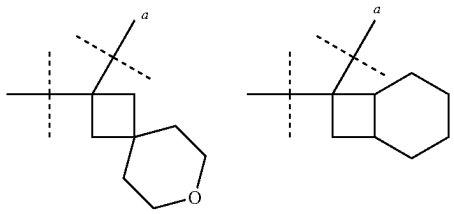
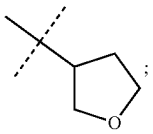
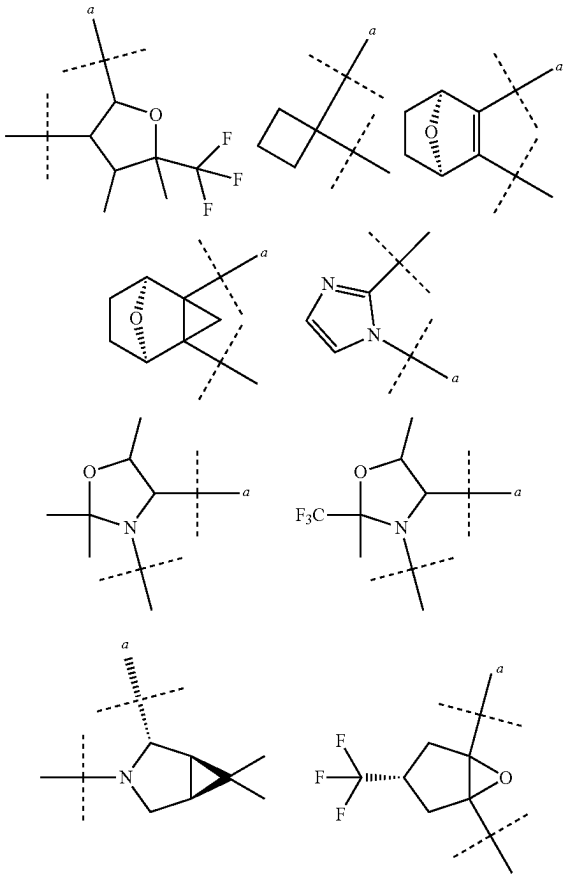


[0051] Preferably, R^a is selected from hydrogen, methyl, trifluoromethyl, and cyclopropyl,



[0052] Preferably, Y^4 is selected from NH, O, or S.

[0053] More preferably, the B ring is selected from the following (where the a-terminal is connected to L_1).



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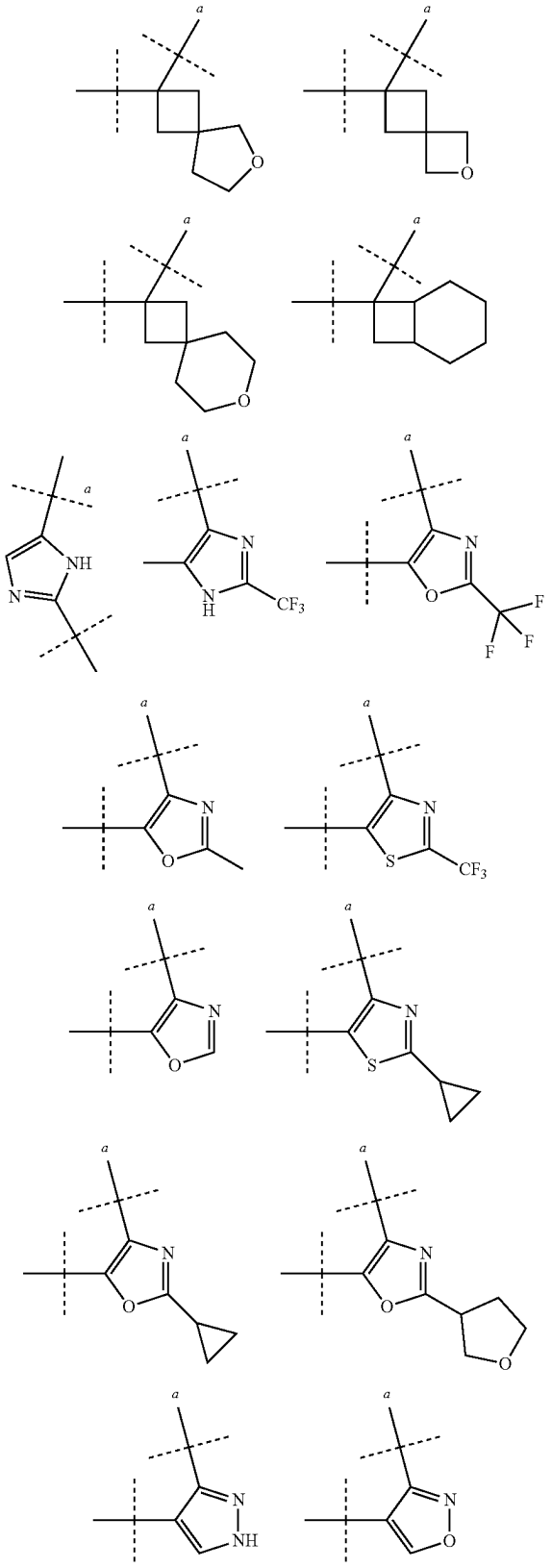
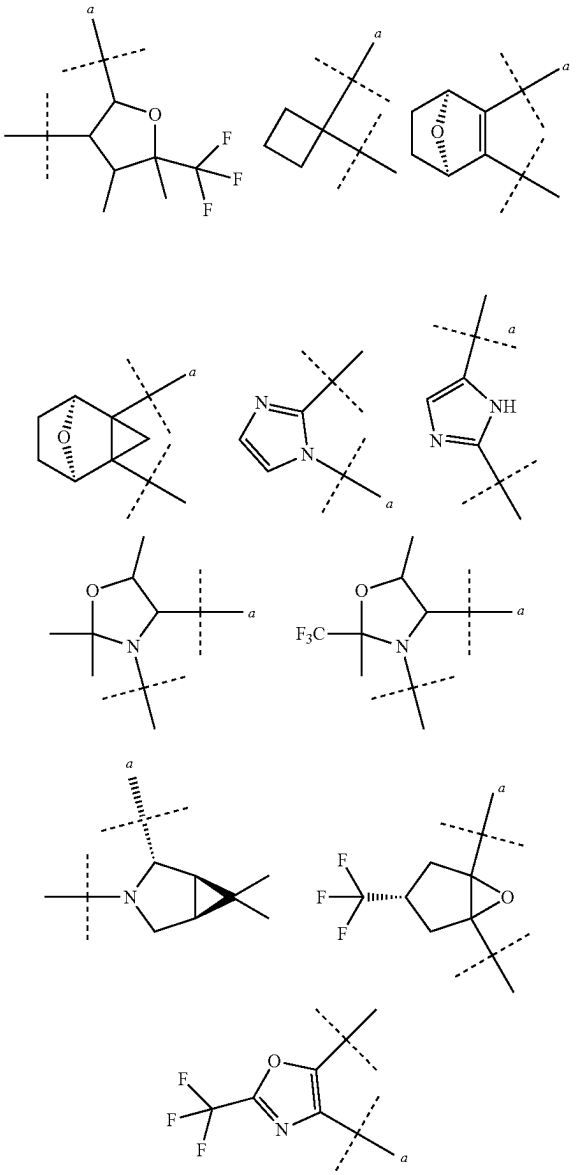
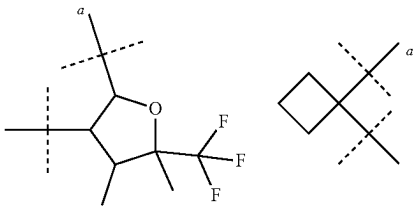


[0054] Preferably, the B ring is selected from the following (where the a-terminal is connected to L_1);



[0055] More preferably, the B ring is selected from the following (where the a-terminal is connected to L_1).



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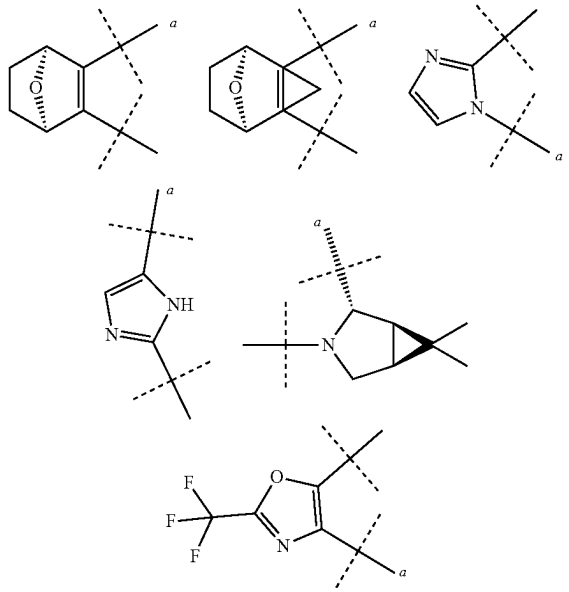
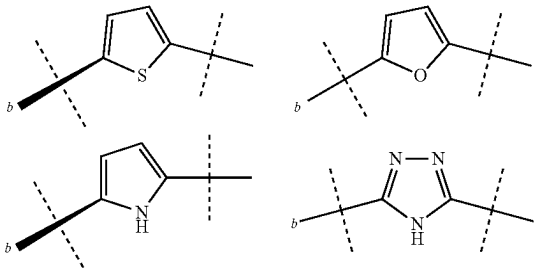


[0056] L_1 is selected from a single bond, —CONR^b, —CO—, —NHCONH—, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups, where the 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0057] R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, C1-C6 alkyl 3-8 membered heterocycloalkyls, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, and —S(O)2C3-C6 cycloalkyls. The C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocycloalkyls may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0058] The 3-8 membered heterocycloalkyls and 5 or 8 membered heteroaromatic groups include, but are not limited to, the following (where the b-terminal is connected to the B ring).



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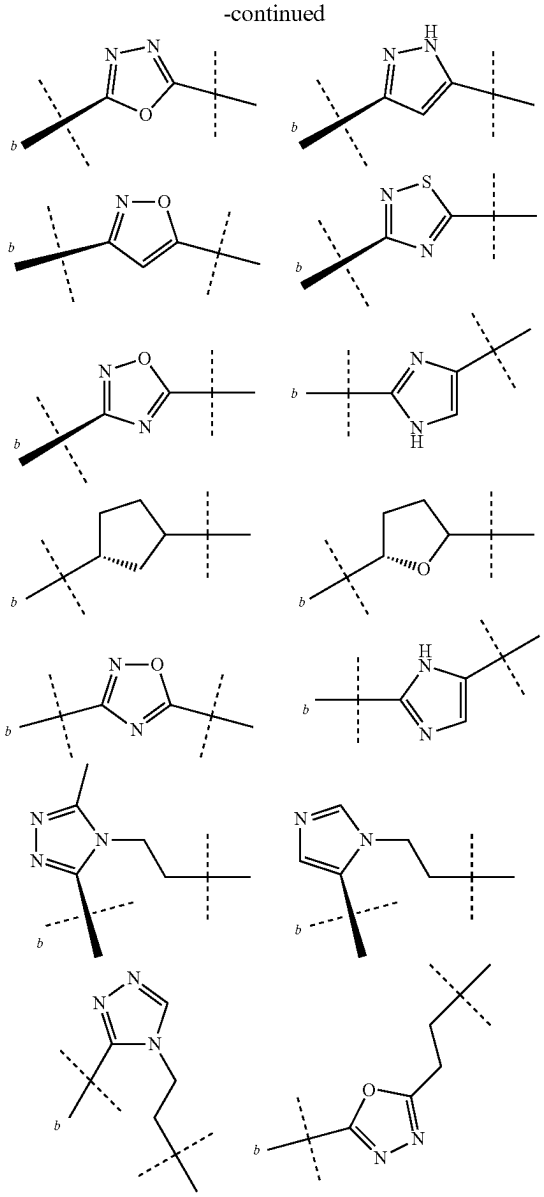
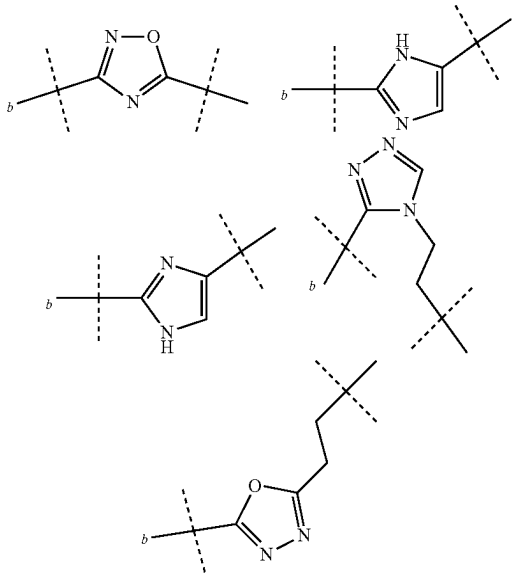


[0059] More preferably, L_1 is selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8 membered heterocycloalkyls, and 5 or 8 membered heteroaromatic groups, where the 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0060] R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, C1-C6 alkyl 3-8 membered heterocycloalkyls, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, and —S(O)2C3-C6 cycloalkyl. The C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocycloalkyls may optionally be substituted with 0-3 additional substituents: deuterium, halogens,

hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0061] The 3-8 membered heterocycloalkyls and 5 or 8 membered heteroaromatic groups include, but are not limited to, the following (where the b-terminal is connected to the B ring).



[0062] More preferably, L_2 is selected from a single bond and —CO—.

[0063] R^1 and R^7 are each independently selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^c-NHR^d, 3-8 membered heterocycloalkyls, 5 or 6 membered heteroaromatic groups. The C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl).

[0064] Alternatively, two adjacent R^1 (or R^7) groups and the atoms they are connected to may form a five-membered ring, and two non-adjacent R^1 (or R^7) groups and the atoms they are connected to may form a heterocyclic alkene group.

[0065] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl), OC(O)(C1-C6 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0 to 3 substituents, which may be deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

[0066] R^e is selected from C1-C6 alkyl and C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0-3 additional substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl.

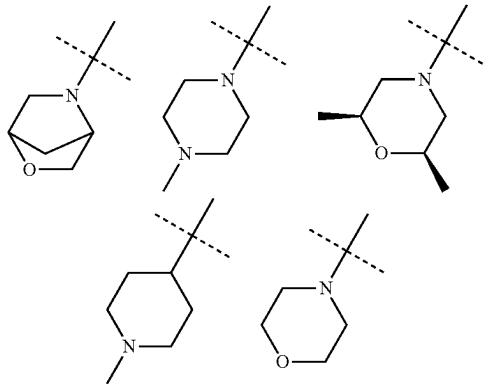
[0067] R2, R3, R4, R5, and R6 are each independently selected from hydrogen, deuterium, halogens, —CONH$_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups. The C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyls, 3-8 membered heterocycloalkenyls, and 5 or 8 membered heteroaromatic groups may optionally be substituted with 0-3 additional substituents: deuterium, halogens, and C1-C3 alkyl.

[0068] X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives.

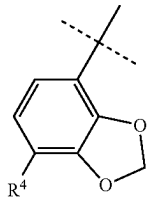
[0069] Y^1, Y^2, Y^3, and Y^4 are each independently selected from CH^2, NH, O, or S.

[0070] n=0, 1, 2, or 3.

[0071] In a preferred embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, F, Cl, Br, I, methoxy, ethoxy, propoxy, isopropoxy, butoxy, [(methylcyclobutyl)methyl]oxy, cyclopropyl, cyclobutyl, cyclohexyl, or 3-6 membered heterocycles; where the heterocycles may contain 1-3 N or O atoms, specifically selected from the following:

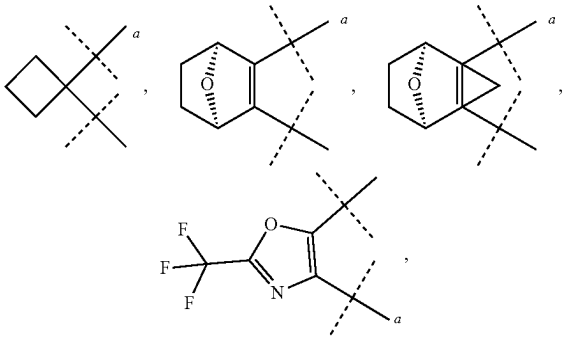


[0072] In one embodiment of the present invention, R^2 (or R^6) and R^3 (or R^5) may together with the atoms to which they are connected form the following structures:



[0073] In one embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, F, and methoxy.

[0074] In some embodiments of the present invention, when the B ring is selected from . . . . (The sentence seems incomplete, if you have more context or specific details, feel free to share them, and I'll continue the translation).



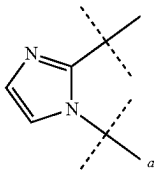
[0075] The A ring is a pyridine ring, and R^1 is —$CONH_2$.

[0076] L_1 is —$CONH_2$, and L_2 is a single bond.

[0077] R^2 and R^6 are each independently selected from H and methoxy.

[0078] R^3, R^4, and R^5 are each independently selected from H and F.

[0079] X^1, X^2, X^3, X^4, and X^5 are selected from CH. In some embodiments of the present invention, when the B ring is selected from



when,

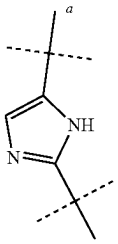
[0080] The A ring is a pyridine ring, and R^1 is —$CONH_2$.

[0081] L_1 and L_2 are single bonds.

[0082] R^2, R^3, R^4, R^5, and R^6 are each independently selected from H, F, methoxy, and —CONH2.

[0083] X^2 and X^4 are each independently selected from CH and N, while X^1, X^3, and X^5 are selected from CH.

[0084] In some embodiments of the present invention, when the B ring is selected from



when,

[0085] The A ring is a pyridine ring, and R^1 is —$CONH_2$.

[0086] L_1 and L2 are single bonds.

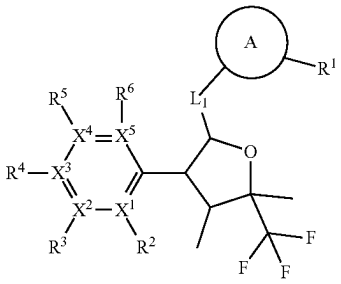
[0087] R^2 and R^6 are each independently selected from H and methoxy.

[0088] R^3, R^4, and R^5 are each independently selected from H and F.

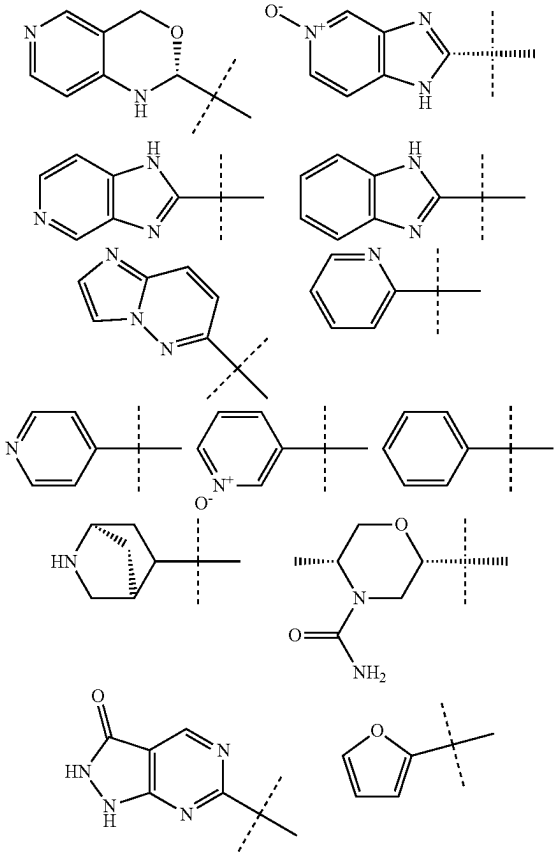
[0089] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0090] Further preferably, in some specific embodiments, a compound as shown in Formula (II), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs.

II



[0091] Wherein the A ring is selected from, but not limited to, the following:



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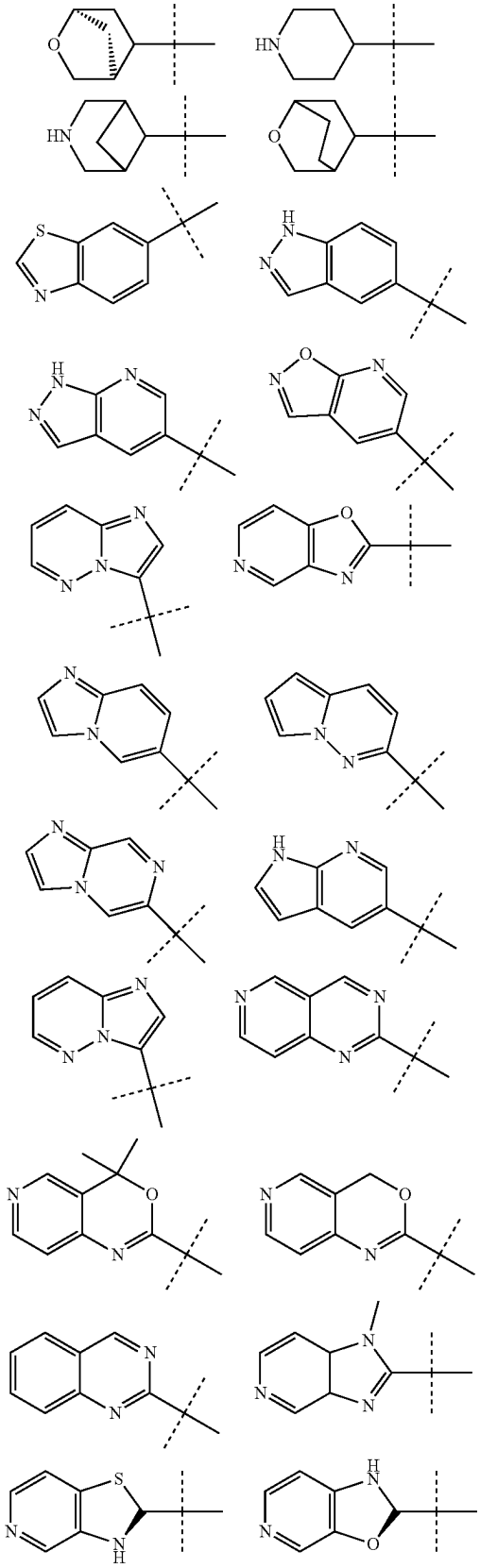

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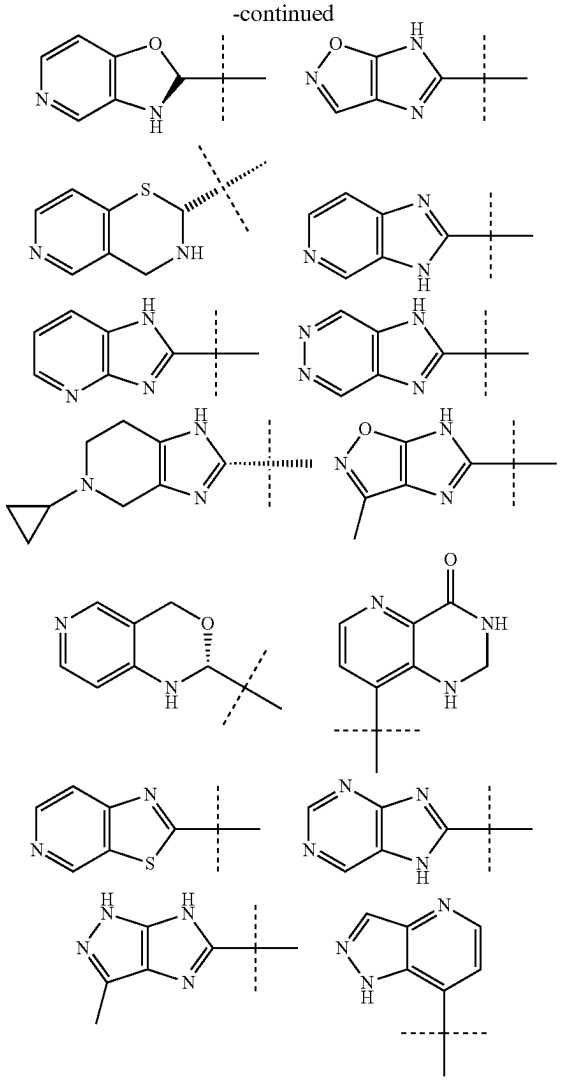
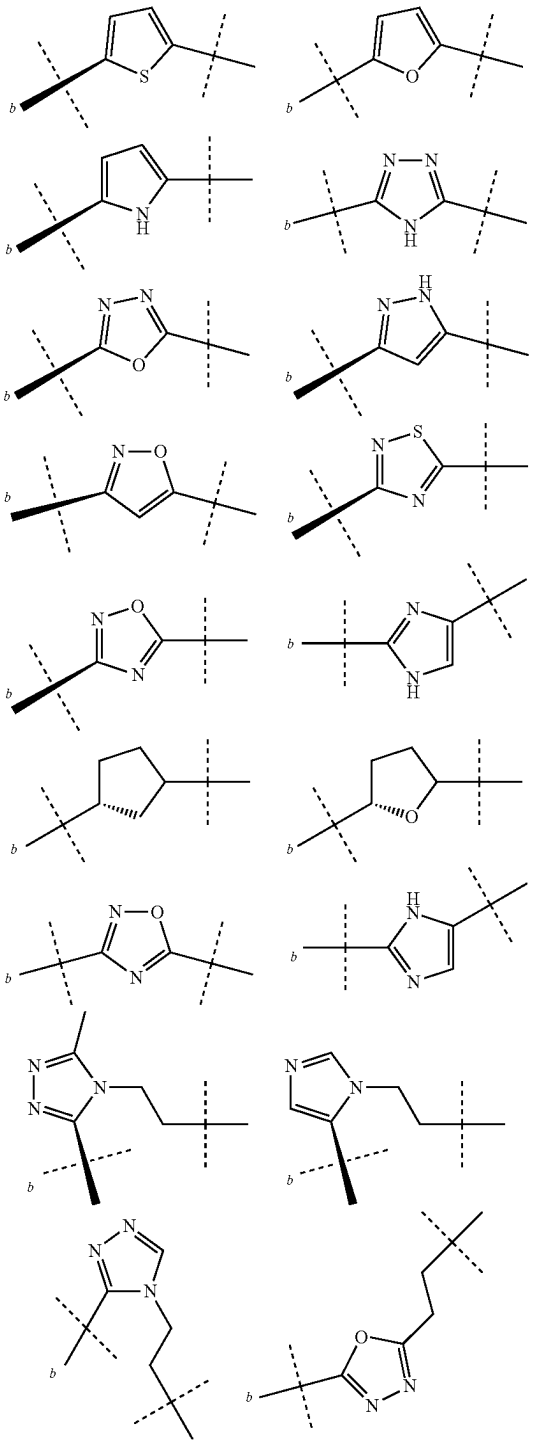


[0092] Wherein the A ring is optionally substituted with 0-5 independent R^1 groups.

[0093] L_1 is selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl groups. The 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted with 0-3 substituents, such as deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0094] R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl-3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)$_2$C1-C6 alkyl, and —S(O)$_2$C3-C6 cycloalkyl. The C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocyclic alkyl groups may optionally be substituted with 0-3 substituents, such as deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl.

[0095] The 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl groups mentioned above include but are not limited to the following (where the b-end is connected to the B ring):



[0096] R^1 is selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —NHCOR^c, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —NHCOR^cNHR^d, 3-8 membered heterocyclic alkyl, 5 or 6 membered heteroaryl, the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted by 0-3 additional substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

Alternatively, two adjacent R^1 positions may form a five-membered ring with the atoms to which they are attached, and two meta-positioned R^1 groups may form a heterocyclic alkenyl with the atoms to which they are attached.

[0097] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, and C1-C6 alkoxy, —C(O)O(C1-C6 alkyl), OC(O)(C1-C6 alkyl), 3-8 membered heterocyclic alkyl groups, 3-8 membered heterocyclic alkenyl groups, and 5 or 8 membered heteroaryl groups, where the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

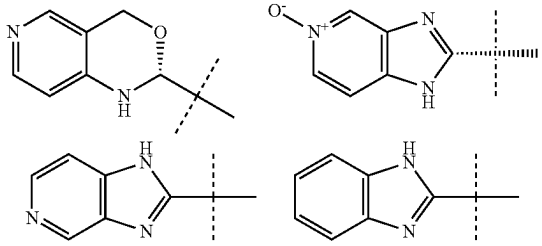
[0098] R^e is selected from C1-C6 alkyl and C3-C6 cycloalkyl groups, where the C1-C6 alkyl and C3-C6 cycloalkyl groups may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl.

[0099] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups, where the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted with 0-3 substituents: deuterium, halogen, or C1-C3 alkyl.

[0100] X^1, X^2, X^3, X^4, and X^5 are each independently selected from O, S, N, CH, or N-oxide derivatives;

[0101] Y^4 is selected from CH_2, NH, O, S.

[0102] Preferably, the A ring is selected from the following:



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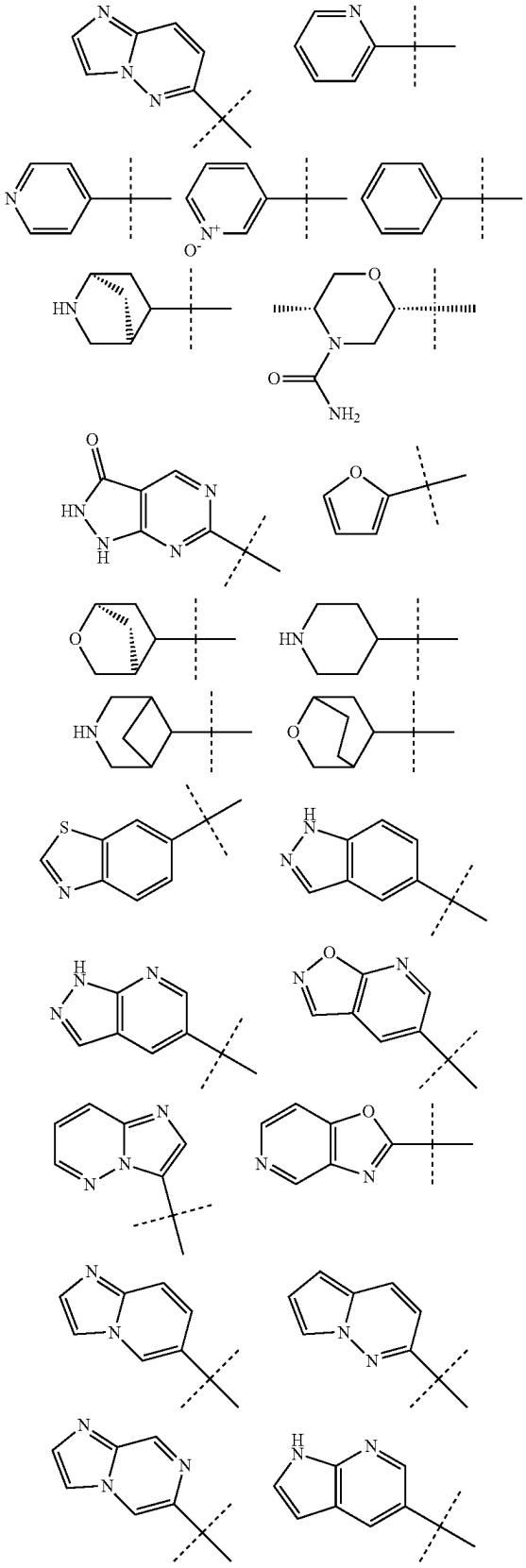

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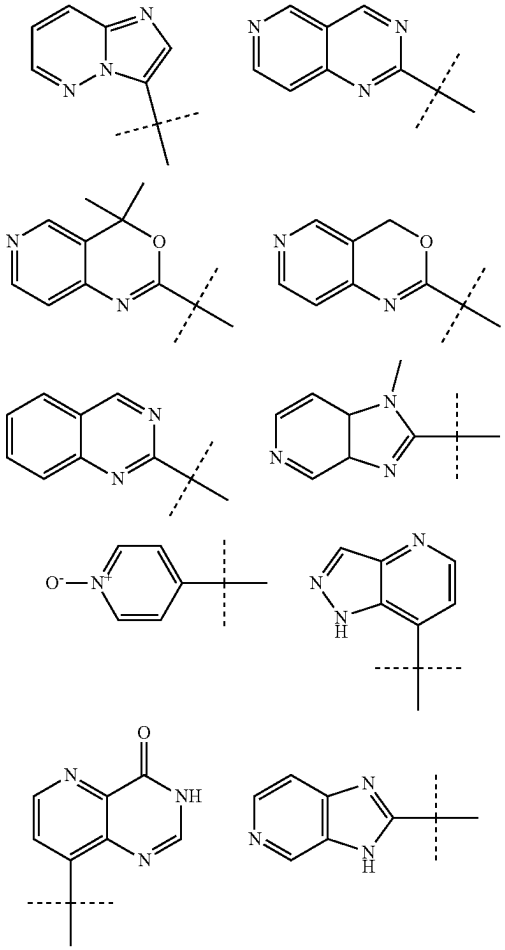
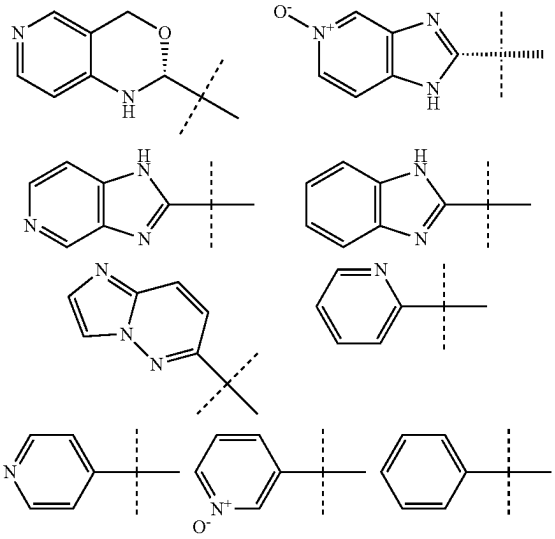


[0103] Preferably, the A ring is selected from the following:



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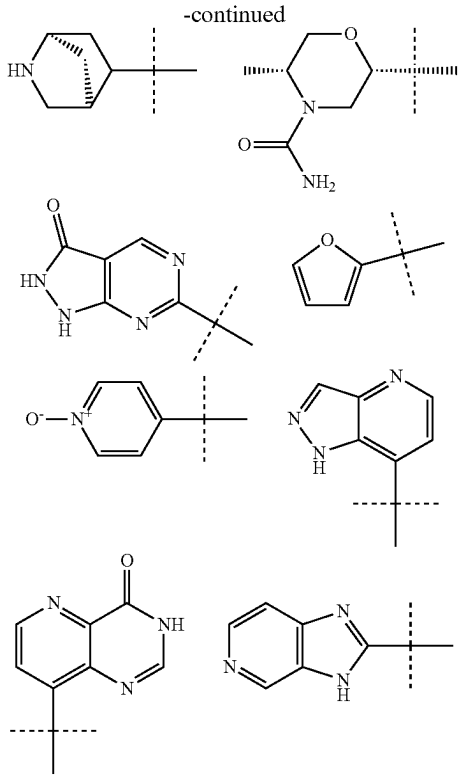
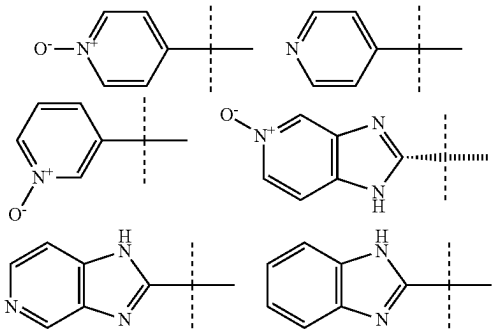


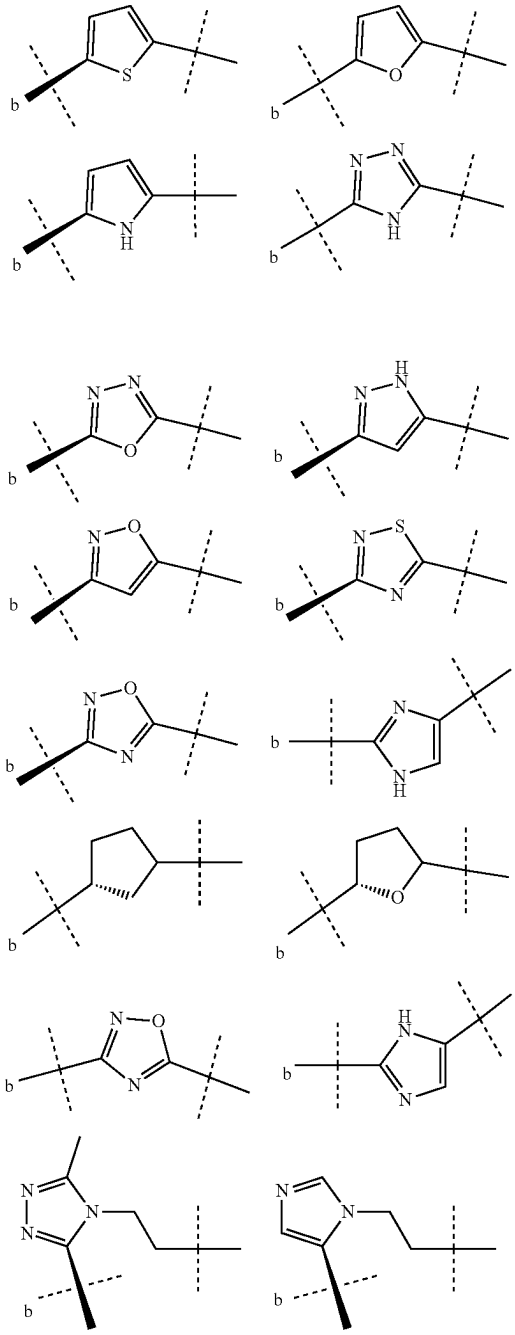
[0104] Preferably, the A ring is selected from the following:



[0105] L_1 is selected from a single bond, —CONRb—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl groups, and 5 or 8 membered heteroaryl groups, where the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

[0106] Rb is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl-3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, —S(O)2C3-C6 cycloalkyl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocyclic alkyl groups may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

[0107] The 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl groups mentioned above include, but are not limited to, the following (where the b-end is connected to the B ring).



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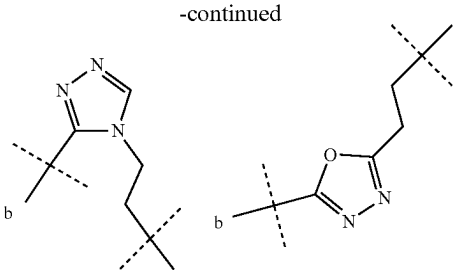
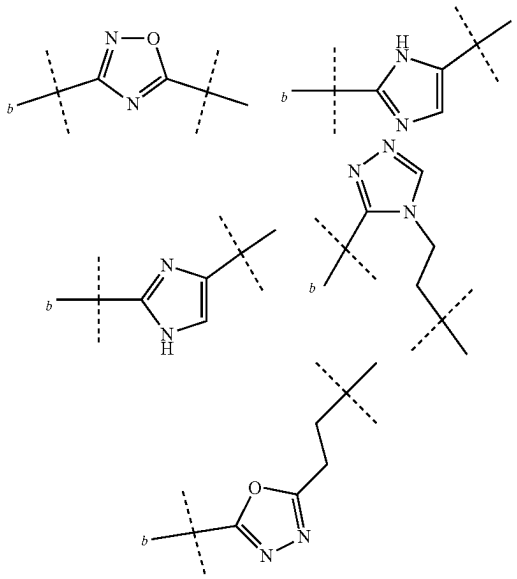
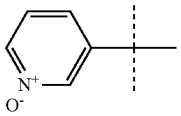


[0108] Preferably, the 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl groups mentioned above include, but are not limited to, the following: (where the b-end is connected to the B ring)



[0109] In some embodiments of the present invention, when the A ring is selected from



When the A ring is selected from,

[0110] R^1 is H;

[0111] L_1 is —$CONH_2$;

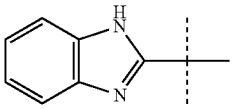
[0112] L_2 is a single bond;

[0113] R^2 and R^6 are each independently selected from H, methoxy;

[0114] R^3, R^4, and R^5 are each independently selected from H, F;

[0115] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0116] In some embodiments of the present invention, when the A ring is selected from



then,

[0117] R^1 is independently selected from hydrogen, deuterium, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8 membered heterocyclic alkyl, 5 or 8 membered heteroaryl groups, where the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted with 0-3 substituents: deuterium, F, Cl, Br, I, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)(methyl), C(O)(ethyl), C(O)(propyl);

[0118] R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups, where the amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C(O)(methyl), C(O)(ethyl), C(O)(propyl), methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoro-methyl, difluoromethyl, trifluoromethyl;

[0119] R^e is selected from methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, where the methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl;

[0120] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups, where the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl groups may optionally be substituted with 0-3 substituents: deuterium, halogen, C1-C3 alkyl;

[0121] X^1, X^2, X^3, X^4, and X^5 are each independently selected from O, S, N, CH, or N-oxide derivatives.

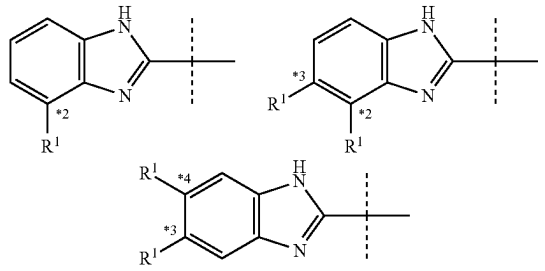
[0122] In some embodiments of the present invention, R^1 is selected from H, F, Cl, Br, I;

[0123] In some embodiments of the present invention, when R^1 is selected from —S(O)(NH)R^c, R^c is selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl;

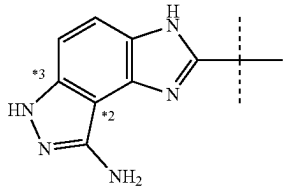
[0124] In some embodiments of the present invention, when R^1 is selected from —CONR^{c}R^d, R^c and R^d are selected from H, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl;

[0125] In some embodiments of the present invention, when R^1 is selected from C(NR^c)NHR^d, R^c is selected from H, and R^d is selected from H, hydroxyl, amino, —OCOR^e, where R^e is selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl; In some embodiments of the present invention, when R^1 is selected from —NHR^c, R^c is selected from H, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl;

[0126] In some embodiments of the present invention, R^1 is preferably at the following position:



[0127] where, when R^1 is located at *2 and *3, it can form the following structure together with the atoms it is connected to:



[0128] In some embodiments of the present invention, R^1 is selected from H, F; In some embodiments of the present invention, when R^1 is selected from —S(O)(NH)R^c, R^c is selected from methyl.

[0129] In some embodiments of the present invention, when R^1 is selected from —CONR^{c}R^d, R^c and R^d are selected from H.

[0130] In some embodiments of the present invention, when R^1 is selected from C(NR^c)NHR^d, R^c is selected from H, and R^d is selected from H, hydroxyl, —OCOR^e, where R* is selected from methyl.

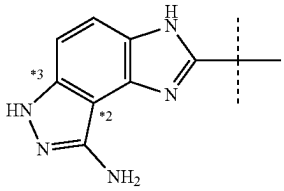
[0131] In some embodiments of the present invention, when R^1 is selected from —NHR^c, R^c is selected from H.

[0132] In some embodiments of the present invention, when the A ring is substituted with only one R^1 and the substitution position is *2, R^1 is selected from —S(O)(NH^2)CH^3;

[0133] In some embodiments of the present invention, when the A ring is substituted with two R^1 groups and the substitution positions are *2 and *3, the R^1 at position *2 is selected from $CONH_2$, $C(NH)NH_2$, C(NH)NHOH, C(NH)NHOC(O)CH_3, and the R^1 at position *3 is F.

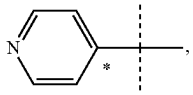
[0134] In some embodiments of the present invention, when the A ring is substituted with two R^1 groups and the substitution positions are *3 and *4, the R^1 at position *3 is independently selected from F, $CONH_2$, and the R^1 at position *4 is selected from $CONH_2$, C(NH)NHOH.

[0135] Preferably, when the A ring is substituted with two R^1 groups and the substitution positions are *3 and *4, the R^1 at position *3 is independently selected from F, and the R^1 at position *4 is selected from $CONH_2$, C(NH)NHOH. Alternatively, when the A ring is substituted with two R^1 groups and R^1 is located at *2 and *3, it can form the following structure together with the atoms it is connected to:



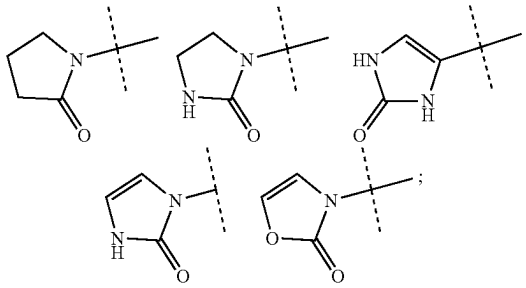
[0136] L_1 and L_2 are single bonds; R^2 and R^6 are each independently selected from H, methoxy; R^3, R^4, and R^5 are each independently selected from H, F; X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0137] In some embodiments of the present invention, when the A ring is selected from

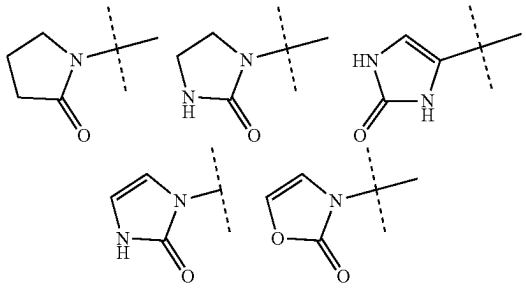


When L_1 is —$CONH_2$;

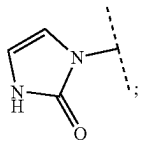
[0138] The A ring is optionally substituted with the following one R^1, and R^1 is located at the * meta position:



[0139] Alternatively, the A ring is substituted with two R^1 groups, both located at the * meta position, where one R^1 is selected from —$CONH_2$, and the other R^1 is selected from the following:

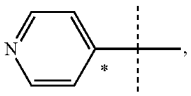


[0140] Preferably, the A ring is optionally substituted with one R^1, and R^1 is located at the * meta position, where R^1 is



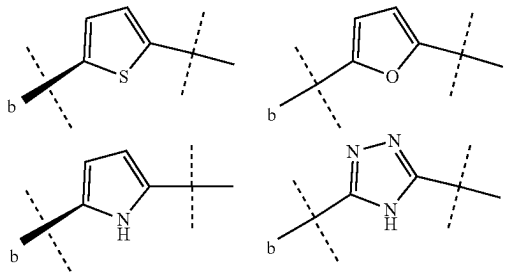
[0141] L_2 is a single bond; R^2 and R^6 are each independently selected from H, methoxy; R^3, R^4, and R^5 are each independently selected from H, F; X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0142] In some embodiments of the present invention, when the A ring is selected from



[0143] L_1 is selected from —CONR^b—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl, where the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkene, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents selected from: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl; R^b is selected from C1-C6 alkyl.

[0144] The above-mentioned 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl include, but are not limited to, the following: (where the b-end is connected to the B ring).



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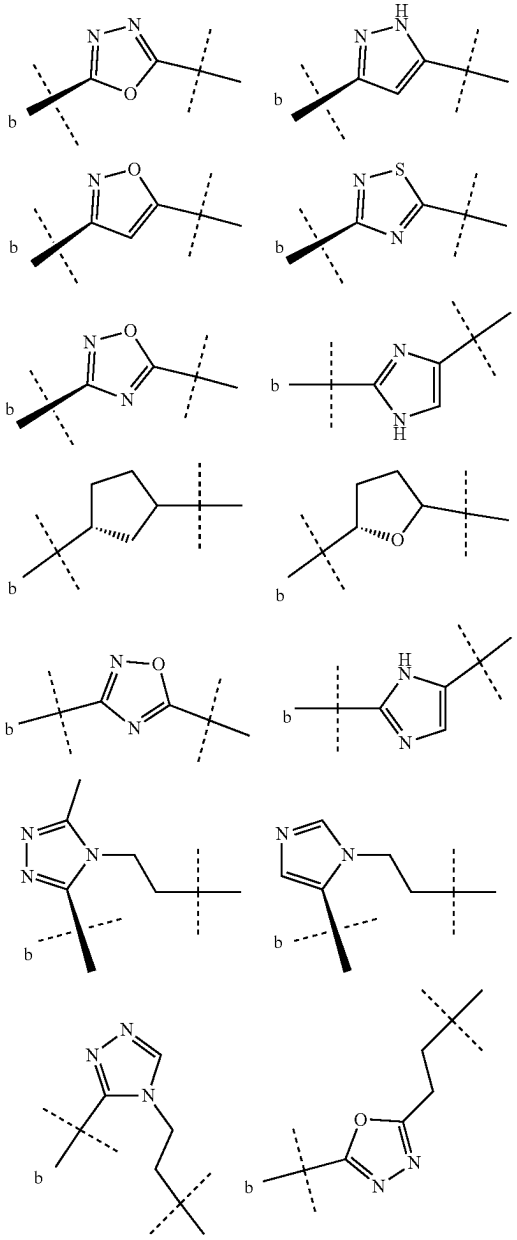
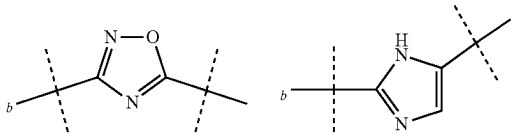


[0145] Preferably, L_1 is selected from —CONR^b—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl, with R^b selected from methyl; The above-mentioned 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl include, but are not limited to, the following: (where the b-end is connected to the B ring)



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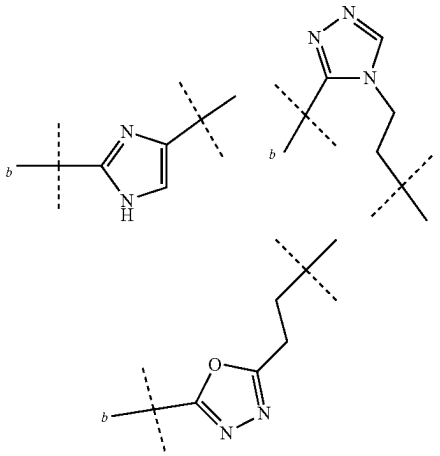
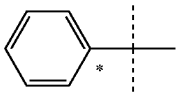


[0146] R^2 and R^6 are each independently selected from H, methoxy;

[0147] R^3, R^4, and R^5 are each independently selected from H, F;

[0148] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0149] In some embodiments of the present invention, when the A ring is selected from



When, R_1 is each independently selected from —P(O)$(CH_2CH_3)_2$, —$NHCH_3$;

[0150] Preferably, the A ring is optionally substituted with two R^1 groups, and R^1 is located at the * meta and para positions;

[0151] L_1 is —$CONH_2$;

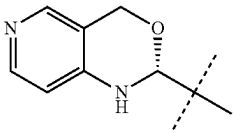
[0152] L_2 is a single bond;

[0153] R^2 and R^6 are each independently selected from H, methoxy;

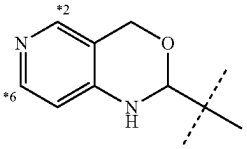
[0154] R^3, R^4, and R^5 are each independently selected from H, F;

[0155] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0156] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is —$CONH_2$, specifically, R^1 is preferably substituted at the following positions:



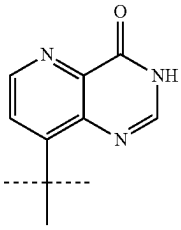
[0157] L_1 and L_2 are single bonds;

[0158] R^2 and R^6 are each independently selected from H, methoxy;

[0159] R^3, R^4, and R^5 are each independently selected from H, F;

[0160] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0161] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is H;

[0162] L_1 is —CONH—;

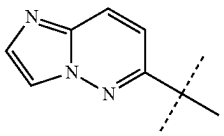
[0163] L_2 is a single bond;

[0164] R^2 and R^6 are each independently selected from H, methoxy;

[0165] R^3, R^4, and R^5 are each independently selected from H, F;

[0166] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0167] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is —$CONH_2$;

[0168] L^1 is —CONH—;

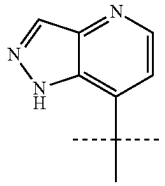
[0169] L^2 is a single bond;

[0170] R^2 and R^6 are each independently selected from H, methoxy;

[0171] R^3, R^4, and R^5 are each independently selected from H, F;

[0172] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0173] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is an amino group;

[0174] L_1 is —CONH—;

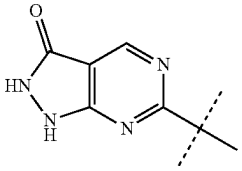
[0175] L_2 is a single bond;

[0176] R^2 and R^6 are each independently selected from H, methoxy;

[0177] R^3, R^4, and R^5 are each independently selected from H, F;

[0178] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0179] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is H;

[0180] L_1 is —CONH—;

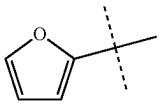
[0181] L_2 is a single bond;

[0182] R^2 and R^6 are each independently selected from H, methoxy;

[0183] R^3, R^4, and R^5 are each independently selected from H, F;

[0184] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0185] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is selected from —$CONH_2$;

[0186] L_1 is —$CONHCH_2$—;

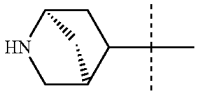
[0187] L_2 is a single bond;

[0188] R^2 and R^6 are each independently selected from H, methoxy;

[0189] R^3, R^4, and R^5 are each independently selected from H, F;

[0190] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0191] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is selected from —$CONH^2$;

[0192] L_1 is —CONH—;

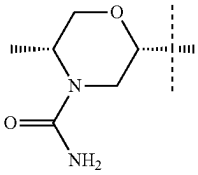
[0193] L_2 is a single bond;

[0194] R^2 and R^6 are each independently selected from H, methoxy;

[0195] R^3, R^4, and R^5 are each independently selected from H, F;

[0196] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0197] In some embodiments of the present invention, when the A ring is selected from



When, R^1 is selected from H;

[0198] L_1 is —$CONHCH_2$—;

[0199] L_2 is a single bond;

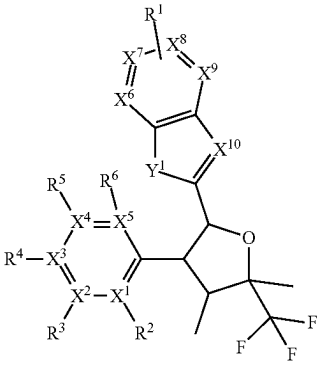
[0200] R^2 and R^6 are each independently selected from H, methoxy;

[0201] R^3, R^4, and R^5 are each independently selected from H, F;

[0202] X^1, X^2, X^3, X^4, and X^5 are selected from CH.

[0203] Further, specifically, in some embodiments, the present invention provides a compound as shown in formulas (II-1) and (II-2), and its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs.

II-1



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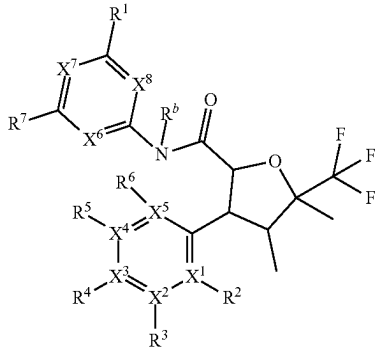
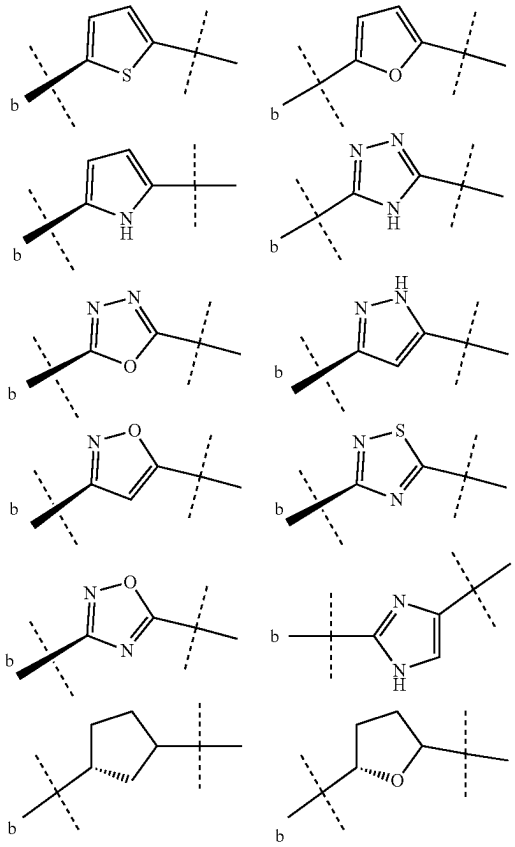
II-2



[0204] Wherein, R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, C1-C6 alkyl-3-8-membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —$S(O)_2$C1-C6 alkyl, —$S(O)_2$C3-C6 cycloalkyl, with the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8-membered heterocyclic alkyl optionally being substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyanide, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl; The 3-8-membered heterocyclic alkyl and 5- or 8-membered heteroaryl groups mentioned above include but are not limited to the following (where the b-end is connected to the B ring).



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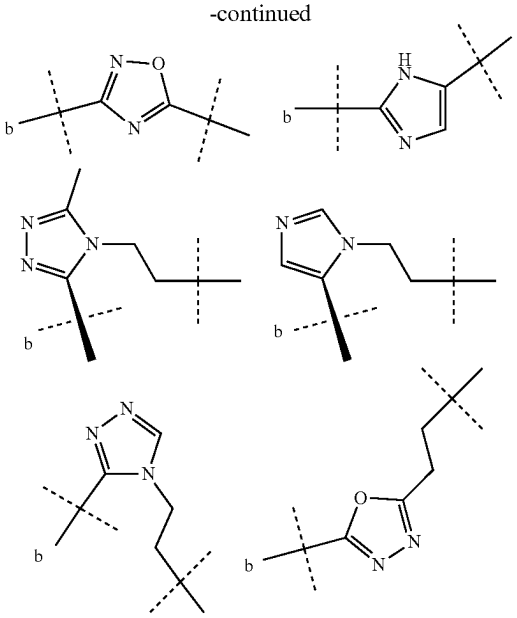
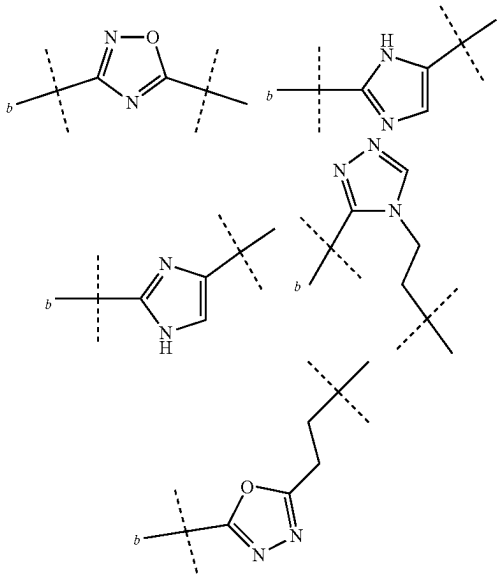


[0205] Preferably, the above-mentioned 3-8 membered heterocyclic alkyl and 5- or 8-membered heteroaryl groups include but are not limited to the following (where the b-end is connected to the B ring).



[0206] R^1 is selected from hydrogen (H), halogens, C1-C6 alkyl groups, C1-C6 alkoxy groups, C3-C6 cycloalkyl groups, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —$NHCOR^c$, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —$NHCOR^cNHR^d$, 3-8 membered heterocyclic alkyl groups, 5- or 6-membered heteroaryl groups. The C1-C6 alkyl groups, C1-C6 alkoxy groups, C3-C6 cycloalkyl groups, 3-8 membered heterocyclic alkyl groups, 3-8 membered heterocyclic alkenyl groups, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0-3

additional substituents selected from deuterium (D), halogens, hydroxyl (—OH), cyano (—CN), amino (—NH_2), C1-C6 alkyl groups, C3-C6 cycloalkyl groups, and CO(C1-C6 alkyl).

[0207] Alternatively, any two adjacent R^1 groups, along with the atoms they are connected to, form a five-membered ring; any two R^1 groups at the meta positions, along with the atoms they are connected to, form a heterocyclic alkenyl group

[0208] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —$OCOR^e$, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0 to 3 substituents, which may be deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl;

[0209] R^e is selected from C1-C6 alkyl groups, C3-C6 cycloalkyl groups, wherein the C1-C6 alkyl and C3-C6 cycloalkyl groups can optionally be substituted with up to 0-3 substituents: deuterium, halogens, hydroxyl groups, cyanide groups, amino groups, C1-C6 alkyl groups, and C3-C6 cycloalkyl groups;

[0210] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl groups, C2-C6 alkenyl groups, C1-C6 halogenated alkyl groups, C1-C6 alkoxy groups, C1-C6 deuterated alkoxy groups, C1-C6 halogenated alkoxy groups, C3-C6 cycloalkyl groups, 3-8-membered heterocyclic alkyl groups, 3-8-membered heterocyclic alkenyl groups, and 5 or 8-membered heteroaryl groups, wherein the C1-C6 alkyl groups, C2-C6 alkenyl groups, C1-C6 alkoxy groups, C3-C6 cycloalkyl groups, 3-8-membered heterocyclic alkyl groups, 3-8-membered heterocyclic alkenyl groups, and 5 or 8-membered heteroaryl groups can each be optionally substituted with up to 0-3 substituents: deuterium, halogens, or C1-C3 alkyl groups;

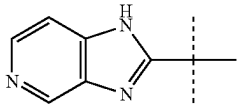
[0211] X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives;

[0212] Y1 is selected from CH_2, NH, O, S;

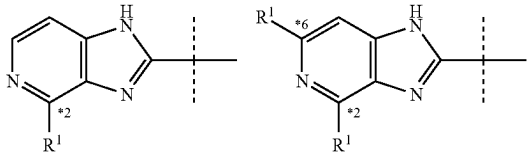
[0213] Preferably, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from N, CH, or N-oxide derivatives;

[0214] Preferably, Y^1 is selected from NH.

[0215] Wherein, when the A ring is



When R^1 is substituted at position 6 and is —$CONH_2$, the R^1 substituted at position 2 is not H.

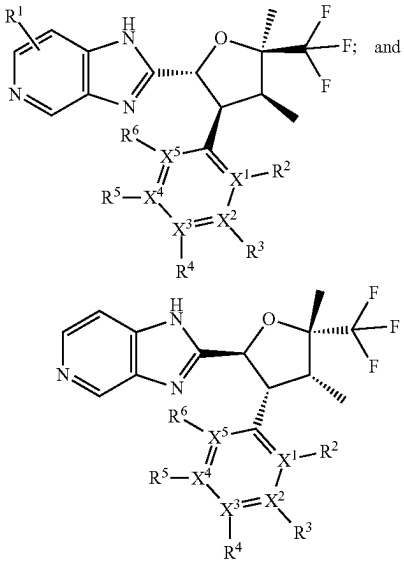


[0216] When the A ring is a pyridine ring with X^7 being N or N—O, R^1 and R^7 can both be hydrogen;

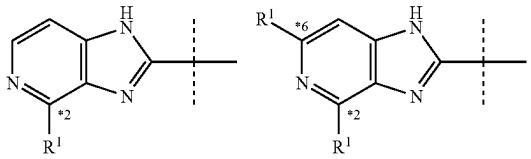
[0217] When R^1 (R^7) is $CONH_2$, the other substituent cannot be hydrogen.

[0218] Furthermore, more specifically, in some embodiments, the present invention provides a compound as shown in formula (II-1A), along with its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs;

(II-1A)



[0219] Among them, the A ring can be optionally substituted by 0 to 3 R^1 groups. R^1 is preferably located at the positions shown below. When R^1 is substituted at position 6 and is —$CONH_2$, the R^1 at position 2 must not be H;



[0220] R^1 is independently selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —$CONR^cR^d$, C(NR^c)NHR^d, —$NHCOR^c$, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —$NHCOR^cNHR^d$, 3-8 membered heterocycloalkyl, 5- or 8-membered heteroaryl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered het-

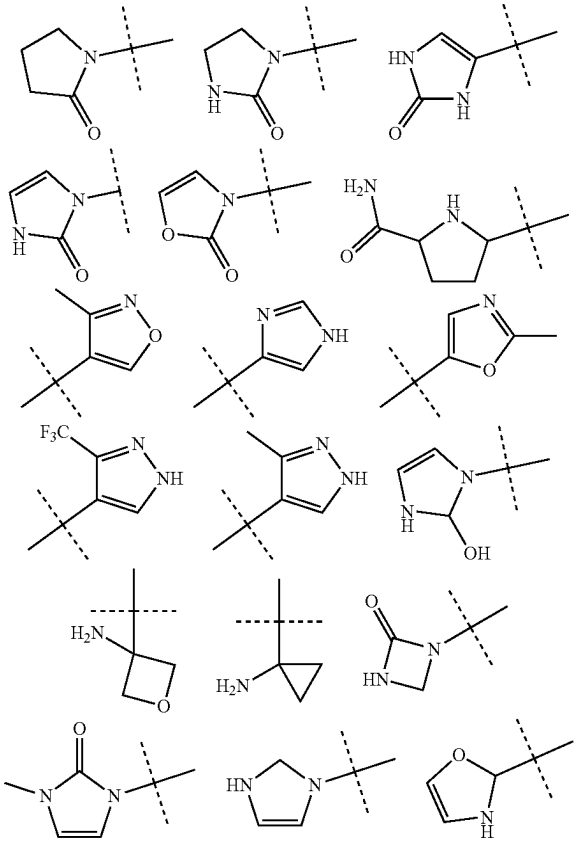
eroaryl groups can optionally be substituted with 0-3 of the following substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or CO(C1-C6 alkyl).

[0221] Alternatively, any two adjacent R^1 (or R^7) groups, along with the atoms they are connected to, can form a five-membered ring, or any two meta-positioned R^1 (or R^7) groups, along with the atoms they are connected to, can form a heteroalkenyl ring.

[0222] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —$OCOR^e$, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0 to 3 substituents, which may be deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

[0223] R^e is selected from C1-C6 alkyl and C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl groups can optionally be substituted with 0-3 of the following substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl.

[0224] The aforementioned 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 6-membered heteroaryl include, but are not limited to, the following:



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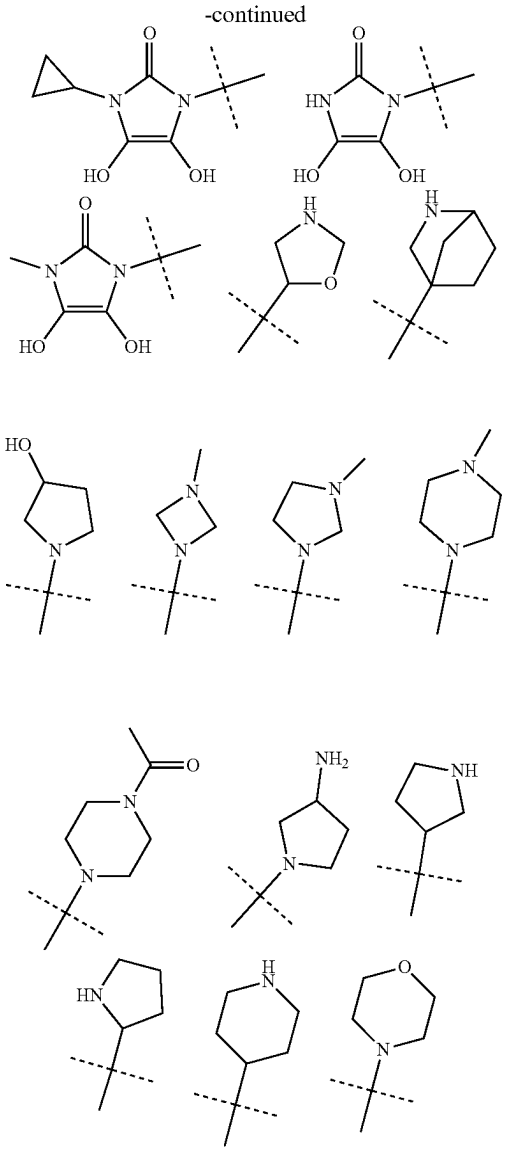
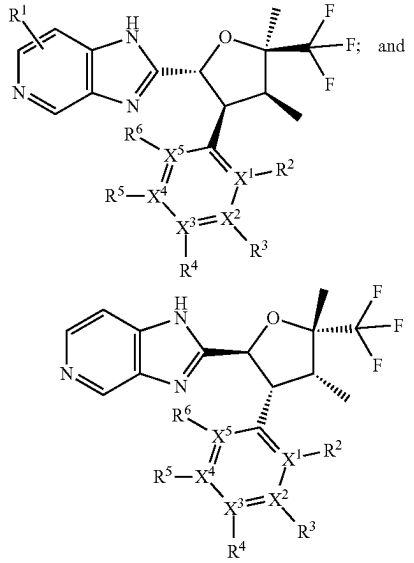


[0225] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl. The C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl groups can optionally be substituted with 0-3 of the following substituents: deuterium, halogen, or C1-C3 alkyl.

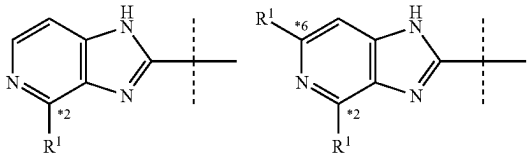
[0226] X^1, X^2, X^3, X^4, and X^5 are each independently selected from O, S, N, CH, or N-oxide derivatives.

[0227] In one embodiment of the present invention, the compound shown in formula (II-1A), its tautomeric isomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, or prodrugs are:

(II-1A)



[0228] Among them, the A ring can optionally be substituted with 0-3 R^1 groups, where R^1 is preferably located at the positions shown below. When R^1 is substituted at position 6 and is —$CONH_2$, the R^1 at position 2 must not be hydrogen (H)



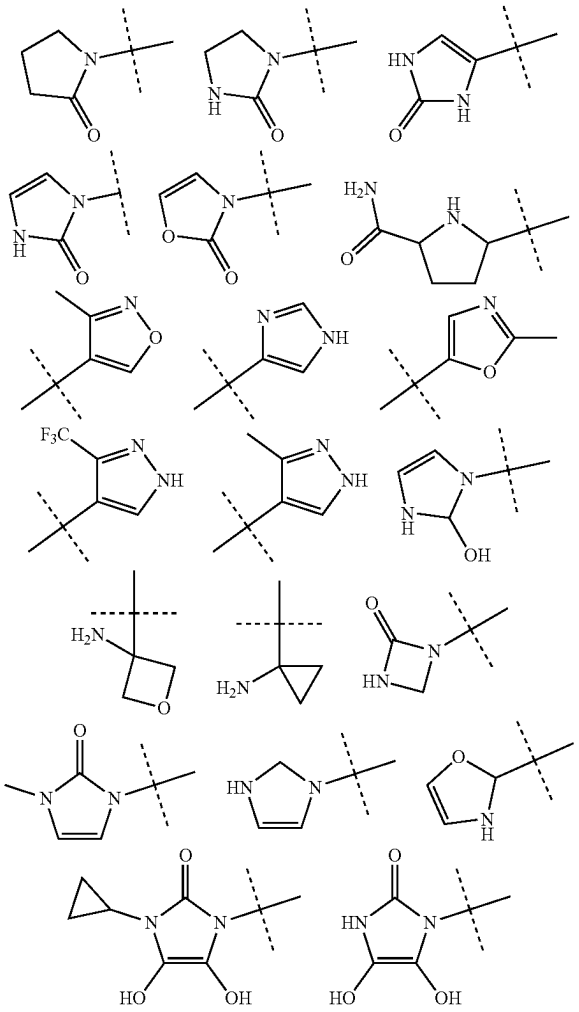
[0229] R^1 is independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —S(O)(NH)R^c, —$CONR^cR^d$, C(NR^c)NHR^d, —$NHCOR^c$, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —$NHCOR^cNHR^d$, 3-8 membered heterocycloalkyl, 5- or 8-membered heteroaryl. The methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl groups can optionally be substituted with 0-3 of the following substituents: deuterium, F, Cl, Br, I, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)(methyl), C(O)(ethyl), C(O)(propyl).

[0230] Alternatively, any two adjacent R^1 (or R^7) groups, along with the atoms they are connected to, can form a five-membered ring, or any two meta-positioned R^1 (or R^7) groups, along with the atoms they are connected to, can form a heteroalkenyl ring.

[0231] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —$OCOR^e$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0 to 3 substituents, which may be deuterium, halogen, hydroxyl, cyano, amino, C(O)(methyl), C(O)(ethyl), C(O)(propyl), methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

[0232] R^e is selected from methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. These methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups can optionally be substituted with 0-3 of the following substituents: deuterium, halogen, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0233] The aforementioned 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 6-membered heteroaryl include, but are not limited to, the following:



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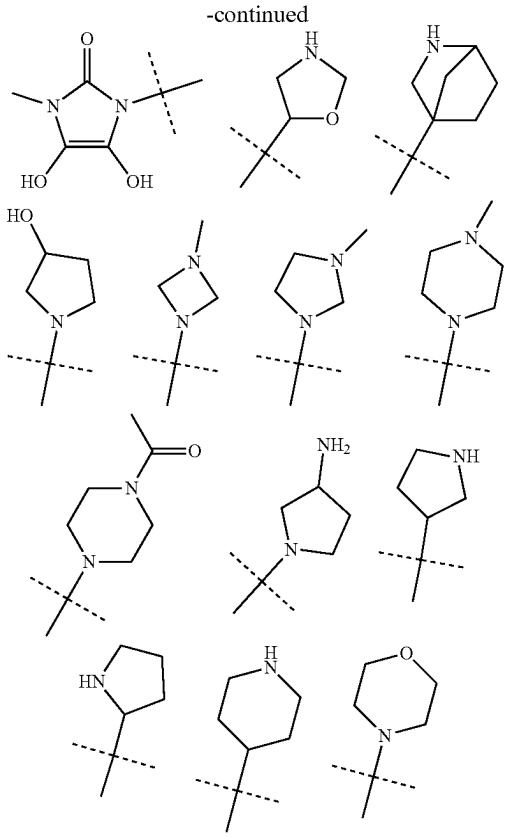


[0234] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, F, Cl, Br, I, —$CONH_2$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-6 membered cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl. These groups, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl, can optionally be substituted with 0-3 of the following substituents: deuterium, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl.

[0235] X^1, X^2, X^3, X^4, and X^5 are each independently selected from N, CH, or N-oxide derivatives.

[0236] In one embodiment of the present invention, R^1 is selected from H, deuterium, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, and (2,3-dihydroxypropyl)oxy.

[0237] In another embodiment, when R^1 is selected as —S(O)(NH)R^c, R^c is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0238] In another embodiment, when R^1 is selected as —$CONR^cR^d$, R^c and R^d are selected from H, amino, methoxy, ethoxy, propoxy, dimethylamino, and diethylamino.

[0239] In another embodiment, when R^1 is selected as $C(NR^c)NHR^d$, R^c and R^d are selected from H, hydroxyl, methoxy, ethoxy, propoxy, —$OCOR^e$, where R^e is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0240] In another embodiment, when R^1 is selected as —$NHCOR^c$, R^c is selected from amino, hydroxyethyl, hydroxypropyl, aminoethyl, and aminopropyl.

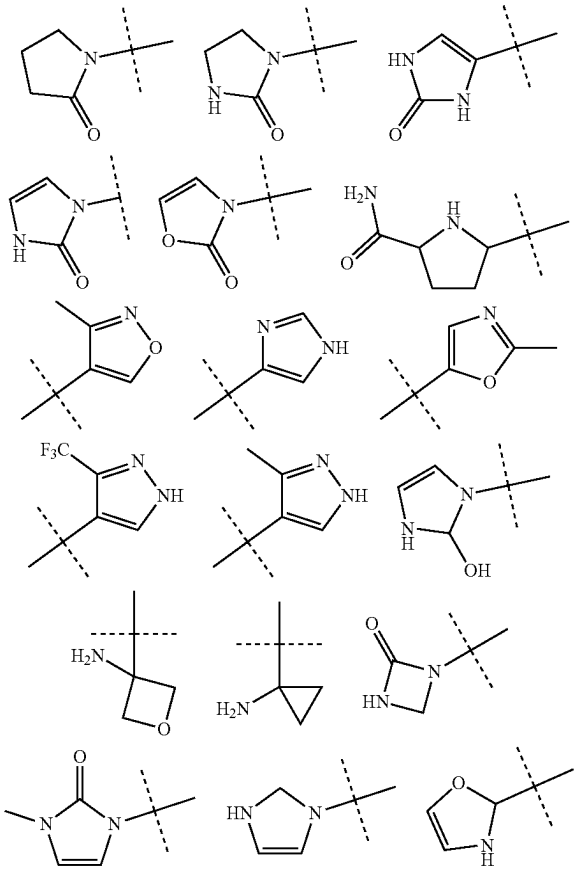
[0241] In another embodiment, when R^1 is selected as —$NHSO_2R^c$, R^c is selected from amino.

[0242] In another embodiment, when R^1 is selected as —$P(O)R^cR^d$, R^c and R^d are selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0243] In another embodiment, when R^1 is selected as —NHR^c, R^c is selected from H, methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0244] In one embodiment of the present invention, when R^1 is selected as —$NHCOR^cNHR^d$, R^c is selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, and R^d is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoromethyl, difluoromethyl, trifluoromethyl, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), —COR^e. R^e is selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-aminoethyl, 1-aminopropyl, 1-aminobutyl, and 1-amino-3-methylbutyl.

[0245] In one embodiment of the present invention, when R^1 is selected from 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl, it includes, but is not limited to, the following structures:



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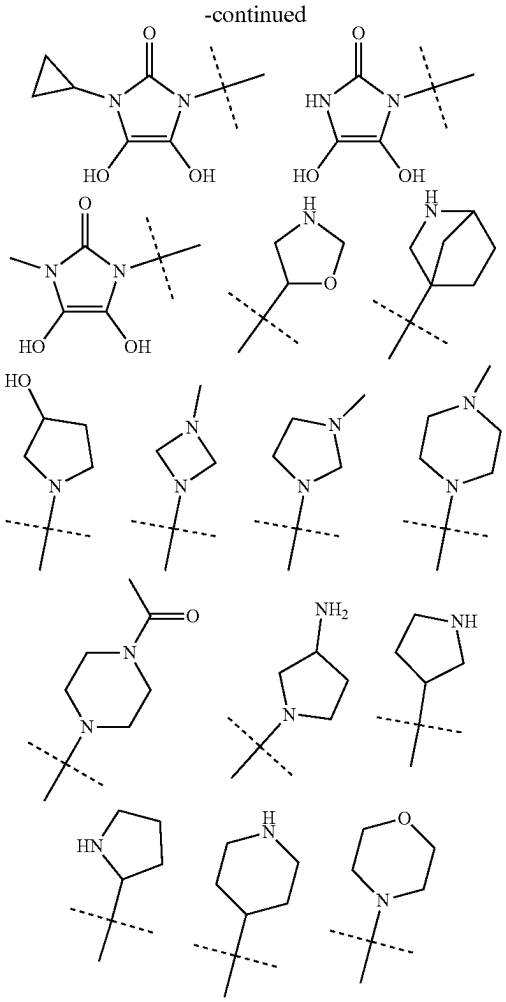


[0246] In one embodiment of the present invention:

[0247] When R^1 is selected from H, deuterium, or (2,3-dihydroxypropyl)oxy;

[0248] When R^1 is selected as —S(O)(NH)R^c, R^c is selected from methyl;

[0249] When R^1 is selected as —CONR^{c}R^d, R^c and R^d are selected from H, amino, methoxy, or diethylamino;

[0250] When R^1 is selected as C(NR^c)NHR^d, R^c and R^d are selected from H, hydroxyl, methoxy, or —OCOR^e, where R* is selected from methyl;

[0251] When R^1 is selected as —NHCOR^c, R^c is selected from amino, hydroxyethyl, or aminoethyl;

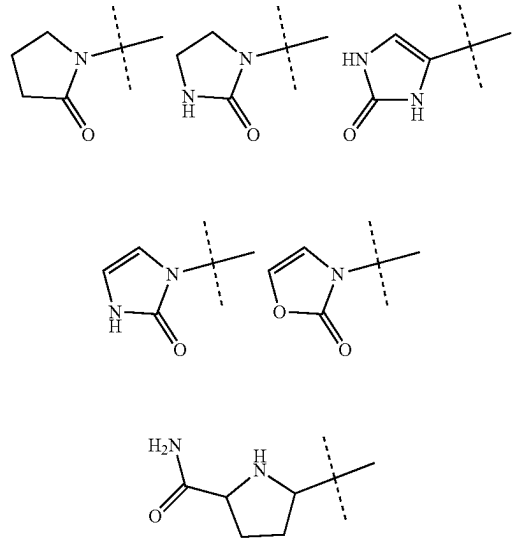
[0252] When R^1 is selected as —NHSO$_2$R^c, R^c is selected from amino;

[0253] When R^1 is selected as —P(O)R^{c}R^d, R^c and R^d are selected from ethyl,

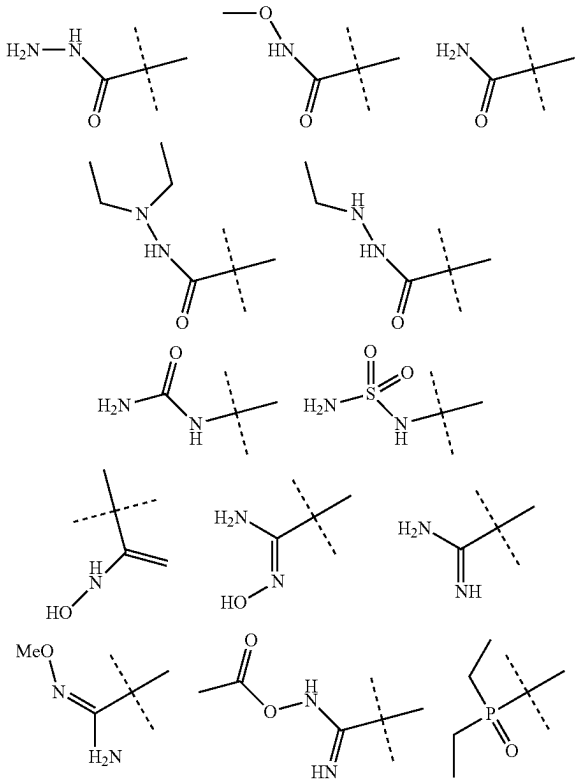
[0254] When R^1 is selected as —NHR^c, R^c is selected from H or methyl

[0255] In one embodiment of the present invention, when R^1 is selected as —NHCOR^{c}NHR^d, R^c is selected from ethyl, R^d is selected from hydrogen, methyl, trifluoromethyl, isopropyl, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), —COR^e, and R^e is selected from isopropyl, cyclopropyl, 1-aminoethyl, 1-amino-3-methylbutyl

[0256] In one embodiment of the present invention, when R^1 is selected from 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5- or 8-membered heteroaryl, it includes, but is not limited to, the following structures:



[0257] Preferably, in one embodiment of the present invention, R^1 is selected from H, D, amino, or the following groups:



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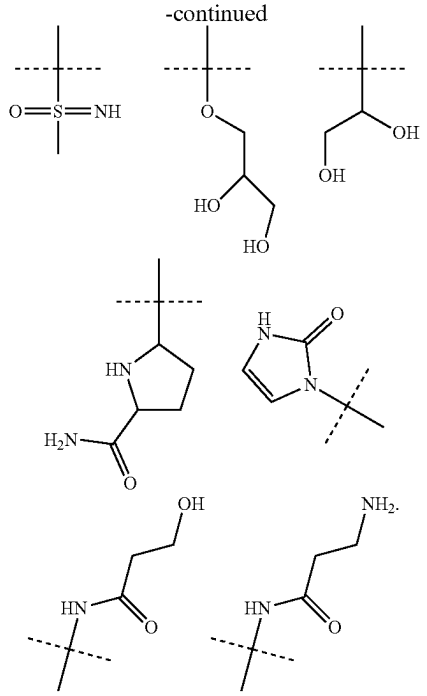
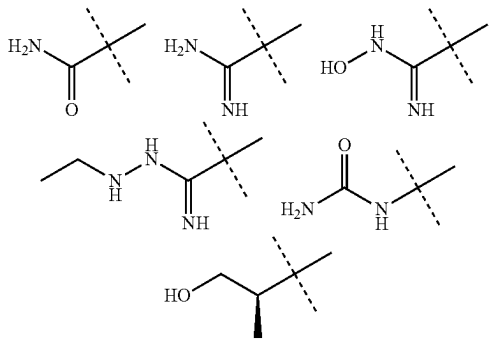
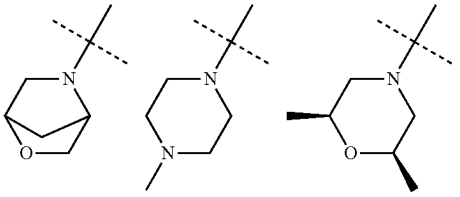


[0258] Further preferably, in one embodiment of the present invention, R^1 is selected from H, amino, or the following groups:



[0259] In one embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen, F, Cl, Br, I, methoxy, ethoxy, propoxy, isopropoxy, butoxy, [(methylcyclobutyl)methyl]oxy, cyclopropyl, cyclobutyl, cyclohexyl, or 3-6 membered heterocycles; wherein the heterocycles may contain 1-3 N or O atoms, and can be specifically selected from the following:



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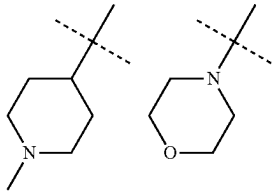
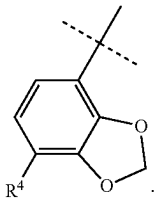


[0260] In one embodiment of the present invention, R^2 (or R^6) and R^3 (or R^5) may together with the atoms to which they are connected form the following structure:

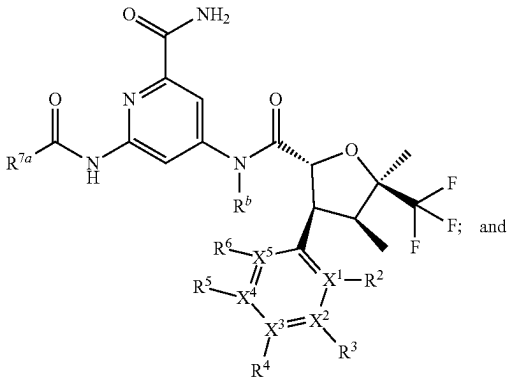


[0261] Preferably, in one embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen (H), fluorine (F), and methoxy. More preferably, R^2 and R^6 are selected from H and methoxy, while R^3, R^4, and R^5 are selected from H and F.

[0262] In one embodiment of the present invention, X^1, X^2, X^3, X^4, and X^5 are independently selected from CH.

[0263] Furthermore, specifically, in certain embodiments, the present invention provides a compound as shown in formula (II-2A), along with its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated forms, metabolites, or prodrugs.

(II-2A)



F; and

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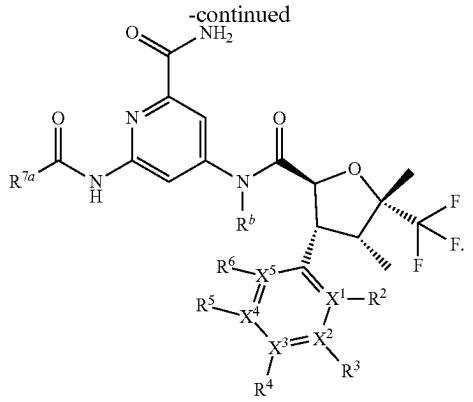


[0264] Wherein, R^b is selected from hydrogen (H), C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C3-C8 heterocyclic alkyl, C1-C6 alkyl-C3-C8 heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, —S(O)2C3-C6 cycloalkyl, wherein the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and C3-C8 heterocyclic alkyl may optionally be substituted with 0-3 substituents, selected from deuterium (D), halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 Cycloalkyl. R^{7a} selected from R^c, —R^cNHR^d;

[0265] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, C1-C6 alkyl, C1-C6 thioalkyl, and C1-C6 alkoxy groups, as well as the 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups, may optionally be substituted with 0 to 3 substituents, which may be deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

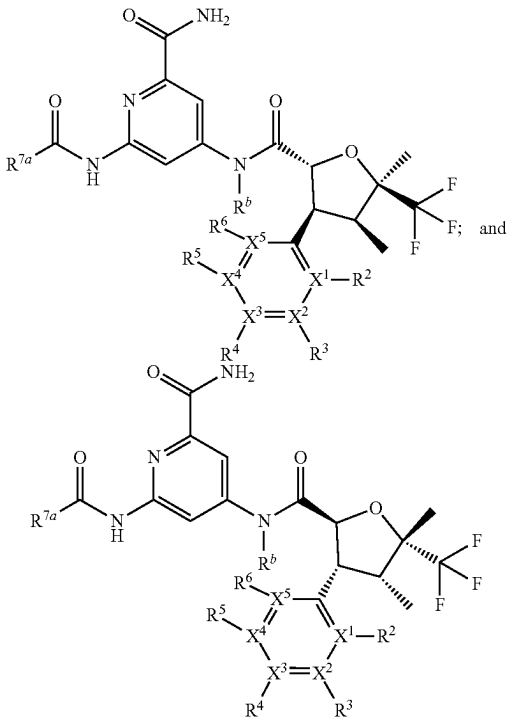
[0266] R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, wherein the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0-3 substituents, selected from deuterium (D), halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl.

[0267] R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen (H), deuterium (D), halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, wherein the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0-3 substituents, selected from deuterium (D), halogen, and C1-C3 alkyl.

[0268] X^1, X^2, X^3, X^4, and X^5 are independently selected from O, S, N, CH, or N-oxide derivatives.

[0269] In one embodiment of the present invention, the compound shown in formula (II-2A), its tautomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, or prodrugs are:

(II-2A)



[0270] wherein,

[0271] R^b is selected from hydrogen (H), methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, cyclopropyl, cyclobutyl, 3-8 membered heterocyclic alkyl, methyl-3-8 membered heterocyclic alkyl, ethyl-3-8 membered heterocyclic alkyl, propyl-3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —$S(O)_2$C1-C6 alkyl, —$S(O)_2$C3-C6 cycloalkyl, wherein the methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, cyclopropyl, cyclobutyl, 3-8 membered heterocyclic alkyl, methyl-3-8 membered heterocyclic alkyl, ethyl-3-8 membered heterocyclic alkyl, and propyl-3-8 membered heterocyclic alkyl may optionally be substituted with 0-3 substituents, selected from deuterium (D), fluorine (F), chlorine (Cl), bromine (Br), hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, C(O)(methyl), C(O)(ethyl), C(O)(propyl), cyclopropyl, and cyclobutyl.

[0272] R^{7a} is selected from R^c or —R^cNHR^d.

[0273] Rc and Rd are independently selected from hydrogen, amino, hydroxyl, —CORe, —OCORe, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups. The amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy,

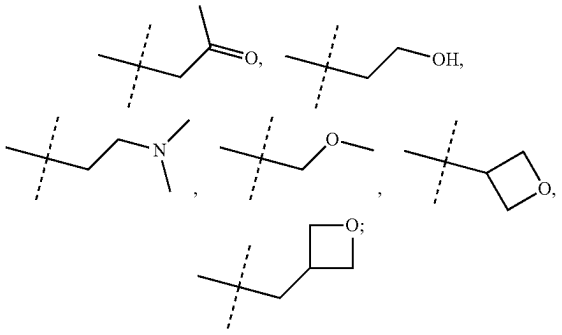
butoxy, 3- to 8-membered heterocyclylalkyls, 3- to 8-membered heterocycloalkenyls, and 5- or 8-membered heteroaryl groups may optionally be substituted with 0 to 3 substituents, which may be deuterium (D), fluorine (F), chlorine (Cl), bromine (Br), hydroxyl, cyano, amino, C(O)(methyl), C(O)(ethyl), C(O)(propyl), methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

[0274] Re is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, wherein the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0-3 substituents, selected from deuterium (D), fluorine (F), chlorine (Cl), bromine (Br), hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

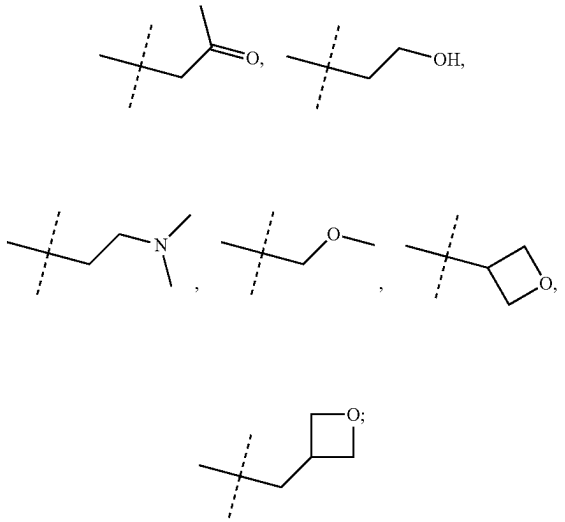
[0275] R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen (H), deuterium (D), fluorine (F), chlorine (Cl), bromine (Br), iodine (I), —$CONH_2$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, wherein the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0-3 substituents, selected from deuterium (D), fluorine (F), chlorine (Cl), bromine (Br), iodine (I), methyl, ethyl, propyl, and isopropyl.

[0276] X^1, X^2, X^3, X^4, and X^5 are independently selected from N, CH, or N-oxide derivatives.

[0277] In one embodiment of the present invention, Rb is selected from H, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, C(O)cyclopropyl, C(O)cyclobutyl, C(O)cyclopentyl, $S(O)_2$cyclopropyl, $S(O)_2$cyclopropyl, $S(O)_2$cyclobutyl, and $S(O)_2$cyclopentyl,



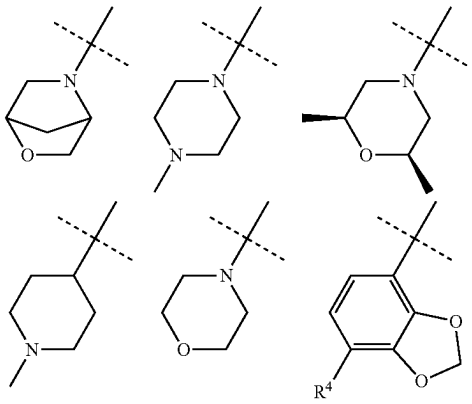
[0278] Further preferably, in one embodiment of the present invention, R^b is selected from H, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $C(O)CH_3$, C(O)cyclopropyl, and $S(O)_2$cyclopropyl.



[0279] Most preferably, in one embodiment of the present invention, R^b is selected from H and methyl. In one selected embodiment of the present invention, R^{7a} is selected from R^cNHR^d, where R^c is selected from methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl, and R^d is selected from hydrogen (H);

[0280] Specifically, in one selected embodiment of the present invention, R^{7a} is:

[0281] In another selected embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen (H), fluorine (F), chlorine (Cl), bromine (Br), iodine (I), methoxy, ethoxy, propoxy, isopropoxy, butoxy, [(methylcyclobutyl)methyl]oxy, cyclopropyl, cyclobutyl, cyclohexyl, and 3- to 6-membered heterocycles; wherein the heterocycle may contain 1 to 3 N or O atoms, and can specifically be selected from the following:



[0282] Preferably, in one embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen (H), fluorine (F), and methoxy; further preferably, R^2 and R^6 are selected from H and methoxy, while R^3, R^4, and R^5 are selected from H and F;

[0283] In one embodiment of the present invention, X^1, X^2, X^3, X^4, and X^5 are each independently selected from CH.

[0284] Further, specifically, in some embodiments, the present invention provides a compound as shown in formulas (III) and (IV), along with its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated forms, metabolites, or prodrugs.

[0285] L_2 is selected from a single bond and —CO—

[0286] R^1 is selected from hydrogen (H), halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8 membered heterocyclic alkyl, 5 or 6 membered heteroaryl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0-3 substituents, selected from deuterium (D), halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

[0287] Alternatively, any two adjacent R^1 (or R^7) may form a five-membered ring with the atoms they are connected to, and any two meta-positioned R^1 (or R^7) may form a heterocyclic alkenyl with the atoms they are connected to.

[0288] R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl. These groups (amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl) may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

[0289] R^e is selected from C1-C6 alkyl and C3-C6 cycloalkyl. These groups may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl.

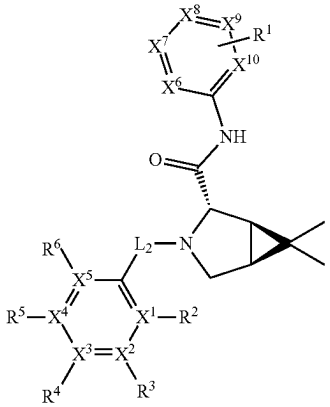
[0290] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —CONH$_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl. These groups may optionally be substituted with 0 to 3 substituents: deuterium, halogen, or C1-C3 alkyl.

[0291] X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives.

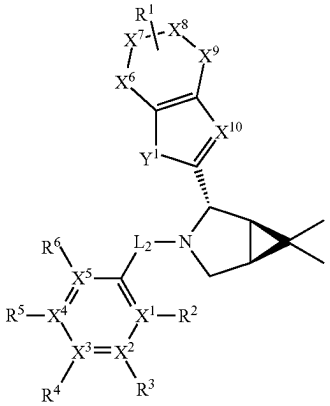
[0292] Y^1 is selected from CH$_2$, NH, O, S.

[0293] In one embodiment of the present invention, the compounds shown in formulas (III) and (IV), their tautomeric isomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, or prodrugs are as follows:

(III)



(IV)



[0294] L_2 is selected from a single bond, —CO—.

[0295] R^1 is selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —S(O)(NH)R^c, —CON R^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8-membered heterocyclic alkyl, 5 or 6-membered heteroaryl. The methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl may optionally be substituted with 0 to 3 substituents: deuterium, F, Cl, Br, I, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)(methyl), C(O)(ethyl), C(O)(propyl);

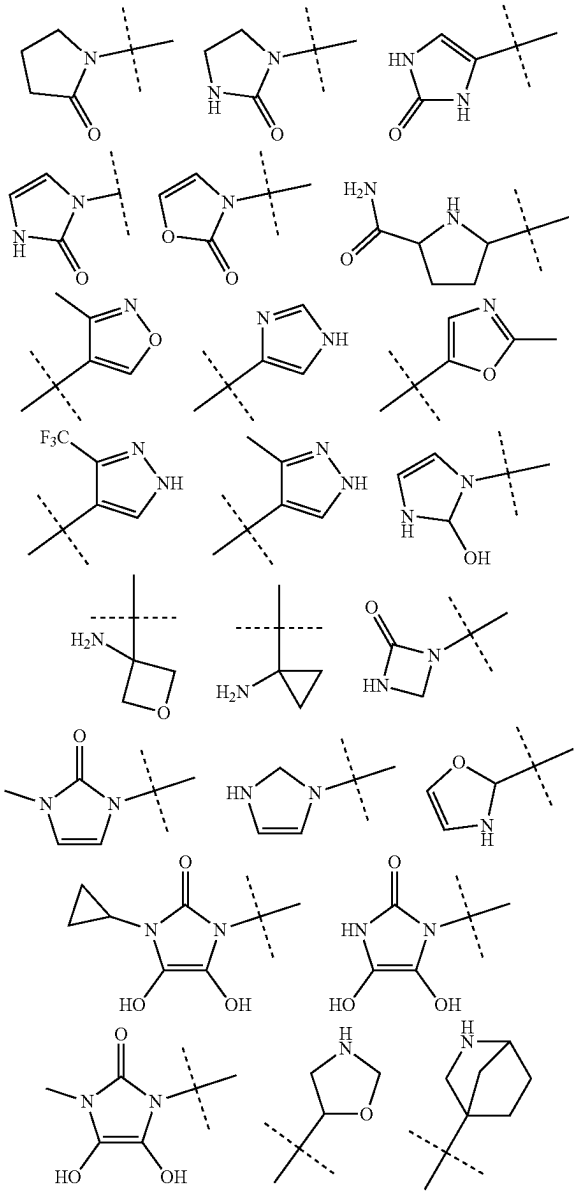
[0296] Alternatively, any two adjacent R^1 (or R^7) groups and the atoms they are connected to form a five-membered ring, and any two meta-positioned R^1 (or R^7) groups and the atoms they are connected to form a heterocyclic alkenyl group;

[0297] R^c and R^d are each independently selected from hydrogen, amino, hydroxy, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaromatic groups, where the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaromatic groups may optionally be substituted

with 0-3 additional substituents: deuterium, halogen, hydroxy, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl.

[0298] R^e is selected from methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and these methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

[0299] The aforementioned 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 6 membered heteroaryl include, but are not limited to, the following:



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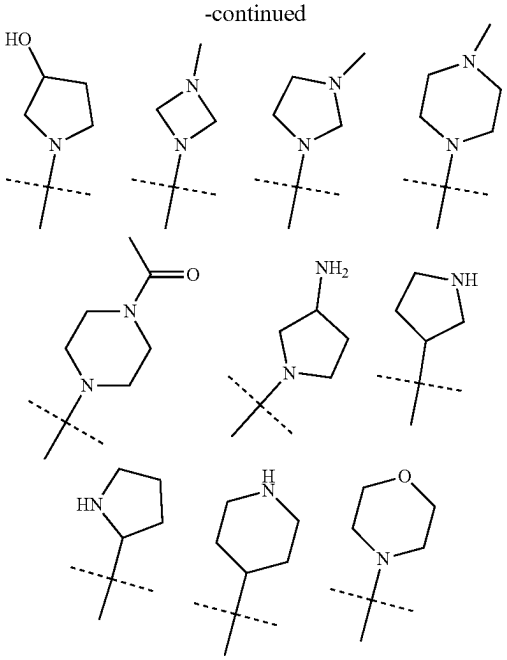
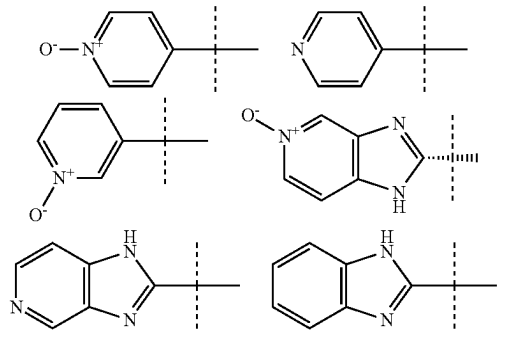


[0300] R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, F, Cl, Br, I, —$CONH_2$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl. These groups, including ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, may optionally be substituted with 0 to 3 substituents: deuterium, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl.

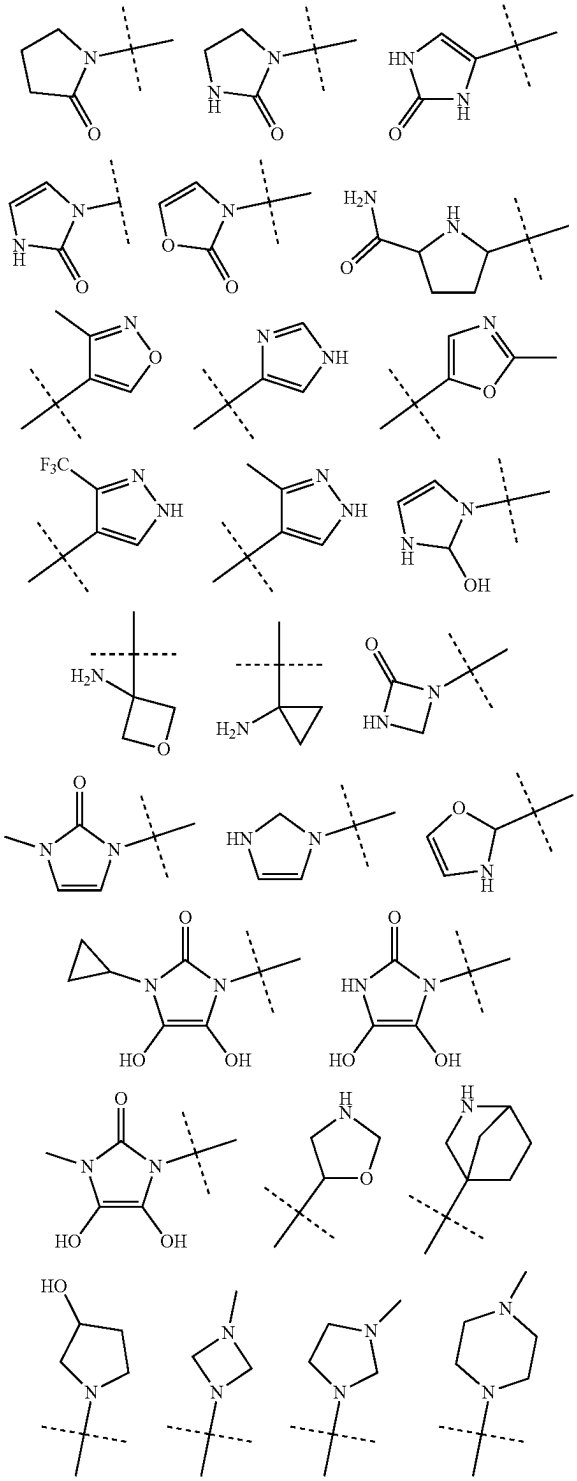
[0301] X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives.

[0302] Y^1 is selected from CH_2, NH, O, S

[0303] In one embodiment of the present invention, the A ring is selected from the following, and may optionally be substituted with 0 to 5 R^1 groups



[0304] In one embodiment of the present invention, when R^1 is selected from 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, it includes, but is not limited to, the following structures:



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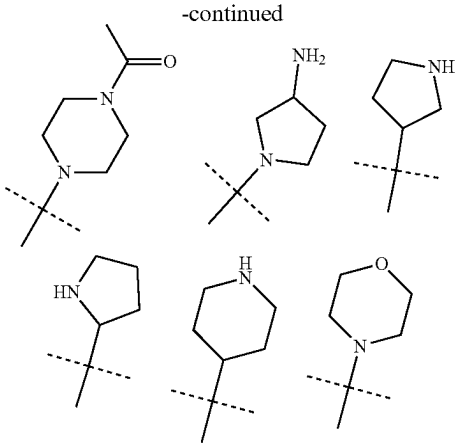


[0305] In one embodiment of the present invention, when R^1 is selected from H, (2,3-dihydroxypropyl)oxy;

[0306] In one embodiment of the present invention, when R^1 is selected from —S(O)(NH)R^c, R^c is selected from methyl;

[0307] In one embodiment of the present invention, when R^1 is selected from —CON R^cR^d, R^c and R^d are selected from H, amino, methoxy, diethylamino;

[0308] In one embodiment of the present invention, when R^1 is selected from C(NR^c)NHR^d, R^c and R^d are selected from H, hydroxyl, methoxy, —OCOR^e, and R* is selected from methyl;

[0309] In one embodiment of the present invention, when R^1 is selected from —NHCOR^c, R^c is selected from amino, hydroxyethyl, aminoethyl;

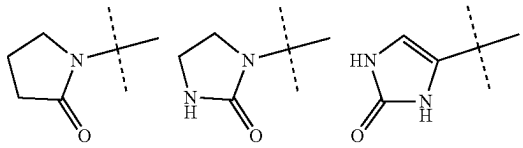
[0310] In one embodiment of the present invention, when R^1 is selected from —NHSO_2R^c, R^c is selected from amino;

[0311] In one embodiment of the present invention, when R^1 is selected from —P(O)R^cR^d, R^c and R^d are selected from ethyl;

[0312] In one embodiment of the present invention, when R^1 is selected from —NHR^c, R^c is selected from H, methyl;

[0313] In one embodiment of the present invention, when R^1 is selected from —NHCOR^cNHR^d, R^c is selected from ethyl, and R^d is selected from H, methyl, trifluoromethyl, isopropyl, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), —COR^e, and R* is selected from isopropyl, cyclopropyl, 1-aminoethyl, 1-amino-3-methylbutyl;

[0314] In one embodiment of the present invention, when R^1 is selected from 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, it includes, but is not limited to, the following structures:



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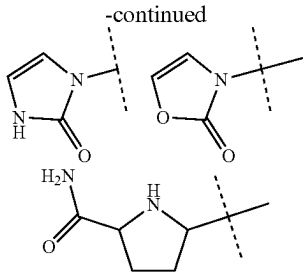
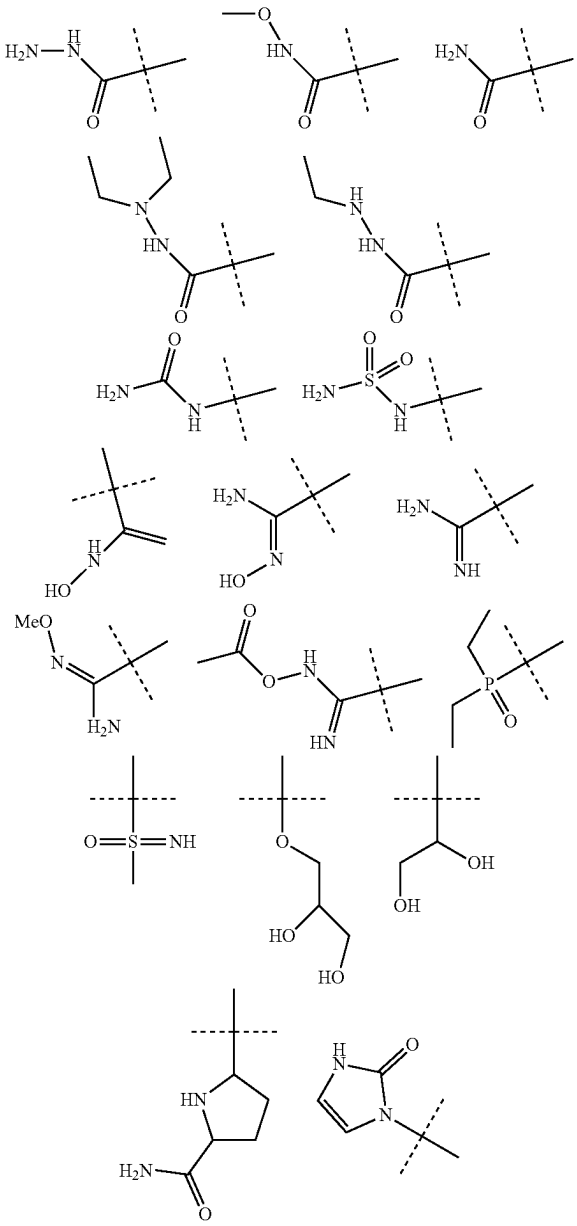


[0315] Preferably, in one embodiment of the present invention, R^1 is selected from H, amino, or the following groups:



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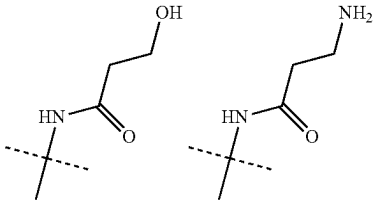
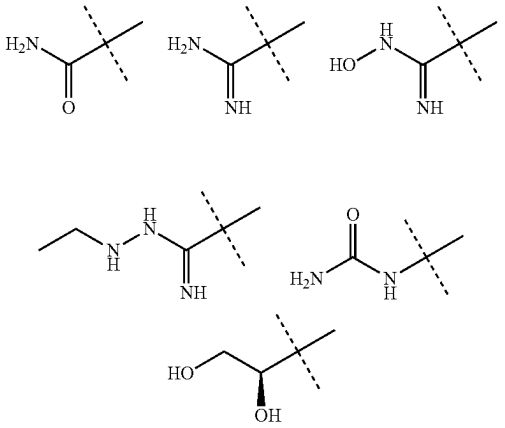
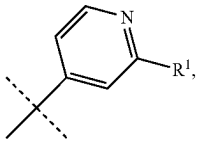


[0316] Further preferably, in one embodiment of the present invention, R^1 is selected from H, amino, or the following groups:

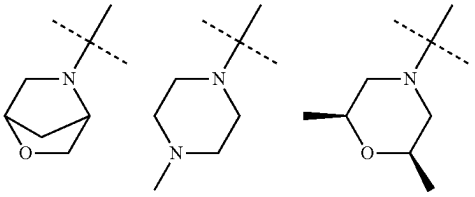


[0317] Most preferably, in one embodiment of the present invention, the A ring is selected from



Wherein, R^1 is selected from —$CONH_2$.

[0318] In one embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, F, Cl, Br, I, methoxy, ethoxy, propoxy, isopropoxy, butoxy, [(methyl cyclobutyl)methyl]oxy, cyclopropyl, cyclobutyl, cyclohexyl, and 3-6 membered heterocycles, wherein the heterocycle may contain 1-3 N or O atoms, and is specifically selected from the following:



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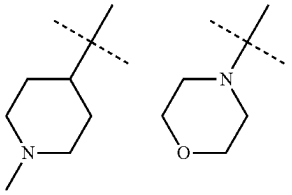
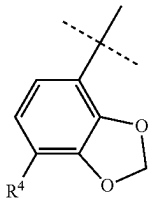


[0319] In one embodiment of the present invention, R^2 (or R^6) and R^3 (or R^5) may together with the atoms they are connected to form the following structures:



[0320] Preferably, in one embodiment of the present invention, R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, F, and methoxy; further preferably, R^2 and R^6 are selected from H and methoxy, and R^3, R^4, and R^5 are selected from H and F.

[0321] In one embodiment of the present invention, X^1, X^2, X^3, X^4, and X^5 are each independently selected from CH.

Terms and Definitions

[0322] Unless otherwise specified, the definitions of groups and terms described in this application specification and claims, including their use as examples, exemplary cases, preferred embodiments, tabulated descriptions, or specific compounds in the embodiments, may be freely combined or used interchangeably. Accordingly, the subsequent group definitions and compound structures should fall within the scope described in this specification.

[0323] The compounds described in this document may possess asymmetric centers. The compounds of this invention containing asymmetrically substituted atoms can exist in optically active or racemic forms. Unless specifically stated otherwise, all chiral, diastereomeric, racemic forms, and all geometric isomeric forms of the described structures are applicable.

[0324] The term "alkyl" as used herein refers to saturated aliphatic hydrocarbon groups, either straight-chain or branched, containing 1 to 20 carbon atoms, preferably 1 to 8 carbon atoms, more preferably 1 to 6 carbon atoms, and even more preferably 1 to 4 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, neopentyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl, as well as their various branched isomers. These alkyl groups may optionally be further substituted with 0 to 6 substituents selected from F, Cl, Br, I, hydroxy, mercapto, nitro, cyano, amino, alkylamino, amido, alkenyl, alkynyl, C1-6 alkyl, C1-6 hydroxyalkyl, C1-6 alkoxy, 3- to 8-membered carbocyclic, 3- to 8-membered heterocyclic, carbocyclic oxy, heterocyclic oxy, carboxy, or carboxylic ester groups. The definition of "alkyl" throughout this document is consistent with this definition.

[0325] The term "C3-C6 cycloalkyl" is understood to represent a saturated monocyclic or bicyclic hydrocarbon ring with 3 to 6 carbon atoms, including fused or bridged polycyclic systems such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. These C3-C6 cycloalkyl groups may optionally be further substituted with 0 to 6 substituents selected from F, Cl, Br, I, =O, hydroxy, mercapto, nitro, cyano, amino, alkylamino, amido, alkenyl, alkynyl, alkyl, hydroxyalkyl, alkoxy, carbocyclic, heterocyclic, carbocyclic oxy, heterocyclic oxy, carboxy, or carboxylic ester groups. The definition of "C3-C6 cycloalkyl" throughout this document is consistent with this definition.

[0326] The term "alkoxy" as used herein refers to —O-alkyl. Non-limiting examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, n-hexyloxy, cyclopropyloxy, and cyclobutyloxy. The alkyl group may optionally be further substituted with 0 to 6 substituents selected from F, Cl, Br, I, hydroxy, mercapto, nitro, cyano, amino, alkylamino, alkenyl, alkynyl, alkyl, hydroxyalkyl, alkoxy, carbocyclic, heterocyclic, carbocyclic oxy, heterocyclic oxy, carboxy, or carboxylic ester groups. The definition of "alkoxy" throughout this document is consistent with this definition.

[0327] The term "thioalkyl" as used herein refers to —S-alkyl. Non-limiting examples of thioalkyl groups include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, sec-butylthio, tert-butylthio, n-penthylthio, and n-hexythio. The alkyl group in the thioalkyl group may optionally be further substituted with 0 to 6 substituents selected from F, Cl, Br, I, hydroxy, nitro, cyano, amino, alkylamino, alkenyl, alkynyl, alkyl, hydroxyalkyl, alkoxy, carbocyclic, heterocyclic, carbocyclic oxy, heterocyclic oxy, carboxy, or carboxylic ester groups. The definition of "thioalkyl" throughout this document is consistent with this definition.

[0328] The term "aromatic," used alone or as part of another group, refers to optionally substituted homoaromatic or heteroaromatic conjugated planar rings or ring systems containing delocalized electrons. These aromatic groups preferably contain 5-14 atoms in the ring portion, including single rings (e.g., furan or benzene), bicyclic, or tricyclic groups. The term "aromatic" includes the definition of "aryl" as described below.

[0329] The term "aryl" or "Ar," used alone or as part of another group in this document, refers to optionally substituted homoaromatic groups, preferably containing 6 to 10 carbon atoms in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl, or substituted naphthyl.

[0330] The term "carbocycle" or "carbocyclic," used alone or as part of another group in this document, refers to optionally substituted aromatic or non-aromatic homoaromatic rings or ring systems in which all atoms in the ring are carbon. Preferably, each ring contains 5 or 6 carbon atoms. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, alkyl, alkoxy, acyl, acyloxy, alkenyl, alkenyloxy, aryl, aryloxy, amino, amido, hemiacetal, carbamoyl, carbocyclic, cyano, ester, ether, halogen, heterocyclic, hydroxyl, ketone, ketal, phosphate, nitro, and thio.

[0331] The term "heteroaryl," used alone or as part of another group in this document, refers to optionally substituted aromatic groups containing at least one heteroatom,

preferably with 5 or 6 atoms in each ring. Preferred heteroaryl groups contain 1 or 2 oxygen atoms and/or 1 to 4 nitrogen atoms and are bonded to the rest of the molecule via a carbon atom. Examples include furyl, benzofuryl, oxazolyl, isoxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, thiazinyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, indazolyl, benzotriazolyl, tetrazolopyrazinyl, carbazolyl, purinyl, quinolinyl, isoquinolinyl, and imidazopyridyl.

[0332] Exemplary substituents for heteroaryl groups include one or more of the following: hydrocarbyl, substituted hydrocarbyl, alkyl, alkoxy, acyl, acyloxy, alkenyl, alkenyloxy, aryl, aryloxy, amino, amido, hemiacetal, carbamoyl, carbocyclic, cyano, ester, ether, halogen, heterocyclic, hydroxyl, ketone, ketal, phosphate, nitro, and thio.

[0333] The term "heterocycloalkyl," used alone or as part of another group in this document, refers to stable, non-aromatic, single-ring or fused-ring (including spiro or bridged systems) saturated hydrocarbon groups containing carbon, hydrogen, and one or more heteroatoms (e.g., nitrogen, oxygen, and sulfur). These groups have a specified number of ring atoms and are connected to the rest of the molecule by a single bond. For example, "3-9 membered heterocycloalkyl" refers to a cyclic group with 3, 4, 5, 6, 7, 8, or 9 atoms, including at least one heteroatom such as nitrogen, oxygen, or sulfur. Examples include, but are not limited to: 4-membered rings: azetidine, oxetane; 5-membered rings: tetrahydrofuran, dioxolane, pyrrolidine, imidazolidine, pyrazolidine, pyrroline; 6-membered rings: tetrahydropyran, piperidine, morpholine, dithiolane, thiomorpholine, piperazine, trithiane; and 7-membered rings: diazepane.

[0334] The term "heterocycloalkenyl," used alone or as part of another group in this document, refers to stable, non-aromatic cyclic structures (single-ring or fused-ring systems) containing one or more heteroatoms selected from O, N, and S and at least one double bond. These non-aromatic structures typically contain 4 to 10 ring members, particularly 4 to 7 members. Fused-ring heterocyclic systems may include carbocyclic rings, provided that at least one ring contains a heteroatom.

[0335] The term "substituted hydrocarbyl" as described herein refers to a hydrocarbyl group that is substituted by at least one non-carbon atom. This includes cases where carbon atoms in the chain are replaced by heteroatoms, such as nitrogen, oxygen, silicon, phosphorus, boron, or halogen atoms, as well as cases where the carbon chain includes additional substituents. These substituents include, but are not limited to, alkyl, alkoxy, acyl, acyloxy, alkenyl, alkenyloxy, aryl, aryloxy, amino, amido, hemiacetal, carbamoyl, carbocyclic, cyano, ester, ether, halogen, heterocyclic, hydroxyl, ketone, ketal, phospho, nitro, and thio groups.

[0336] The terms "comprise," "include," and "have" as used herein are intended to be inclusive, meaning that additional elements or features may be present beyond those listed. After the detailed description of this invention, it is evident that modifications and variations may be made without departing from the scope of the invention as defined by the appended claims.

[0337] Examples of pain described in this document include acute pain, chronic pain, pain caused by soft tissue injury or peripheral damage, postherpetic neuralgia, occipital neuralgia, trigeminal neuralgia, segmental neuralgia or intercostal neuralgia, central pain, neuropathic pain, migraine, pain associated with osteoarthritis or rheumatoid arthritis, pain related to bruises, sprains, or trauma, spinal pain, pain caused by spinal cord or brainstem injury, lower back pain, sciatica, dental pain, myofascial pain syndrome, pain from episiotomy, gout pain, burn-induced pain, cardiac pain, muscle pain, eye pain, inflammatory pain, oral-facial pain, abdominal pain, pain associated with dysmenorrhea, childbirth pain or endometriosis, somatic pain, pain related to nerve or nerve root injury, amputation-related pain, trigeminal neuralgia, neuroma, or vasculitis, pain caused by diabetic neuropathy (or diabetic peripheral neuropathy), chemotherapy-induced neuropathy, atypical facial neuralgia, lower back neuralgia, trigeminal neuralgia, occipital neuralgia, segmental neuralgia or intercostal neuralgia, HIV-related neuropathy, AIDS-related neuropathy, hyperalgesia, burn pain, breakthrough pain, chemotherapy-induced pain, occipital neuralgia, psychogenic pain, gallstone-related pain, cancer-associated neuropathic or non-neuropathic pain, phantom limb pain, functional abdominal pain, headache, acute or chronic tension headache, sinus headache, cluster headache, temporomandibular joint (TMJ) pain, maxillary sinus pain, pain caused by ankylosing spondylitis, postoperative pain, scar pain, chronic non-neuropathic pain, pain attributed to hyperlipidemia, fibromyalgia, and fibromyositis.

[0338] The term "pharmaceutical composition" as described herein refers to a mixture containing one or more of the compounds disclosed in this document or their pharmaceutically acceptable salts, along with other chemical components such as pharmaceutically acceptable carriers and excipients. The purpose of the pharmaceutical composition is to facilitate administration to a biological system, enhance the absorption of active ingredients, and enable the desired biological activity.

[0339] The term "pharmaceutically acceptable salt" as described herein refers to salts of the compounds disclosed in this document, which may include inorganic or organic salts. Such salts are safe and effective when used in mammalian bodies and exhibit the desired biological activity. These salts can be prepared during the final isolation and purification of the compound or by reacting appropriate functional groups with suitable bases or acids. Common bases used to form pharmaceutically acceptable salts include inorganic bases such as sodium hydroxide and potassium hydroxide, as well as organic bases like ammonia. Common acids used to form pharmaceutically acceptable salts include both inorganic and organic acids.

[0340] The term "pharmaceutically acceptable" as used herein refers to compounds, materials, compositions, and/or dosage forms that, within the scope of reasonable medical judgment, are suitable for contact with patient tissues without causing excessive toxicity, irritation, allergic reactions, or other complications, while maintaining a favorable benefit-to-risk ratio and being effective for their intended use.

[0341] Other features and advantages of the present invention will be described in the subsequent sections of this

specification and will become apparent from the specification or through the practice of the invention. The objectives and other advantages of the invention can be achieved and attained through the structures particularly pointed out in the specification and claims.

EXAMPLES

[0342] The following text provides a detailed explanation of the general compounds of the invention, their preparation methods, and their uses in conjunction with specific embodiments. The following embodiments are typical examples and explanations of the invention and should not be construed as limiting the scope of the invention. Any technology implemented based on the above content of the invention is covered by the scope of protection intended by the invention.

[0343] Unless otherwise indicated, the raw materials and reagents used in the following examples are commercially available or can be prepared by known methods. Compounds are named according to the conventional naming rules in the field, commercially available reagents (including the abbreviations) are named according to the supplier's catalog.

General Methods

[0344] ^{1}H NMR and ^{19}F NMR spectra were recorded in DMSO-d_6, MeOD and $CDCl_3$ on a BrukerAVANCE NEO 400 MHz, 500 MHz or 600 MHz digital NMR spectrometer. The resonances (δ) were given in ppm relative to tetramethylsilane (TMS). The following abbreviations were used to designate chemical shift multiplicities: s=singlet, d=doublet, t=triplet, multiplet=(denotes complex pattern), dd=doublet of doublets, dt=doublet of triplets. Mass spectra and compound purity were obtained by SHIMADZU LCMS-2020 (ShimNex UP C18 50*4.6 mm 5 μm 2.000 mL/min 2.6 min, column temperature: 40° C.).

Abbreviations

[0345] ACN: Acetonitrile

[0346] DCPP: 1,3-Bis(dicyclohexylphosphino)propane bis(tetrafluoroborate)

[0347] DHP: 3,4-Dihydro-2H-pyran

[0348] DIBAH: Diisobutylaluminium hydride

[0349] DIEA: N,N-Diisopropylethylamine

[0350] DMAc: N,N-Dimethylacetamide

[0351] DPPP: 1,3-Bis(diphenylphosphino)propane

[0352] FA: Formic acid

[0353] IPA: Isopropyl alcohol

[0354] NBS: N-Bromosuccinimide

[0355] NIS: N-Iodosuccinimide

[0356] NMI: 1-Methylimidazole

[0357] TCFH: Chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate

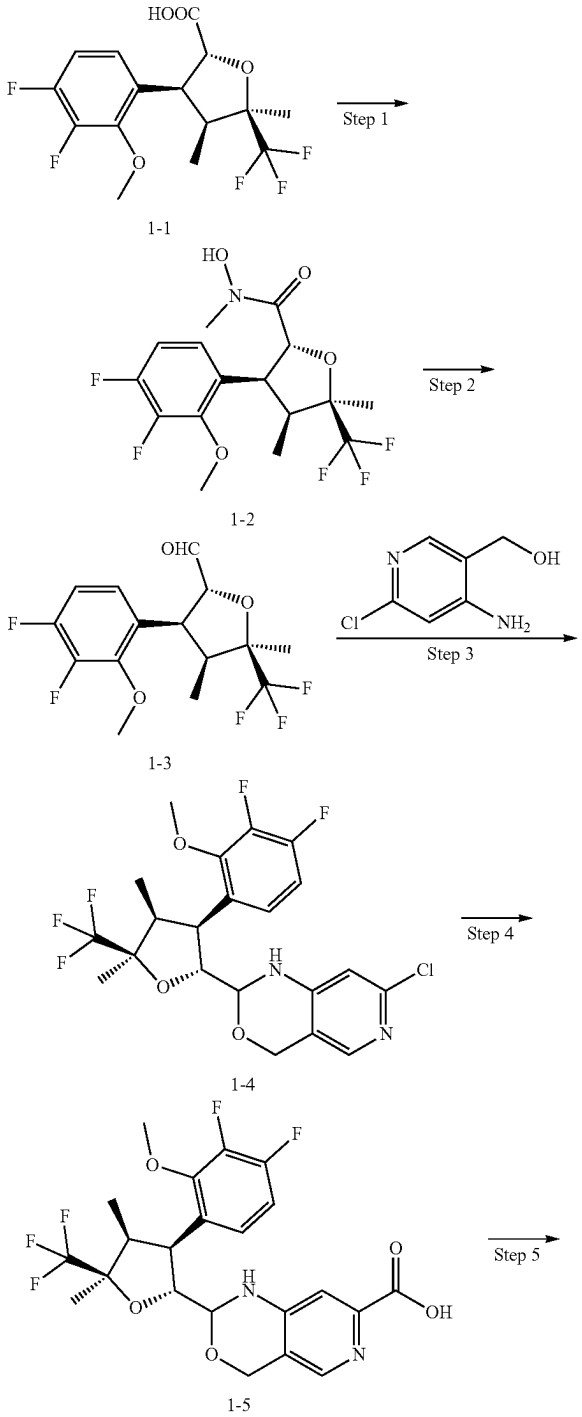
[0358] TMSI: N-(Trimethylsilyl)imidazole

[0359] TEA: Triethylamine

General Scheme Provides a Process of the Synthesis for Preparing TM1-1~TM1-34

Example 1-1

(±)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1,4-dihydro-2h-pyrido[4,3-d][1,3]oxazine-7-carboxamide (TM1-1)



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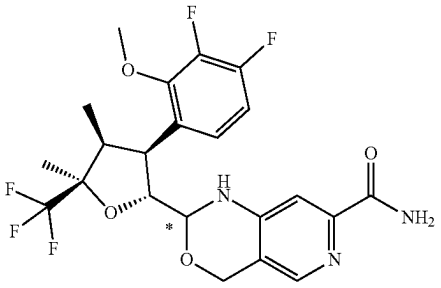
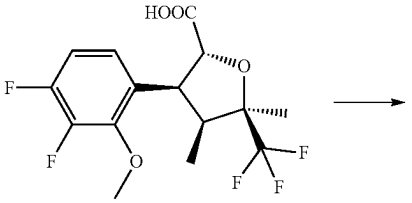
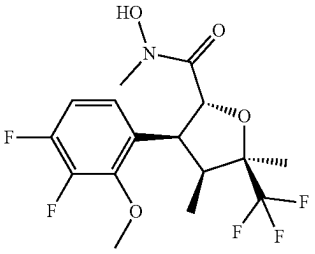


TM1-1

Step 1: General Procedure for Preparation of Intermediate 1-2



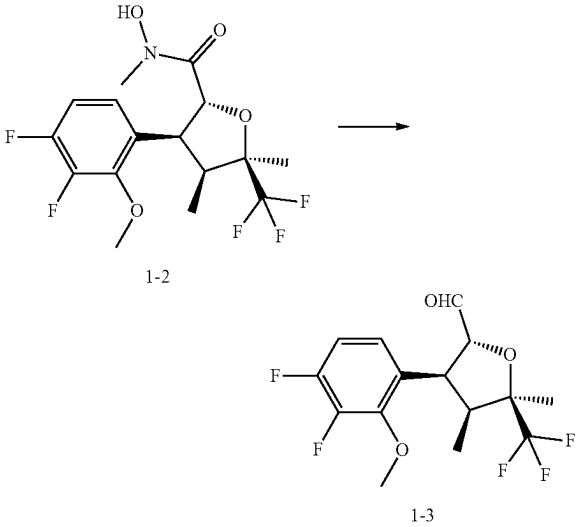
1-1



1-2

[0360] To a mixture of compound 1-1 (200 mg, 0.56 mmol), N, O-dimethylhydroxylamine hydrochloride (82 mg, 0.85 mmol) in dry ACN (4.0 mL) was added NMI (186 mg, 2.26 mmol) and TCFH (316 mg, 1.13 mmol), then the reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. The resulting mixture was diluted with H_2O (30 mL). The resulting mixture was extracted with EA (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography (MeOH/DCM=0%~5%) to afford compound 1-2 (480 mg, 85.71% yield) as a colorless oil. LCMS: m/z=398.1 $[M+1]^+$.

Step 2: General Procedure for Preparation of Intermediate 1-3

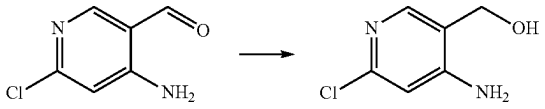


1-2

1-3

[0361] To a solution of compound 1-2 (480 mg, 1.21 mmol) in dry THF (10.0 mL) was added DIBAH (1.0M in hexane, 3.6 mL, 3.60 mmol) at −65° C. under argon, then the reaction mixture was stirred at −65° C. for 1 h. The reaction was detected by LCMS. The resulting mixture was quenched with saturated aqueous potassium sodium tartrate (10 mL) and stirred at r.t. for 10 min, then extracted with EA (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give crude compound 1-3 (380 mg, 93.1% yield) as a colorless oil.

Step 3: a). General Procedure for Preparation of Intermediate 2-2

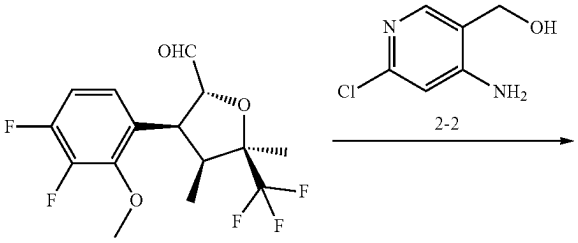


2-1

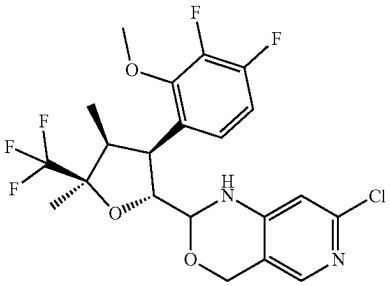
2-2

[0362] To a solution of compound 2-1 (800 mg, 5.11 mmol) in THF (10.0 mL) and MeOH (20.0 mL) was added $NaBH_4$ (232 mg, 6.13 mmol), then the reaction mixture was stirred at r.t. for 1 h. The reaction was detected by LCMS. The resulting mixture was diluted with H_2O (50 mL). The resulting mixture was extracted with EA (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography (MeOH/DCM=0%~10%) to give the intermediate 2-2 (540 mg, 66.7% yield) as a gray solid. LCMS: m/z=189.0 $[M+H]^+$.

B). General Procedure for Preparation of Intermediate 1-4



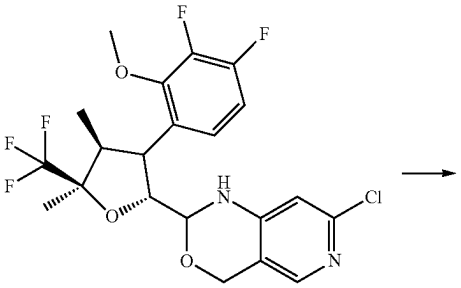
1-3



1-4

[0363] To a solution of compound 1-3 (380 mg, 1.12 mmol) and compound 2-2 (195 mg, 1.23 mmol) in dry 2-MeTHF (10.0 mL) was added MgSO4 (400 mg) and 5 drops of AcOH, then the reaction mixture was stirred at 90° C. for 16 h. The reaction was detected by LCMS, reaction completely, the mixture was filtered and the filter cake washed with THF, the filtrate was concentrated, the residue was purified by silica gel column chromatography (MeOH/DCM=0%~5%) to afford compound 1-4 (270 mg, 50.3% yield) as a colorless oil. LCMS: m/z=479.0 $[M+1]^+$.

Step 4: General Procedure for Preparation of Intermediate 1-5



1-4

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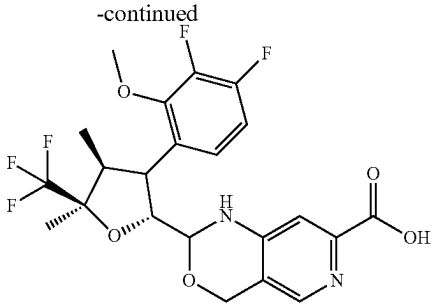
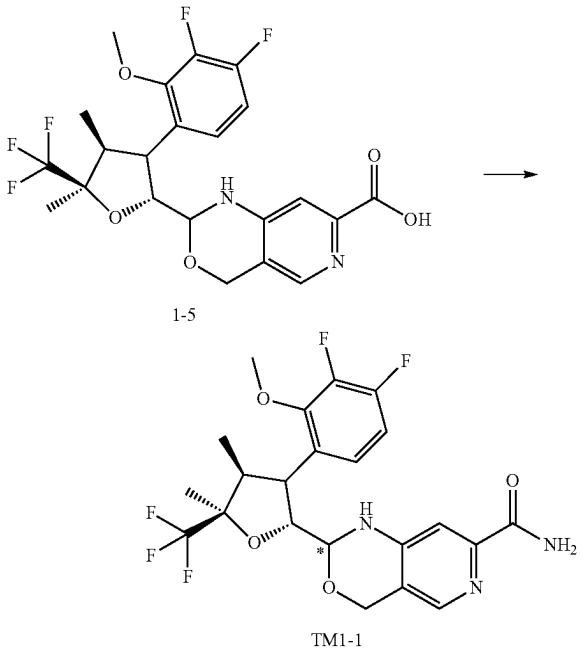


1-5

[0364] To a mixture of compound 1-4 (270 mg, 0.56 mmol), DCPP (171 mg, 0.28 mmol) in DMSO (8.0 mL) and water (0.8 mL) was added K_2CO_3 (232 mg, 1.68 mmol) and $Pd(OAc)_2$ (25 mg, 0.11 mmol), then the whole mixture was stirred at 100° C. under CO atmosphere for 16 h. The reaction was detected by LCMS, reaction completely, filtered, the filtrated was adjust pH=6 with 1 N HCl, purified by prep-HPLC (5%~60% ACN/0.1% FA) to afford compound 1-5 (120 mg, 43.96%) as a light brown solid. LCMS: m/z=489.0 $[M+1]^+$.

Step 6: General Procedure for Preparation of TM1-1 (±)



[0365] To a mixture of compound 1-5 (100 mg, 0.20 mmol), NH_4Cl (32 mg, 0.60 mmol) in dry DMF (2.5 mL) was added HATU (114 mg, 0.30 mmol) and DIEA (155 mg, 1.20 mmol), then the reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. The resulting mixture was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~60%) to afford the isomer compound TM1-1a (65.23 mg, 66.97% yield, 100% purity at 214 nm) as a

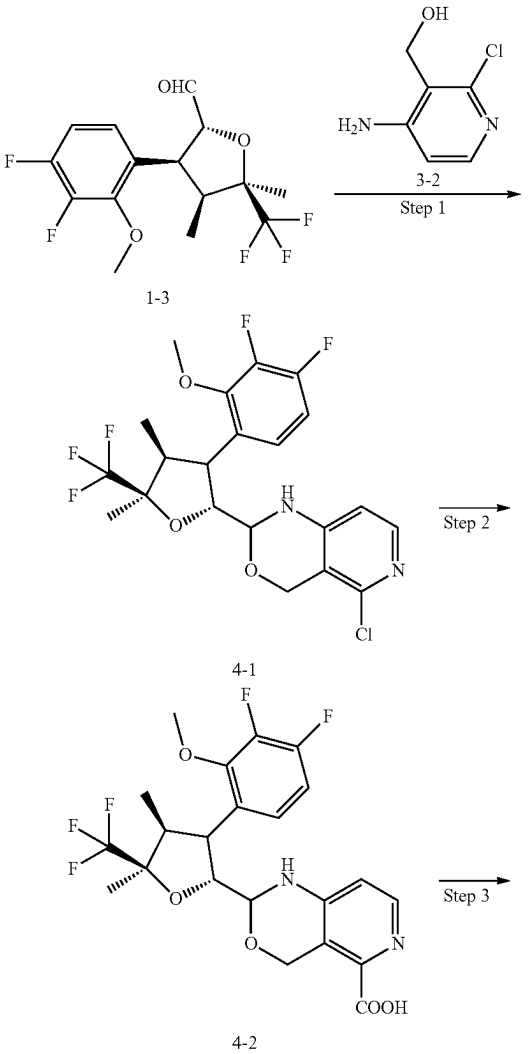
white solid and TM1-1b (65.23 mg, 66.97% yield, 100% purity at 214 nm) as a white solid.

[0366] TM1-1a LCMS: Rt=8.478 min, 488.3 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) b 7.89 (s, 2H), 7.40 (d, J=2.8 Hz, 1H), 7.31 (s, 1H), 7.29 (s, 1H), 7.17-7.02 (m, 2H), 4.87-4.71 (m, 4H), 4.21-4.14 (m, 1H), 3.89 (d, J=1.9 Hz, 3H), 2.66 (s, 1H), 1.53 (s, 3H), 0.69 (d, J=6.2 Hz, 3H).

[0367] TM1-1b. LCMS: Rt=8.562 min, 488.3 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) b 7.88 (d, J=5.2 Hz, 2H), 7.38 (s, 2H), 7.29 (s, 1H), 7.14 (dd, J=9.2, 3.7 Hz, 2H), 4.87-4.82 (m, 1H), 4.78 (s, 2H), 4.64-4.57 (m, 1H), 4.14 (d, J=8.8 Hz, 1H), 3.91 (d, J=1.8 Hz, 3H), 2.70 (s, 1H), 1.51 (s, 3H), 0.69 (d, J=6.1 Hz, 3H).

Example 1-2

(±)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1,4-dihydro-2h-pyrido[4,3-d][1,3]oxazine-5-carboxamide (TM1-2)



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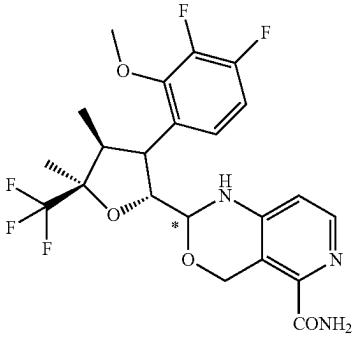
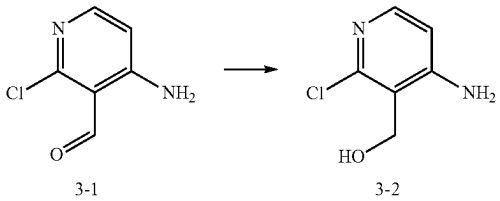


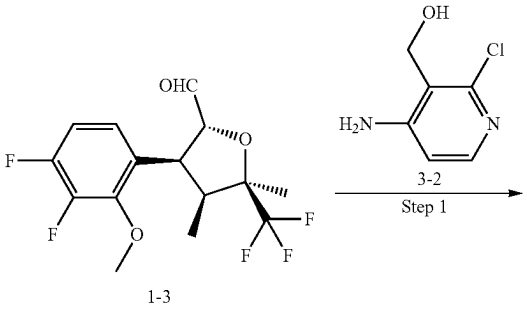
TM1-2

Step 1: A). General Procedure for Preparation of Intermediate 3-2



[0368] To a solution of compound 3-1 (800 mg, 5.11 mmol) in THF (10.0 mL) and MeOH (20.0 mL) was added $NaBH_4$ (232 mg, 6.13 mmol), then the reaction mixture was stirred at r.t. for 1 h. The reaction was detected by LCMS. The resulting mixture was diluted with H_2O (50 mL). The resulting mixture was extracted with EA (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography (MeOH/DCM=0%~10%) to give compound 3-2 (640 mg, 79.05% yield) as a white solid. LCMS: m/z=159.2 $[M+H]^+$.

B). General Procedure for Preparation of Intermediate 4-1



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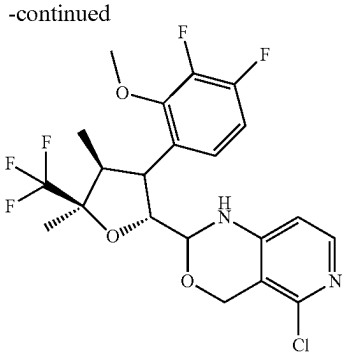
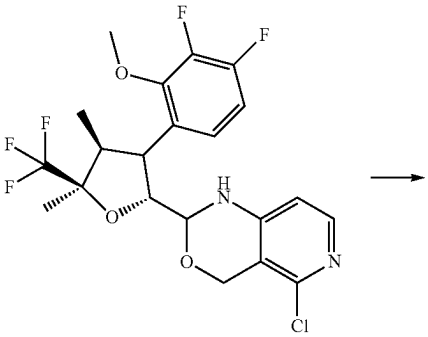


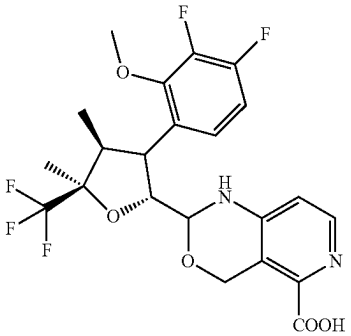
4-1

[0369] To a solution of compound 1-3 (400 mg, 1.18 mmol) and compound 3-2 (187 mg, 1.18 mmol) in dry 2-MeTHF (10.0 mL) was added MgSO4 (400 mg) and 5 drops of AcOH, then the reaction mixture was stirred at 90° C. for 16 h. The reaction was detected by LCMS, reaction completely, the mixture was filtered and the filter cake washed with THF, the filtrate was concentrated, the residue was purified by silica gel column chromatography (MeOH/DCM=0%~5%) to afford compound 4-1 (130 mg, 23.05% yield) as a colorless oil. LCMS: m/z=479.1 $[M+1]^+$.

Step 2: General Procedure for Preparation of Intermediate 4-2



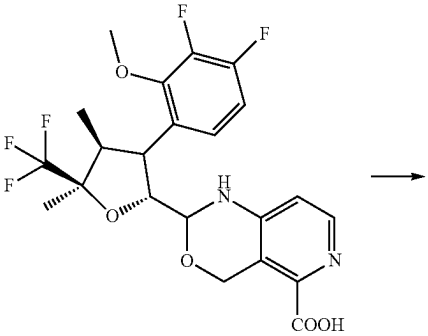
4-1



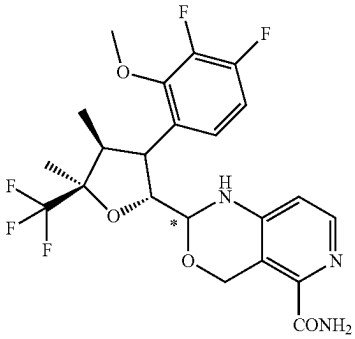
4-2

[0370] To a mixture of compound 4-1 (270 mg, 0.56 mmol), DCPP (171 mg, 0.28 mmol) in DMSO (8.0 mL) and water (0.8 mL) was added K_2CO_3 (232 mg, 1.68 mmol) and $Pd(OAc)_2$ (25 mg, 0.11 mmol), then the whole mixture was stirred at 100° C. under CO atmosphere for 16 h. The reaction was detected by LCMS before filtered. And then the filtrated was adjust pH=6 with 1 N HCl, purified by prep-HPLC (5%~60% ACN/0.1% FA) to afford compound 4-2 (120 mg, 43.96%) as a light brown solid. LCMS: m/z=489.0 $[M+1]^+$.

Step 3: General Procedure for Preparation of Compound TM1-2 (±)



4-2



TM1-2

[0371] To a mixture of compound 4-2 (180 mg, 0.061 mmol), NH_4Cl (99 mg, 1.85 mmol) in dry DMF (4 mL) was added HATU (211 mg, 0.56 mmol) and DIEA ((287 mg, 2.22 mmol), then the reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. The resulting mixture was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~60%) to afford the isomer of TM1-2, TM1-2a (39.27 mg, 21.82% yield, 100% purity at 214 nm) as a white solid and TM1-2b (42.57 mg, 23.65% yield, 98.23% purity at 214 nm) as a white solid.

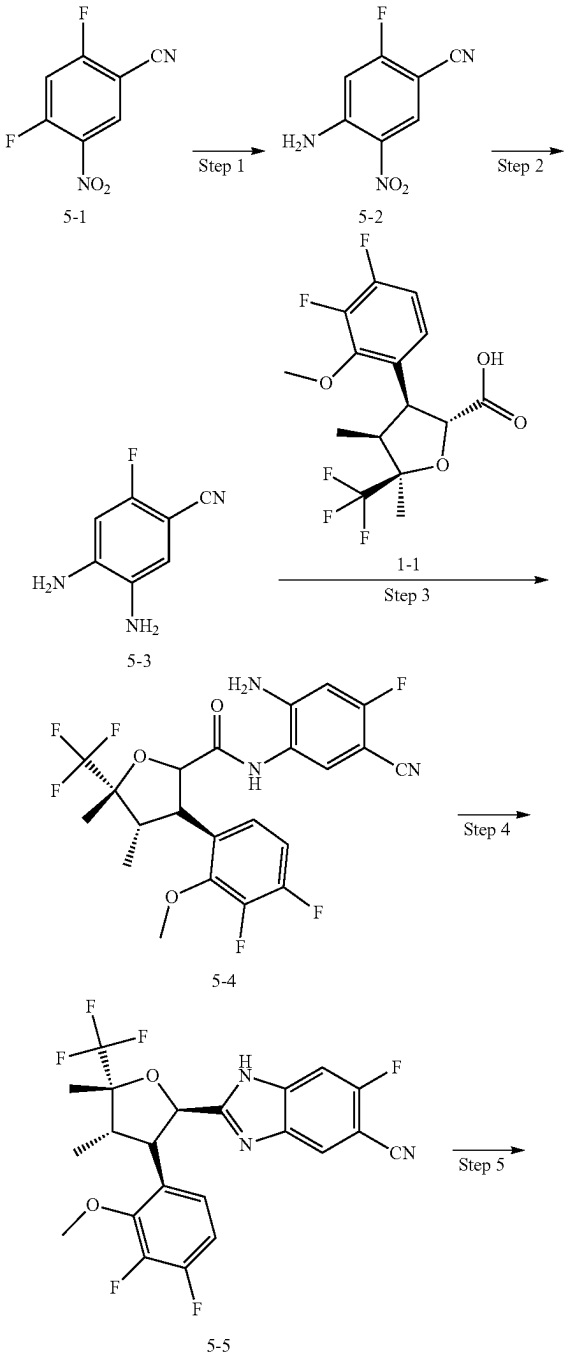
[0372] TM1-2a. LCMS: Rt=8.695 min, m/z=488.3 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J=5.5 Hz, 1H), 7.92 (d, J=2.3 Hz, 1H), 7.39 (s, 1H), 7.34 (s, 1H), 7.14 (dd, J=13.3, 8.4 Hz, 2H), 6.74 (d, J=5.5 Hz, 1H), 5.19 (d, J=16.2 Hz, 1H), 4.96 (d, J=16.2 Hz, 1H), 4.79 (d, J=4.3 Hz, 1H), 4.56 (dd, J=8.5, 4.6 Hz, 1H), 4.13 (t, J=8.6 Hz, 1H), 3.91 (d, J=1.3 Hz, 3H), 2.72 (dd, J=15.6, 7.7 Hz, 1H), 1.52 (s, 3H), 0.69 (d, J=6.5 Hz, 3H).

[0373] TM1-2b. LCMS: Rt=8.560 min, m/z=488.3 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J=5.5 Hz, 1H), 7.93 (s, 1H), 7.39 (s, 1H), 7.34 (s, 1H), 7.17-7.00 (m, 2H), 6.70 (d, J=5.5 Hz, 1H), 5.27 (d, J=16.3 Hz, 1H),

4.94 (d, J=16.3 Hz, 1H), 4.78-4.65 (m, 2H), 4.22-4.13 (m, 1H), 3.91 (d, J=1.6 Hz, 3H), 2.70-2.61 (m, 1H), 1.51 (s, 3H), 0.70 (d, J=6.2 Hz, 3H).

Example 1-3

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-fluoro-N-hydroxy-1H-benzo[d]imidazole-5-carboxamide (TM1-3)



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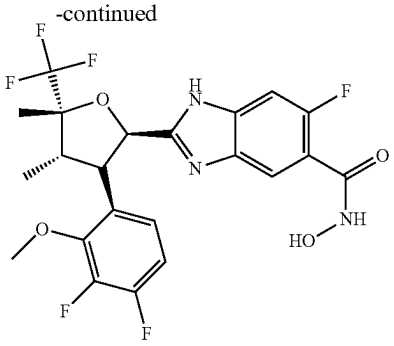
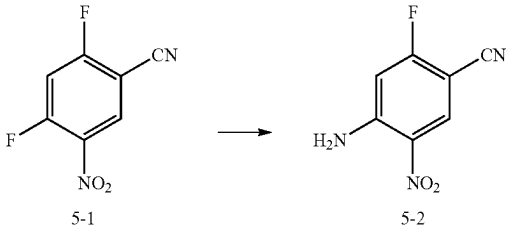


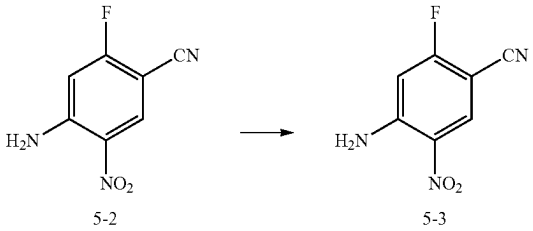
TM1-3

Step 1: General Procedure for Preparation of Intermediate 5-2



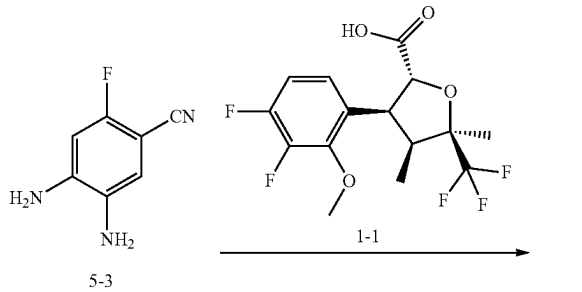
[0374] The compound 5-1 (1.00 g, 5.43 mmol) was dissolved with absolute ethanol (10 mL) in a single-neck flask before the addition of NH_3—H_2O (33 mg, 0.48 mmol), and the reaction mixture was stirred at for 12 h under r.t. Later, the reaction mixture was concentrated and the crude product washed with water for several times to get abundant yellow solid, 5-2 (0.95 g, 97% yield), without further purification and directly used for next reaction. LCMS: m/z=181.16 $[M+H]^+$.

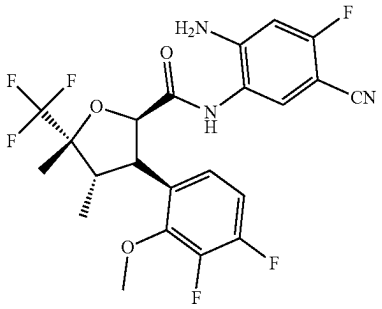
Step 2: General Procedure for Preparation of Intermediate 5-3



[0375] The compound 5-2 (0.95 g, 5.24 mmol) dissolved with EA (30 mL) and acetic acid (5 mL) in a single-neck flask before the addition of Zn powder (3.43 g, 50 mmol), and the reaction mixture was stirred at for 12 h under r.t. The filtrate was obtained and diluted with MeOH (10 mL). Later the concentrate was kept in NH_3—H_2O (20 mL) for the whole night until the crude product formed as a beige solid 5-3 (0.71 g). Finally, the product washed with water for several time and dried without further purification. LCMS: m/z=152.09 $[M+H]^+$.

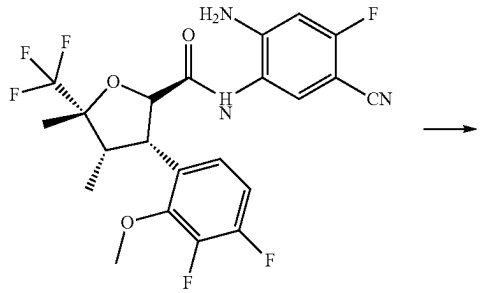
Step 3: General Procedure for Preparation of Intermediate 5-4





[0376] HATU (910 mg, 2.38 mmol) and DIPEA (0.62 mL, 3.57 mmol) were added to a solution of compound 5-3 (180 mg, 1.20 mmol) and compound 1-1 (496 mg, 1.40 mmol) in anhydrous dichloromethane (15 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was concentrated, then extracted with water (15 mL) and saturated salt water solution (15 mL) before drying over anhydrous Na_2SO_4. Later the organic solution was concentrated and purified by column chromatography (PE/EA=2/1 to 1/1) to get the desired product 5-4 (509 mg, 87% yield) as a light-yellow oil. LCMS: m/z=288.24 [M+H]+.

Step 4: General Procedure for Preparation of Intermediate 5-4



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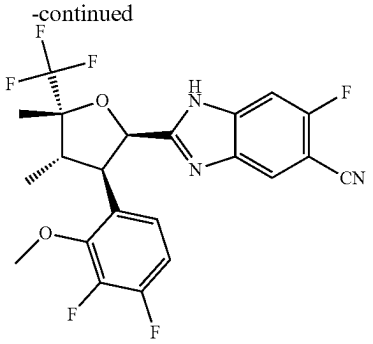
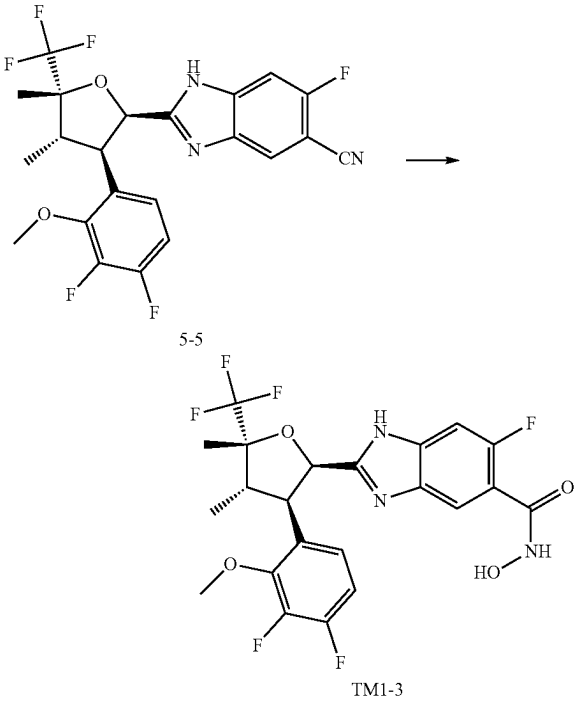


[0377] The compound 5-4 (509 mg, 1.04 mmol) was added to AcOH (5 mL) in a single-neck flask before the reaction mixture was stirred at 120° C. for 2 h. The resulting mixture was concentrated, diluted with $NaHCO_3$ solution (5 mL) to keep the pH value at 8-9 and the crude product was obtained before filtration. Later the product was purified by column chromatography (PE/EA=100/50) to get the pure product 5-5 (390 mg, 79% yield), as a pale yellow solid. LCMS: m/z=470.18 $[M+H]^+$.

Step 5: General Procedure for Preparation of Compound TM1-3

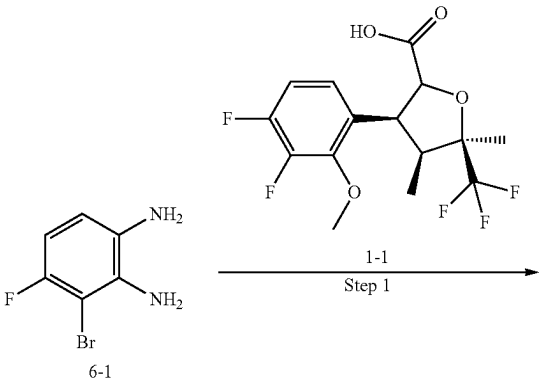


[0378] The compound 5-5 (76 mg, 0.15 mmol) was dissolved with absolute ethanol (5 mL) in a single-neck flask before the addition of hydroxylamine hydrochloride (21 mg, 0.30 mmol) and NaHCO3 (25 mg, 0.30 mmol), and the reaction mixture was stirred at for 12 h under 40° C. Later, the filtrate was obtained, concentrated and purified by column chromatography to get the final product TM1-3 (38 mg,

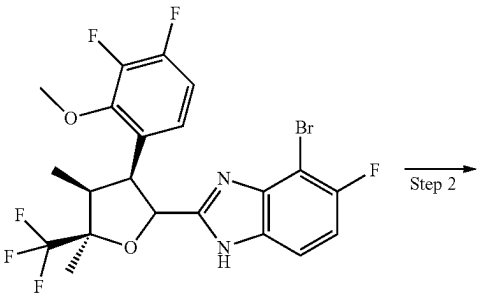
37% yield, 98.35% purity at 214 nm) as a pale yellow solid. LCMS: m/z=503.25 $[M+H]^+$. 1H NMR (600 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.23 (s, 2H), 7.73 (s, 1H), 7.51 (m, 1H), 7.44 (s, 1H), 7.21 (t, J=6.0 Hz, 1H), 5.50 (s, 1H), 3.54 (d, J=12.0 Hz, 3H), 2.05-1.98 (m, 4H), 1.69-1.53 (m, 3H).

Example 1-4

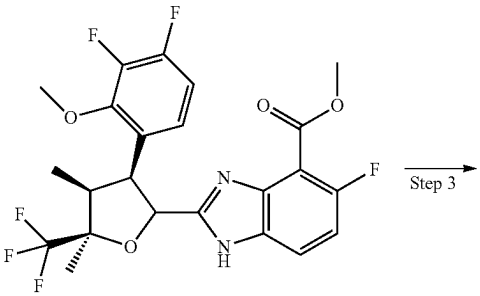
2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-1H-benzo[d]imidazole-4-carboxamide (TM1-4)



6-1



6-2



6-3

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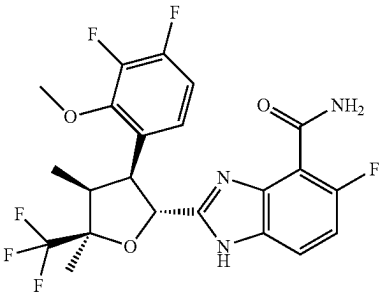
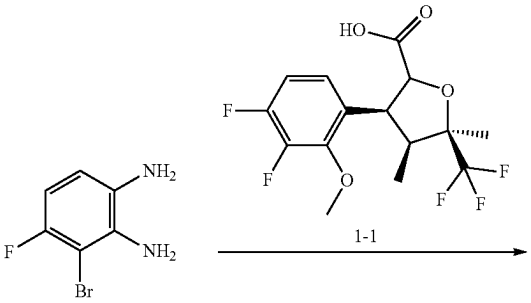
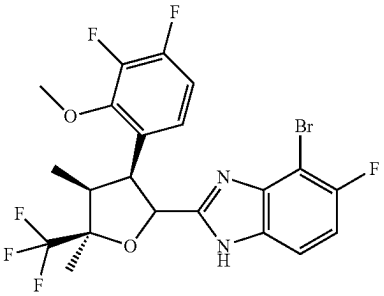


TM1-4

Step 1: General Procedure for Preparation of Intermediate 6-1



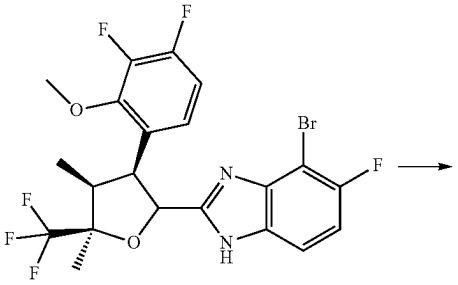
6-1



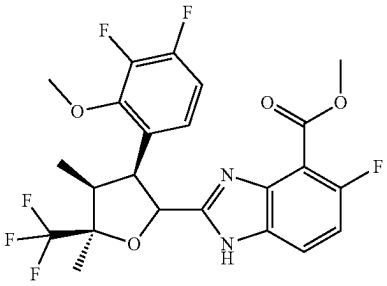
6-2

[0379] NMI (208 mg, 2.54 mmol) and TCFH (714 mg, 2.54 mmol) were added to a solution of compound 1-1 (450 mg, 1.27 mmol) and compound 6-1 (261 mg, 1.27 mmol) in ACN (9 mL), and the reaction mixture was stirred at r.t. for overnight. The resulting mixture was concentrated, diluted with water (40 mL), extracted with EA (40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product 6-2 (558 mg, 83% yield) as a white solid. LCMS: m/z=525.0 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 6-2



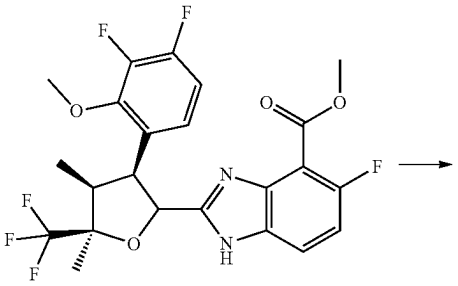
6-2



6-3

[0380] Compound 6-2 (600 mg, 1.15 mmol), Pd(dppf)Cl_2 (84 mg, 0.11 mmol), TEA (348 mg, 3.44 mmol) were added to ACN (6 mL) and MeOH (6 mL), the reaction mixture was stirred at 100° C. under CO (3 MPa) for overnight. The resulting mixture was concentrated, diluted with water (20 mL), extracted with EA (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated to get residue. The residue was purified by silica gel column chromatography, eluted with EA in PE (10%~60%) to give compound 6-3 (67 mg, 11% yield) as a white solid. LCMS: m/z=503.3 $[M+H]^+$.

Step 3: General Procedure for Preparation of Compound TM1-4



6-3

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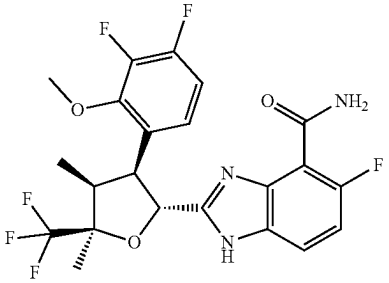
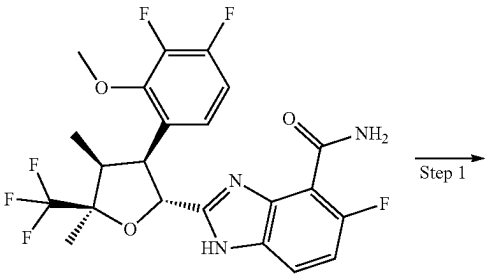


TM1-4

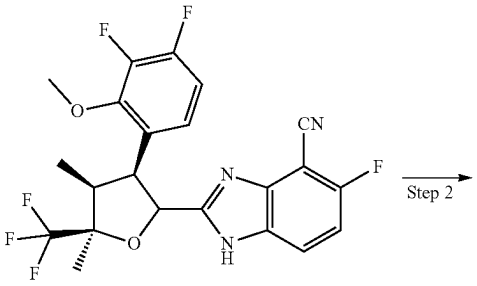
[0381] Compound 6-3 (70 mg, 0.14 mmol) was added to a solution of NH_3 in MeOH (7M, 1 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with water (10 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated and purified by HPLC to get compound TM1-4 (10.58 mg, 15.98% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=488.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.79 (d, J=60.3 Hz, 3H), 7.10 (dt, J=15.8, 7.9 Hz, 3H), 5.85 (d, J=9.8 Hz, 1H), 4.67 (s, 1H), 3.97 (d, J=1.9 Hz, 3H), 2.95-2.82 (m, 1H), 1.64 (s, 3H), 0.78 (d, J=5.9 Hz, 3H).

Example 1-5

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-N-hydroxy-1H-benzo[d]imidazole-4-carboximidamide (TM1-5)



TM1-4



7-1

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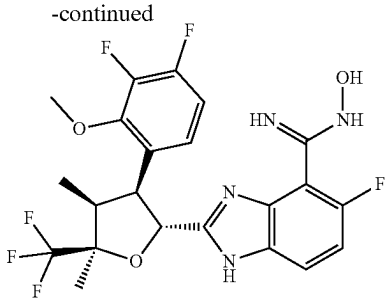
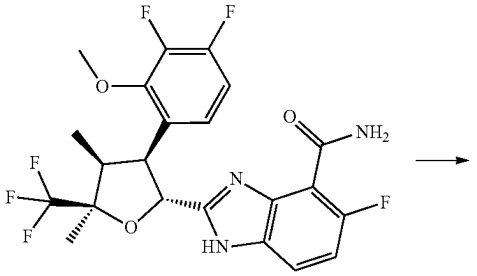
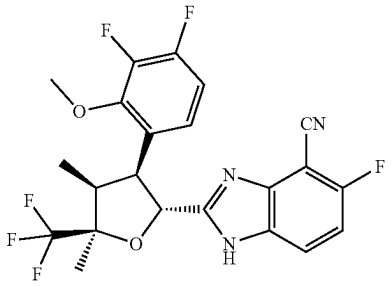


TM1-5

Step 1: General Procedure for Preparation of Intermediate 7-1



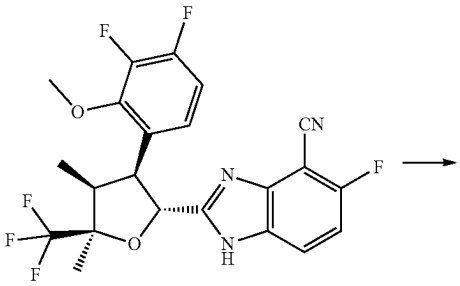
TM1-4



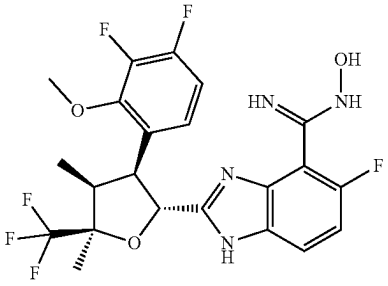
7-1

[0382] TFAA (194 mg, 0.92 mmol) was added to a solution of the previously synthesized compound TM1-4 (150 mg, 0.31 mmol) in Pyridine (3 mL) at 0° C. The reaction mixture was then stirred rt for 16 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) to get compound 7-1 (97 mg, 67% yield) as a white solid. LCMS: m/z=470.3 $[M+H]^+$.

Step 1: General Procedure for Preparation of Compound TM1-5



7-1

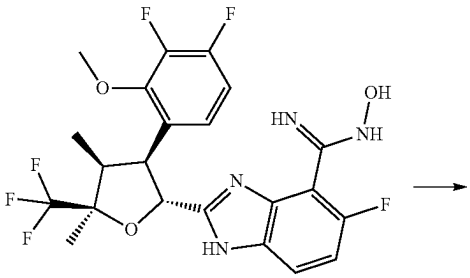


TM1-5

[0383] NH_2—OH·HCl (24 mg, 0.35 mmol) and DIEA (48 mg, 0.38 mmol) were added to a solution of compound 7-1 (110 mg, 0.23 mmol) in EtOH (2.2 mL), and the reaction mixture was stirred at 80° C. under N_2 for 3 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by prep-HPLC to get compound TM1-5 (67 mg, 56.90% yield, 98.59% purity at 214 nm) as a white solid. LCMS: m/z=503.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.26-12.23 (m, 1H), 9.80 (s, 1H), 8.34 (s, 1H), 7.59 (s, 1H), 7.29-6.92 (m, 3H), 5.98 (s, 2H), 5.78 (d, J=11.0 Hz, 1H), 4.66 (s, 1H), 3.97 (d, J=1.9 Hz, 3H), 2.97-2.76 (m, 1H), 1.63 (s, 3H), 0.79 (s, 3H).

Example 1-6

N-acetoxy-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-yl)-5-fluoro-1H-benzo[d]imidazole-4-carboximidamide (TM1-6)



TM1-5

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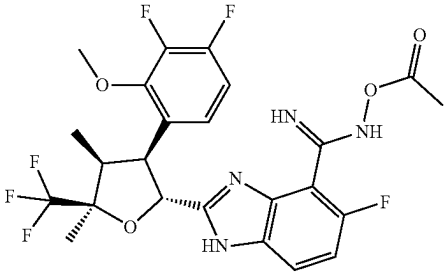
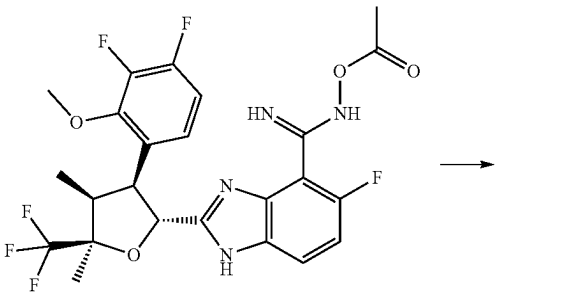


TM1-6

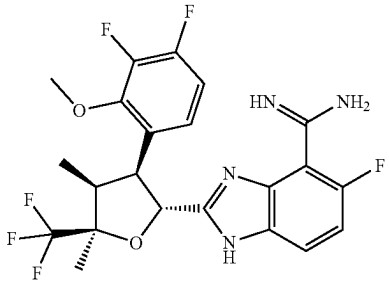
[0384] The previously synthesized compound TM1-5 (55 mg, 0.11 mmol) and Ac_2O (0.2 mL) were added to AcOH (1 mL) at r.t. The reaction mixture was stirred rt for 3 h. The reaction mixture was concentrated and purified by prep-HPLC to get TM1-6 (20.23 mg, 33% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=545.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.19-12.43 (m, 1H), 7.64 (d, J=48.1 Hz, 1H), 7.27-6.92 (m, 5H), 5.74 (d, J=11.2 Hz, 1H), 4.62 (s, 1H), 3.96 (d, J=2.1 Hz, 3H), 2.88 (s, 1H), 2.15 (d, J=20.1 Hz, 3H), 1.64 (s, 3H), 0.79 (s, 3H).

Example 1-7

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-1H-benzo[d]imidazole-4-carboximidamide (TM1-8)



TM1-6

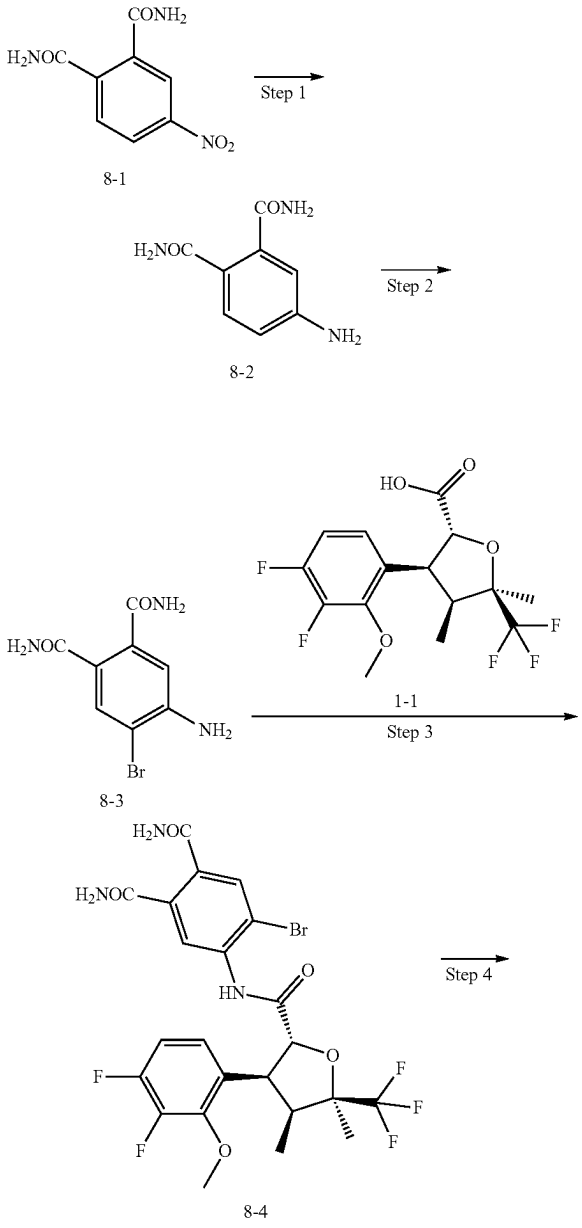


TM1-7

[0385] $Pd(OH)_2$ (20%, 5 mg) was added to a solution of previously synthesized compound TM1-6 (50 mg, 0.09 mmol) in AcOH (0.5 mL), the reaction mixture was stirred at r.t. under H2 atmosphere for overnight. The resulting mixture was filtered, the filtrate was concentrated, purified by prep-HPLC to give the desired product TM1-7 (7.92 mg, 17.73% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=487.2 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 8.54 (s, 2H), 7.84 (dd, J=8.9, 4.4 Hz, 1H), 7.34-7.13 (m, 2H), 6.94 (dd, J=17.0, 9.3 Hz, 1H), 5.80 (d, J=11.2 Hz, 1H), 4.44 (dd, J=11.1, 7.9 Hz, 1H), 3.98 (d, J=2.4 Hz, 3H), 2.92 (t, J=7.7 Hz, 1H), 1.70 (s, 3H), 0.94-0.87 (m, 3H).

Example 1-8

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-benzo[d]imidazole-5,6-dicarboxamide (TM1-8)



8-1

8-2

8-3

8-4

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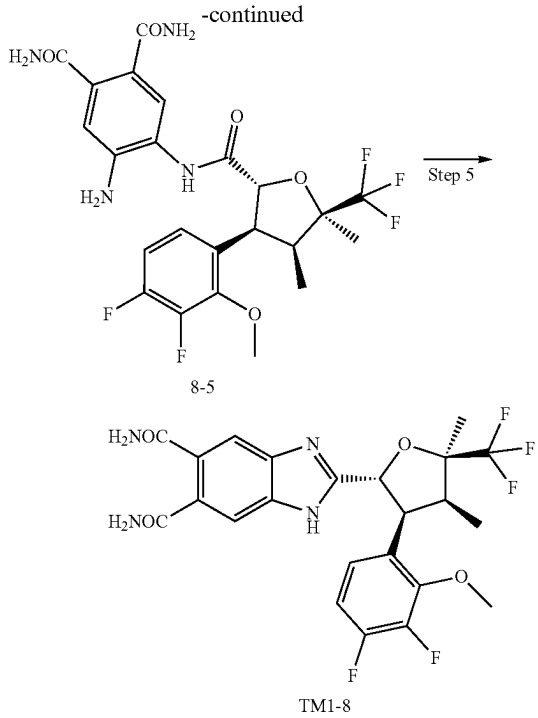
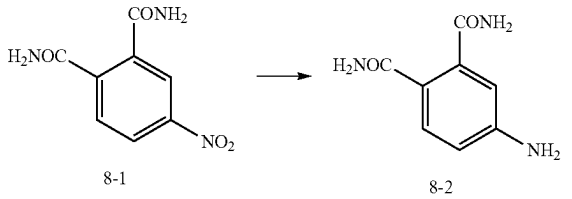
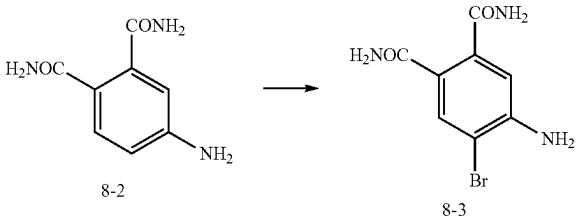


Step 1: General Procedure for Preparation of Intermediate 8-2



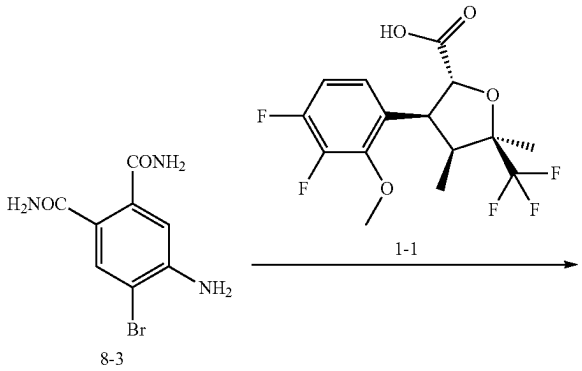
[0386] To a solution of compound 8-1 (5.0 g, 23.9 mmol) in MeOH (200 mL) was added Pd/C (1.0 g), then the mixture was stirred at r.t. under H2 atmosphere. The reaction was detected by LCMS. The mixture was concentrated to give the crude desired product 8-2 (4.7 g, 109.30% yield) as a brown solid. LCMS: m/z=177.8 $[M-H]^-$.

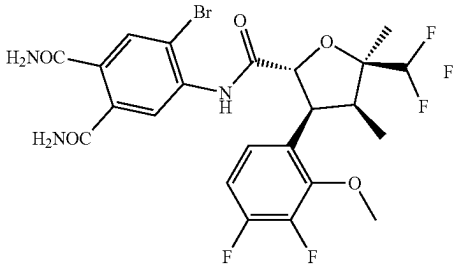
Step 2: General Procedure for Preparation of Intermediate 8-3



[0387] To a mixture of compound 8-2 (0.9 g, 5.0 mmol) in DMF (18 mL) was added NBS (0.7 g, 4.0 mmol) at 0° C. Then the whole mixture was stirred at r.t. for 3 h. The reaction was detected by LCMS. The mixture was purified by prep-HPLC (ACN/0.1% FA=0%~20%) to afford compound 8-3 (140 mg, 10.77% yield) as a white solid. LCMS: m/z=256.2 $[M-H]^-$.

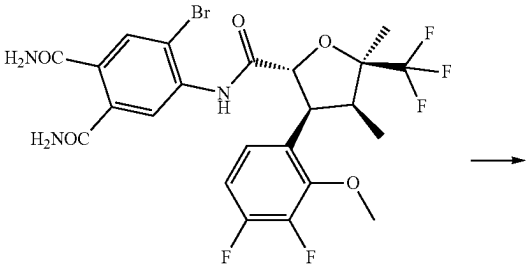
Step 3: General Procedure for Preparation of Intermediate 8-4



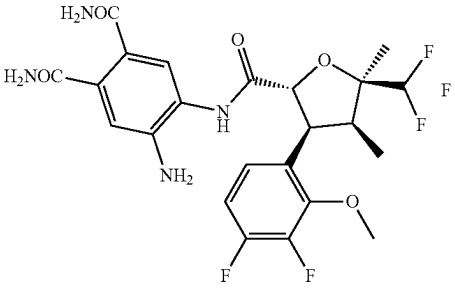


[0388] NMI (50 mg, 0.62 mmol) and TCFH (173 mg, 0.62 mmol) were added to a solution of compound 8-3 (79 mg, 0.31 mmol) and compound 1-1 (109 mg, 0.31 mmol) in ACN (2 mL), and the reaction mixture was stirred at r.t. for overnight. The resulting mixture was concentrated, diluted with water (10 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product 8-4 (70 mg, 38% yield) as a white solid. LCMS: m/z=594.0 $[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 8-5



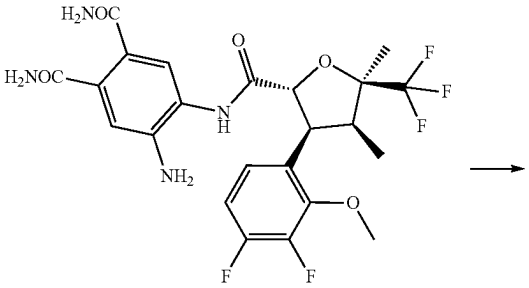
8-4



8-5

[0389] Compound 8-4 (45 mg, 0.08 mmol), $NH_3 \cdot H_2O$ (3 mg, 0.08 mmol), CuI (1 mg, 0.01 mmol), ethanediamide, N1,N2-bis(5-methyl[1,1'-biphenyl]-2-yl)-(3 mg, 0.01 mmol), and K_3PO_4 (16 mg, 0.08 mmol) were added to DMSO (0.6 mL), the reaction mixture was stirred at 60° C. under N2 for overnight. The reaction mixture was diluted with water, extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried and concentrated to afford compound 8-5 (40 mg, crude) as a yellow oil. LCMS: m/z=529.2 $[M-H]^-$.

Step 5: General Procedure for Preparation of Compound TM1-8



8-5

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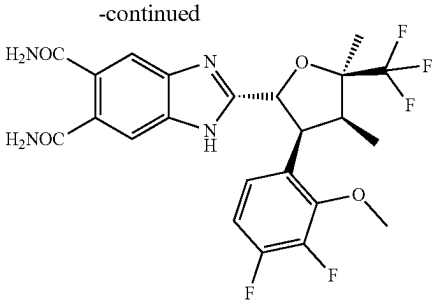
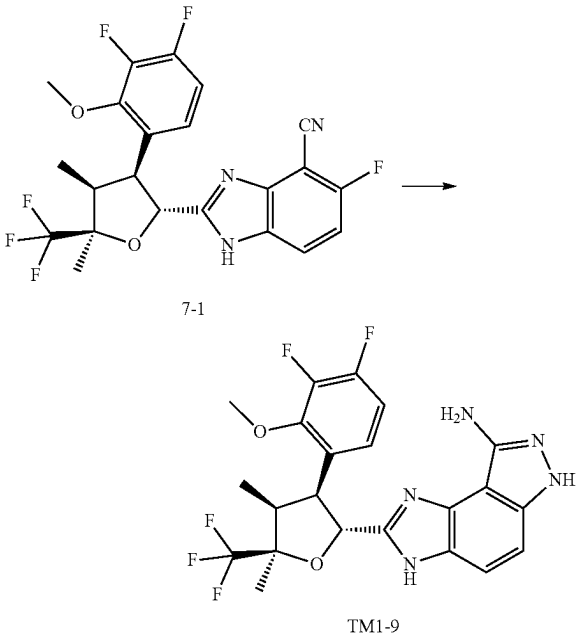


TM1-8

[0390] Compound 8-5 (40 mg, 0.075 mmol) was added to AcOH (1 mL), the reaction mixture was stirred at 80° C. for overnight. The resulting mixture was concentrated, diluted with $NaHCO_3$ solution (10 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product TM1-8 (1.53 mg, 3.96% yield, 92.95% purity at 214 nm) as a white solid. LCMS: m/z=513.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.77 (d, J=31.7 Hz, 2H), 7.09 (s, 1H), 6.92 (dd, J=17.2, 9.2 Hz, 1H), 5.70 (d, J=11.0 Hz, 1H), 4.51-4.34 (m, 1H), 3.96 (d, J=1.6 Hz, 3H), 3.01-2.86 (m, 1H), 1.71 (s, 3H), 0.89 (d, J=6.3 Hz, 3H).

Example 1-9

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine 5-oxide (TM1-9)



7-1

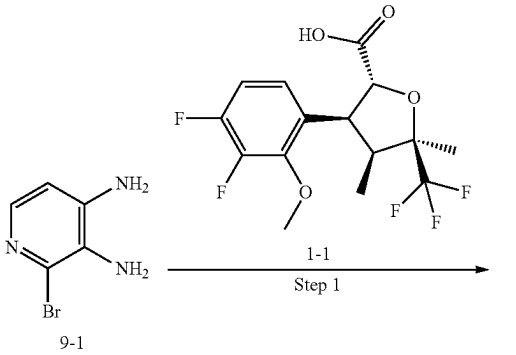
TM1-9

[0391] To a solution of compound 7-1 (shown in TM1-5; 65 mg, 0.14 mmol) in EtOH (5 mL) was added NH_2—

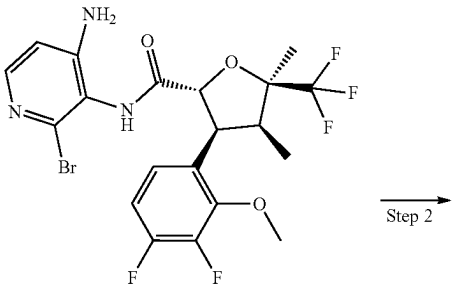
$NH_2 \cdot H_2O$ (2.5 mL). The reaction mixture was stirred at 100° C. in sealed tube for 2 h. The mixture was diluted with H_2O, extracted with EA, the combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by prep-HPLC to afford compound TM1-9 (3.28 mg, 4.57% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=482.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 7.49 (d, J=8.4 Hz, 1H), 7.19 (d, J=5.6 Hz, 1H), 7.02 (s, 1H), 6.90 (s, 1H), 5.70 (d, J=11.9 Hz, 1H), 4.50 (s, 1H), 4.00 (s, 3H), 2.98 (s, 1H), 1.71 (s, 3H), 0.88 (s, 3H).

Example 1-10

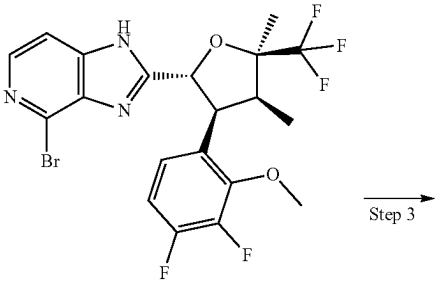
2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-4-carboxamide (TM1-10)



9-1



9-2



9-3

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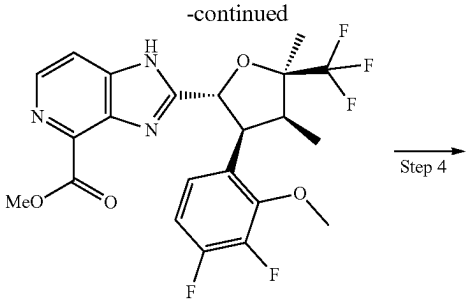

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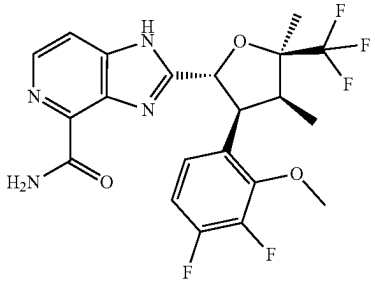
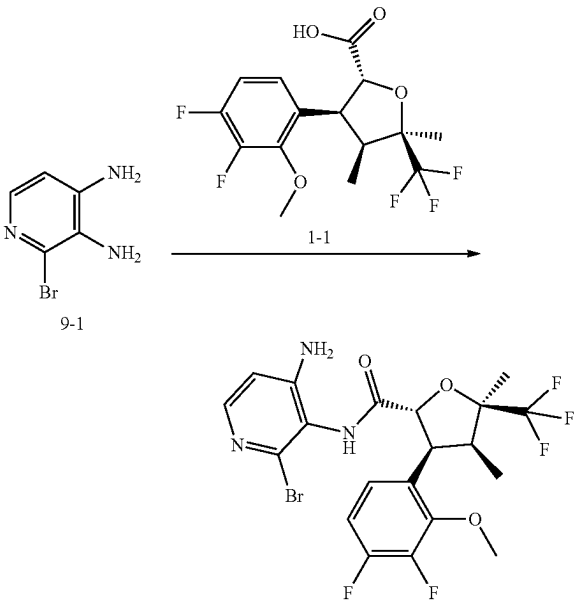


TM1-10

Step 1: General Procedure for Preparation of Intermediate 9-2



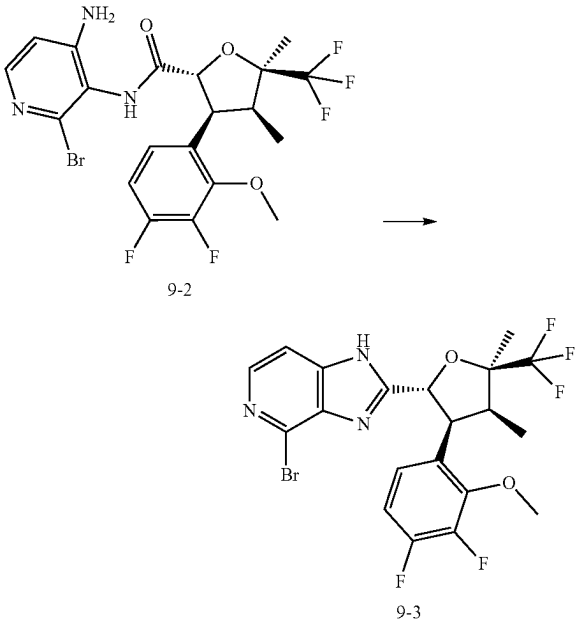
9-1

9-2

[0392] NMI (70 mg, 0.851 mmol) and TCFH (239 mg, 0.851 mmol) were added to a solution of compound 9-1 (80 mg, 0.426 mmol) and compound 1-1 (151 mg, 0.426 mmol) in ACN (3 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was concentrated, diluted with water (5 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried

over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product 9-2 (130 mg, 58% yield) as a white solid. LCMS: m/z=526.0 $[M+H+2]^+$.

Step 2: General Procedure for Preparation of Intermediate 9-3

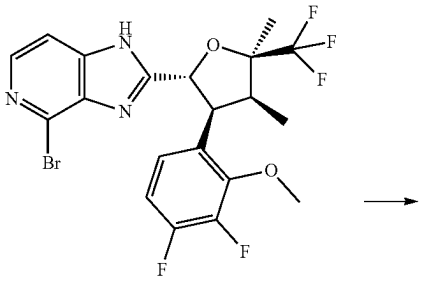


9-2

9-3

[0393] Compound 9-2 (130 mg, 0.248 mmol) was added to AcOH (2 mL), the reaction mixture was stirred at 80° C. for 16 h. The resulting mixture was concentrated, diluted with $NaHCO_3$ solution (5 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated, purified by prep-HPLC (ACN/0.01% FA in H_2O=0%~50%) to get the desired product 9-3 (80 mg, 63% yield) as a white solid. LCMS: m/z=507.6 $[M+H+2]^+$.

Step 3: General Procedure for Preparation of Intermediate 9-4



9-3

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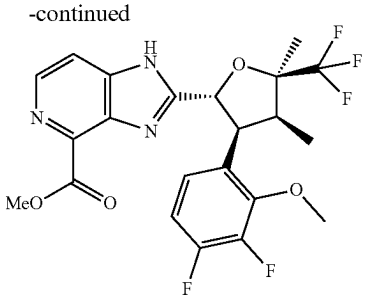
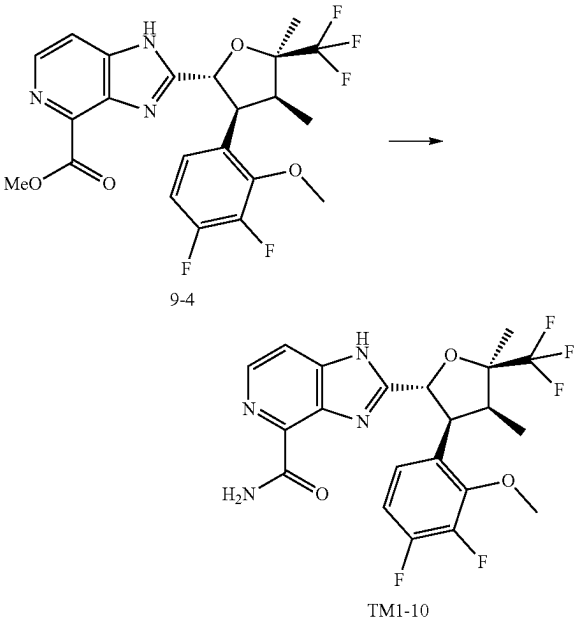


9-4

[0394] Compound 9-3 (73 mg, 0.144 mmol), $Pd(dppf)Cl_2$ (11 mg, 0.014 mmol), TEA (44 mg, 0.433 mmol) were added to ACN (0.5 mL) and MeOH (0.5 mL), the reaction mixture was stirred at 100° C. under CO (2 MPa) for 16 h. The resulting mixture was concentrated, diluted with water (3 mL), extracted with EA (3 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, concentrated to get residue. The residue was purified by silica gel column chromatography, eluted with EA in PE (10%~60%) to give the desired product 9-4 (55 mg, 78% yield) as a yellow oil. LCMS: m/z=486.2 $[M+H]^+$.

Step 5: General Procedure for Preparation of Compound TM1-10



9-4

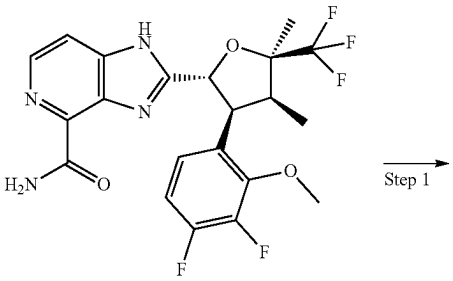
TM1-10

[0395] Compound 9-4 (40 mg, 0.082 mmol was added to a solution of NH_3 in MeOH (7M, 0.5 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with water (5 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated and purified by HPLC to get the compound TM1-10 (19.01 mg, 34% yield, 96.89% purity at 214 nm) as a white solid. LCMS: m/z=471.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ

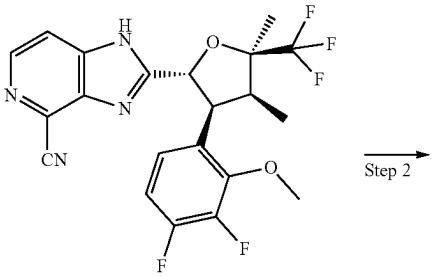
13.18 (s, 1H), 8.34 (d, J=5.6 Hz, 1H), 8.25 (s, 1H), 7.84 (d, J=5.6 Hz, 2H), 7.19-7.05 (m, 2H), 5.98 (d, J=11.2 Hz, 1H), 4.80-4.67 (m, 1H), 3.97 (d, J=2.0 Hz, 3H), 2.98-2.83 (m, 1H), 1.65 (s, 3H), 0.79 (d, J=6.0 Hz, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ −73.48 (s, CF_3), −138.07--138.13 (d, F), −154.84--154.89 (d, F).

Example 1-11

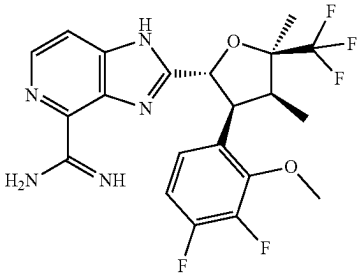
2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-4-carboximidamide (TM1-11)



TM1-10

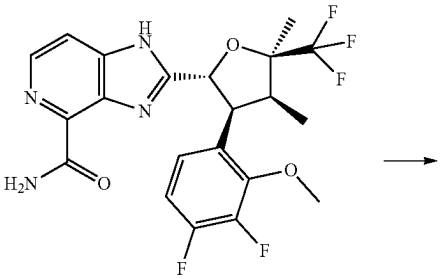


10-1

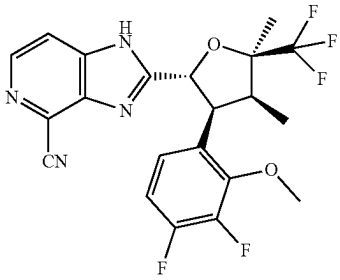


TM1-11

Step 1: General Procedure for Preparation of Intermediate 10-1



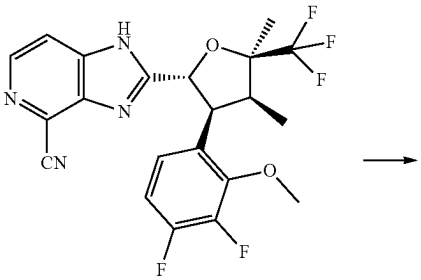
TM1-10



10-1

[0396] TFAA (228 mg, 1.09 mmol) was added to a solution of compound TM1-10 (180 mg, 0.38 mmol) in Pyridine (3.5 mL) at 0° C. The reaction mixture was stirred rt for 16 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) to get compound 10-1 (150 mg, 86% yield) as a white solid. LCMS: m/z=453.2 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-11



10-1

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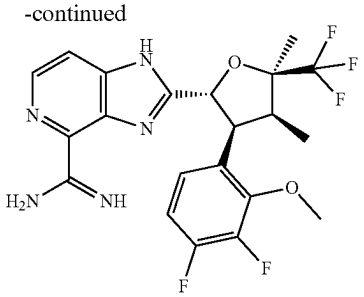
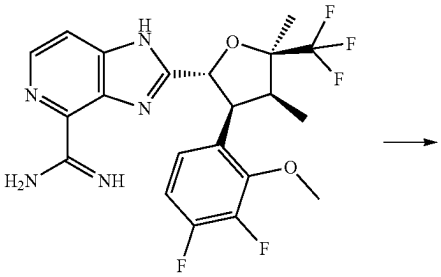


TM1-11

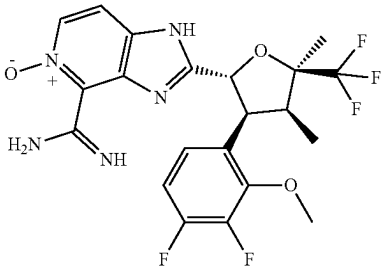
[0397] LiHMDS (1M, 0.27 mL, 0.27 mmol) was added to a solution of compound 10-1 (30 mg, 0.07 mmol) in THF (0.5 mL) at 0° C. under N2, and the reaction mixture was stirred at r.t. for 4 h. HCl in EtOH (2M, 0.27 mL, 0.53 mmol) was added to the mixture at 0° C. The mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with EtOH (2 mL) and water (2 mL), finally purified by HPLC to get the desired product TM1-11 (11 mg, 35% yield, 98.01% purity at 214 nm) as a white solid. LCMS: m/z=470.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.50 (d, J=124.7 Hz, 4H), 8.46 (d, J=5.3 Hz, 1H), 7.88 (d, J=5.4 Hz, 1H), 7.27-7.18 (m, 1H), 7.10 (dd, J=17.2, 9.4 Hz, 1H), 5.87 (d, J=11.1 Hz, 1H), 4.68-4.49 (m, 1H), 3.96 (d, J=2.1 Hz, 3H), 2.90 (p, J=7.3 Hz, 1H), 1.68 (s, 3H), 0.83 (d, J=6.3 Hz, 3H).

Example 1-12

4-carbamimidoyl-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine 5-oxide (TM1-12)



TM1-11

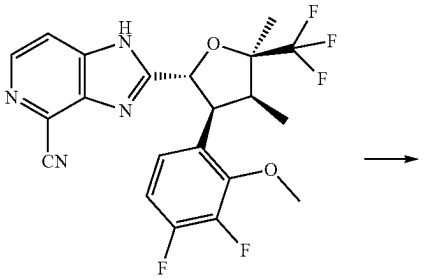


TM1-12

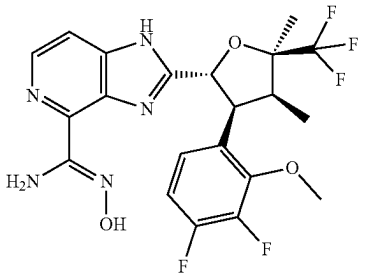
[0398] To a solution of the previously synthesized compound TM1-11 (90 mg, 0.19 mmol) in AcOH (2 mL) was added H_2O_2 (1 mL). The reaction mixture was stirred at 70° C. for 16 h. The resulting mixture was diluted with $NaHCO_3$ solution (10 mL), extracted with DCM (2×10 mL), The organic phases were combined, washed with brine (10 mL), dried over Na_2SO_4, concentrated and purified by prep-HPLC to give the desired product TM1-12 (14.12 mg, 15.17% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=486.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 2H), 8.96 (s, 2H), 8.03 (d, J=6.8 Hz, 1H), 7.66 (d, J=6.8 Hz, 1H), 7.21-6.97 (m, 2H), 5.65 (d, J=11.0 Hz, 1H), 4.68 (dd, J=11.0, 7.4 Hz, 1H), 3.95 (d, J=1.9 Hz, 3H), 2.90-2.76 (m, 1H), 1.61 (s, 3H), 0.81 (d, J=5.9 Hz, 3H).

Example 1-13

(Z)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-N'-hydroxy-1H-imidazo[4,5-c]pyridine-4-carboximidamide (TM1-13)



10-1



TM1-13

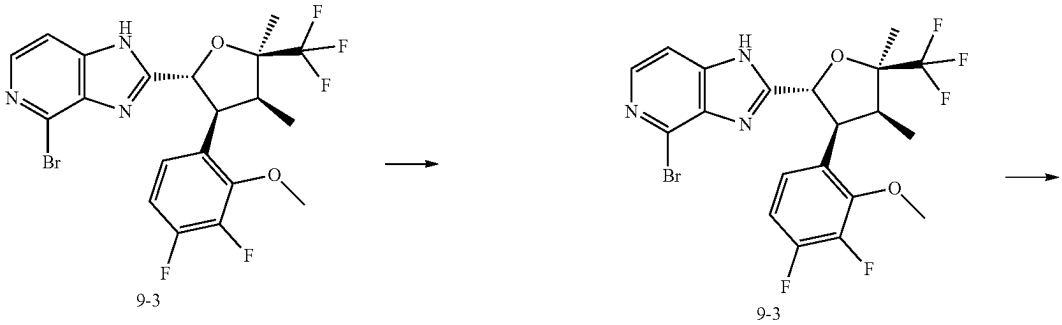
[0399] NH_2—OH·HCl (14 mg, 0.20 mmol) and DIEA (27 mg, 14 mmol) were added to a solution of the previously synthesized compound 10-1 (shown in TM1-11; 70 mg, 0.15 mmol) in EtOH (1 mL), and the reaction mixture was stirred at 80° C. under N2 for 3 h. The resulting mixture was concentrated, diluted with water (2 mL), extracted with EA (2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, concentrated, and finally purified by HPLC to get compound TM1-13 (41 mg, 54% yield, 96.72% purity at 214 nm) as a white solid. LCMS: m/z=486.3 [M+H]+. 1H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 9.94 (s, 1H), 8.30 (d, J=5.6 Hz, 1H), 7.65 (d, J=5.6 Hz, 1H), 7.13-7.05 (m, 2H), 6.13-5.95 (m, 3H), 4.68 (dd, J=10.8, 7.7 Hz, 1H), 3.97 (d, J=2.2 Hz, 3H), 2.89 (t, J=3.8 Hz, 1H), 1.64 (s, 3H), 0.79 (d, J=5.8 Hz, 3H).

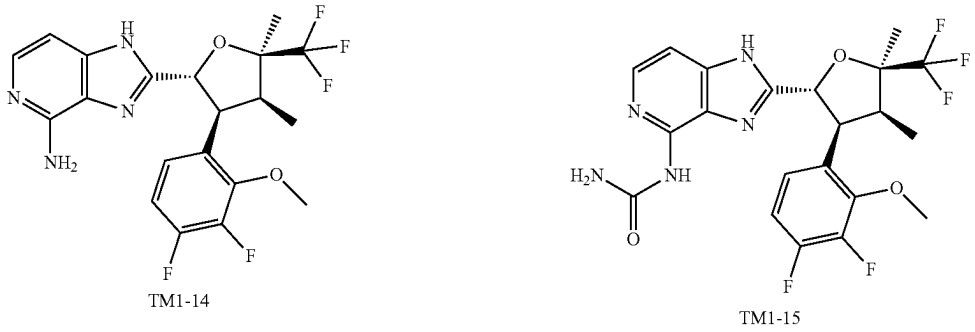
Example 1-14

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-amine (TM1-14)

Example 1-15

1-(2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-yl)urea (TM1-15)



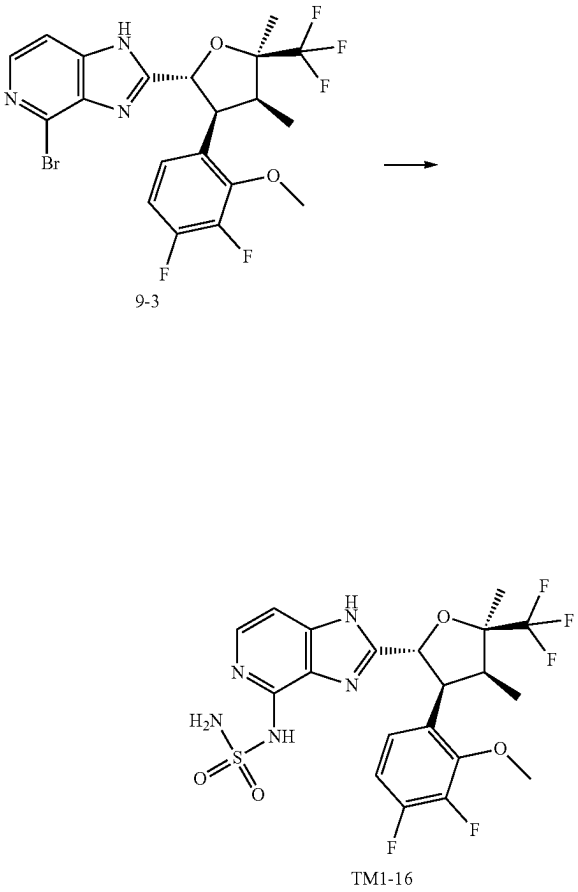


[0400] To a solution of the previously synthesized compound 9-3 (shown in TM1-10; 60 mg, 0.12 mmol) was dissolved in DMAc (2 mL), and then the solution was added sulfuric diamide (114.2 mg, 1.2 mmol), t-BuXphos-Pd G3 (11.4 mg, 0.0144 mmol) and Cs_2CO_3 (117 mg, 0.36 mmol) at 100° C. for 16 h. The reaction was detected by LCMS. The residue was purified by silica gel column chromatography, then eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product TM1-14 (13.80 mg, 26.02% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=443.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 0.5H), 7.60 (d, J=5.8 Hz, 1H), 7.09 (dd, J=16.1, 7.9 Hz, 2H), 6.72 (d, J=5.8 Hz, 1H), 6.26 (s, 2H), 5.65 (d, J=11.2 Hz, 1H), 4.55-4.47 (m, 1H), 3.98 (s, 3H), 2.92-2.85 (m, 1H), 1.64 (s, 3H), 0.79 (d, J=6.4 Hz, 3H).

[0401] To a solution of the previously synthesized compound 9-3 (shown in TM1-10; 80 mg, 0.16 mmol) was dissolved in DMAc (4 mL), and then the solution was added urea (95.14 mg, 1.6 mmol), t-BuXphos-Pd G3 (15.3 mg, 0.019 mmol) and Cs_2CO_3 (156 mg, 0.48 mmol) at 100° C. for 16 h. The reaction was detected by LCMS. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product TM1-15 (15.31 mg, 19.73% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=486.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J=128.5 Hz, 1.5H), 7.89 (d, J=5.7 Hz, 1H), 7.32-6.87 (m, 4H), 5.82 (d, J=10.8 Hz, 1H), 4.58-4.38 (m, 1H), 3.96 (d, J=1.6 Hz, 3H), 2.94-2.84 (m, 1H), 1.67 (s, 3H), 0.80 (d, J=6.0 Hz, 3H).

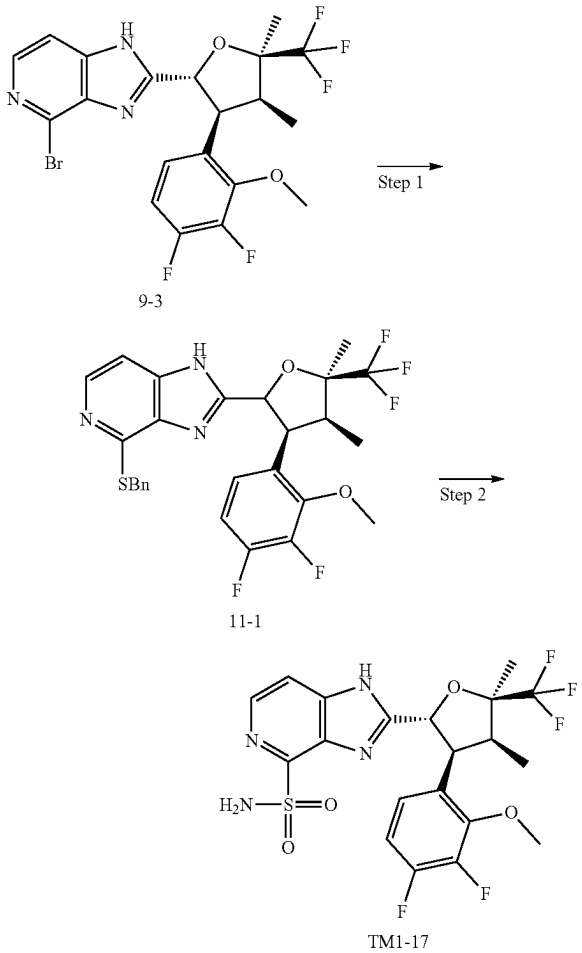
Example 1-16

N-{2-[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolan-2-yl]-1H-imidazo[4,5-c]pyridin-4-yl}aminosulfonamide (TM1-16)



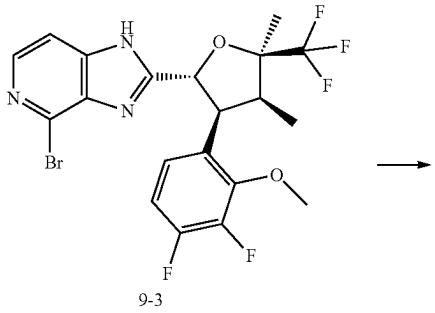
Example 1-17

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-4-sulfonamide (TM1-17)



[0402] The previously synthesized compound 9-3 (shown in TM1-10; 300 mg, 0.59 mmol), sulfuric diamide (569 mg, 5.93 mmol), t-Buxphos-Pd-G3 (47 mg, 0.06 mmol), and Cs_2CO_3 (580 mg, 1.78 mmol) were added to DMA (30 mL), the reaction mixture was stirred at 70° C. under N2 for overnight. The resulting mixture was diluted with water (40 mL), extracted with EA (40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, concentrated to get residue. The residue was purified by prep-HPLC to afford the product TM1-16 (25.73 mg, 8.33% yield, 95.25% purity at 214 nm) as a white solid. LCMS: m/z=522.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 14.11-12.86 (m, 1H), 11.62 (s, 1H), 7.51 (s, 1H), 7.10 (s, 2H), 6.91 (s, 1H), 6.49 (s, 2H), 5.73 (s, 1H), 4.51 (d, J=67.5 Hz, 1H), 3.96 (d, J=1.4 Hz, 3H), 2.92-2.82 (m, 1H), 1.64 (s, 3H), 0.78 (s, 3H).

Step 1: General Procedure for Preparation of Intermediate 11-1



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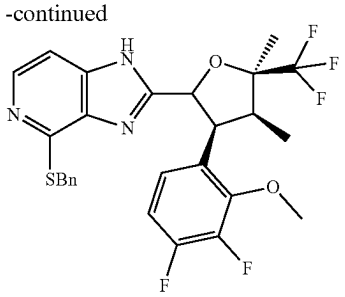
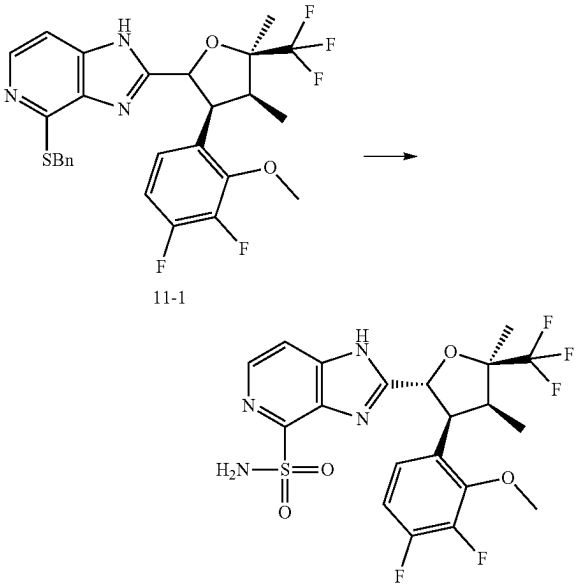


11-1

[0403] The previously synthesized compound 9-3 (shown in TM1-10; 50 mg, 0.10 mmol), phenylmethanethiol (12 mg, 0.10 mmol), DIEA (26 mg, 0.20 mmol), $Pd_2(dba)_3$ (23 mg, 0.02 mmol), and xantphos (29 mg, 0.05 mmol) were added to 1,4-dioxane (0.5 mL), and the reaction mixture was stirred at 100° C. for overnight. The resulting mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (0%~50% EA/PE) to afford the compound 11-1 (28 mg, 51% yield) as a white solid. LCMS: m/z=550.6 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-17



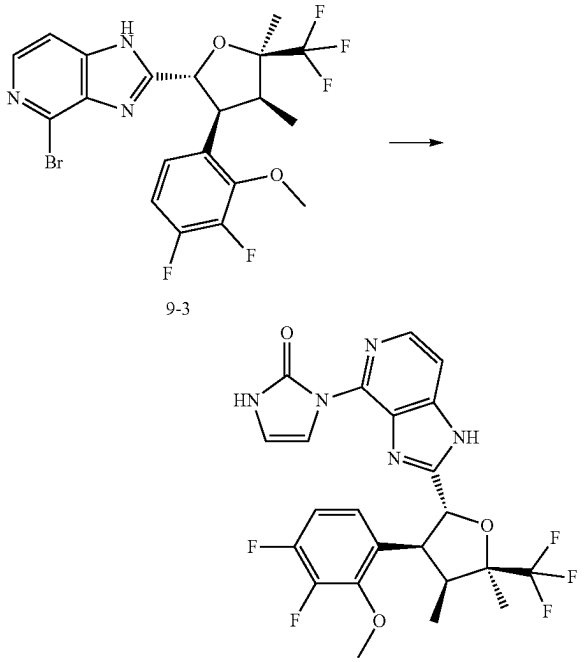
11-1

TM1-17

[0404] To a solution of compound 11-1 (40 mg, 0.07 mmol) in a mixture of ACN (1.2 ml), AcOH (0.03 mL), and water (0.03 mL) at 0° C. was added 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (23 mg, 0.08 mmol) and the reaction mixture allowed to stir for 30 min. Then NH_3 in MeOH (7M, 0.16 mL) was added and the reaction mixture allowed to warm to ambient temperature and stir for 30 min. The reaction mixture was diluted with water and EA and the aqueous layer extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by HPLC to afford the target compound TM1-17 (5.09 mg, 13.81% yield, 99.32% purity at 214 nm) as a white solid. LCMS: m/z=507.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 8.39 (s, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.12 (dd, J=17.2, 8.5 Hz, 3H), 5.98 (s, 1H), 4.74 (s, 1H), 3.97 (d, J=2.0 Hz, 3H), 2.91 (t, J=7.7 Hz, 1H), 1.65 (s, 3H), 0.80 (d, J=6.4 Hz, 3H).

Example 1-18

1-(2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-yl)-1,3-dihydro-2h-imidazol-2-one (TM1-18)



9-3

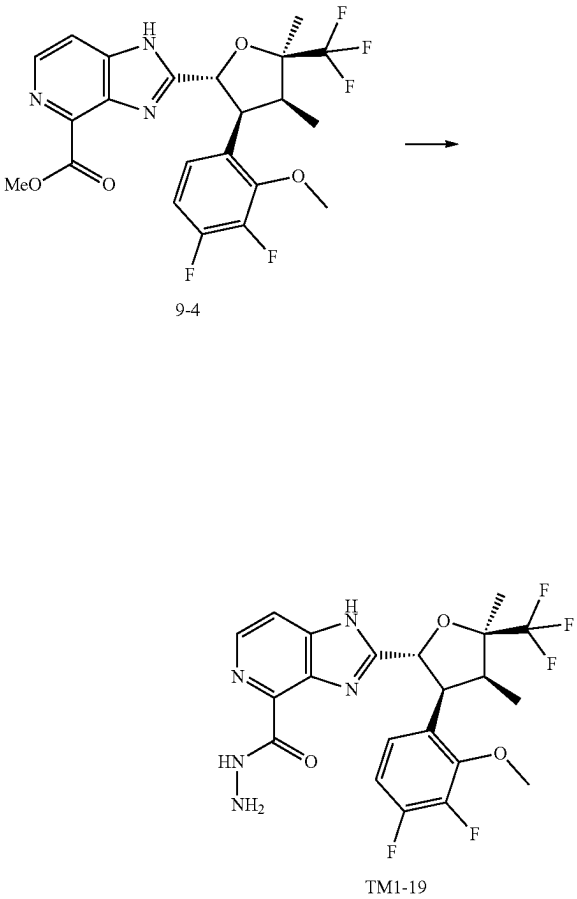
TM1-18

[0405] To a solution of previously synthesized compound 9-3 (shown in TM1-10; 300 mg, 0.59 mmol) was dissolved in DMAc (15 mL), and then the solution was added 1,3-dihydro-2h-imidazol-2-one (499 mg, 5.9 mmol), brettphos-Pd G4 (65.2 mg, 0.071 mmol) and Cs_2CO_3 (575.3 mg, 1.77 mmol) at 95° C. for 4 h. The reaction was detected by LCMS. The reaction mixture was added EA (20 mL). The resulting mixture was extracted with EA (2×50 mL). The organic phases were combined, washed with brine (20 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% NH_4HCO_3 in H_2O (5%~95%) to give the product TM1-18 (32.42 mg, 10.80% yield, 92.73% purity at 214 nm) as a white solid. LCMS: m/z=510.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H),

10.77 (s, 1H), 8.12 (d, J=5.5 Hz, 1H), 7.52 (d, J=5.6 Hz, 1H), 7.30-7.21 (m, 2H), 7.11 (d, J=8.4 Hz, 1H), 6.76 (s, 1H), 6.01 (d, J=7.0 Hz, 1H), 4.52 (dd, J=11.0, 7.5 Hz, 1H), 3.95 (d, J=2.1 Hz, 3H), 2.88 (t, J=7.5 Hz, 1H), 1.66 (s, 3H), 0.80 (d, J=6.0 Hz, 3H).

Example 1-19

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-4-carbohydrazide (TM1-19)

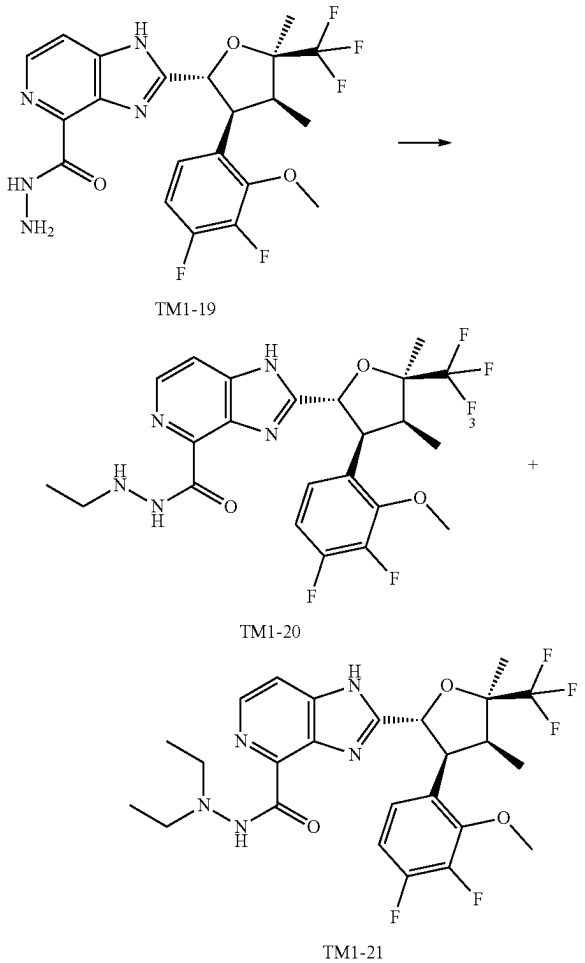


[0406] NH_2—$NH_2 \cdot H_2O$ (1 mL) was added to a solution of previously synthesized compound 9-4 (shown in TM1-10; 80 mg, 0.16 mmol) in MeOH (1 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with water (5 mL), extracted with EA (5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, concentrated and purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) to get the target compound TM1-19 (55 mg, 69% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=486.3 $[M+H+2]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 10.05 (s, 1H), 8.32 (d, J=5.4 Hz, 1H), 7.81 (d, J=5.0 Hz, 1H), 7.17-7.00 (m, 2H), 5.98 (d, J=11.0 Hz, 1H), 5.14-4.30 (m, 3H), 3.96 (d, J=2.1 Hz, 3H), 2.98-2.84 (m, 1H), 1.66 (s, 3H), 0.79 (d, J=6.1 Hz, 3H).

Example 1-20

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-N'-ethyl-1H-imidazo[4,5-c]pyridine-4-carbohydrazide (TM1-20)

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-N',N'-diethyl-1H-imidazo[4,5-c]pyridine-4-carbohydrazide (TM1-21)



[0407] To a solution of the previously synthesized compound TM1-19 (60 mg, 0.13 mmol) in MeOH (1 ml) was added CH_3CHO (5M, 0.02 mL, 0.09 mmol), AcONa (7 mg, 0.09 mmol) and AcOH (5 mg, 0.09 mmol) at 0° C. for 30 min. To this mixture was added $NaBH_3CN$ (6 mg, 0.09 mmol) at 0° C., the reaction mixture was stirred at r.t. for 12 h under nitrogen. The reaction mixture was diluted with EA (10 mL) and water (5 mL). The layers were separated and the water layer was extracted with EA (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude product. The residue was purified through preparative liquid chromatography (0.1% FA in H_2O/ACN=5%~95%) to afford TM1-20 (9.39 mg, 14.79%

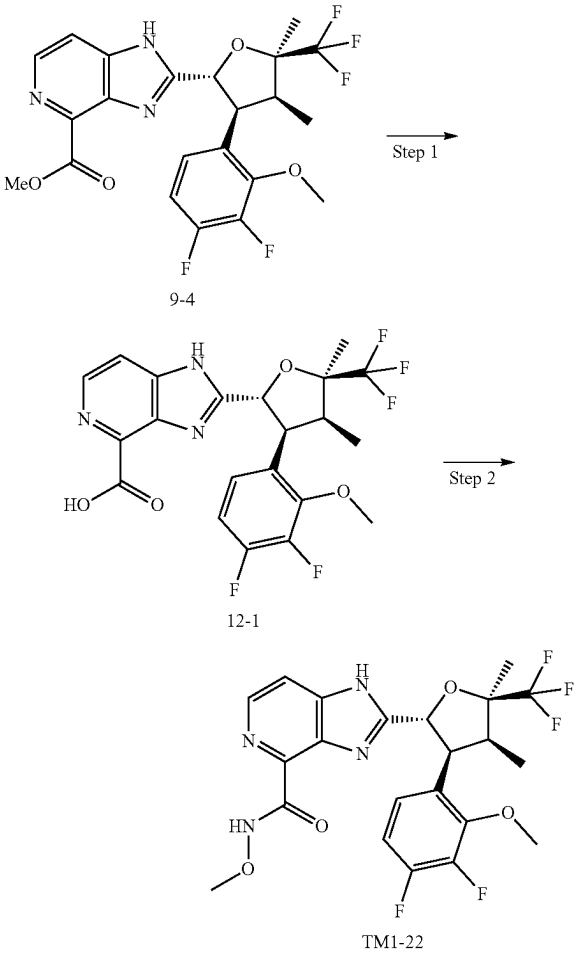
yield, 95.93% purity at 214 nm) and TM1-21 (10.35 mg, 15.46% yield, 100% purity at 214 nm) as a white solid.

[0408] TM1-20. LCMS: m/z=514.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 10.27 (s, 1H), 8.33 (d, J=5.4 Hz, 1H), 7.83 (s, 1H), 7.12 (dd, J=17.4, 7.7 Hz, 2H), 5.96 (d, J=10.9 Hz, 1H), 5.09 (s, 1H), 4.73 (s, 1H), 3.96 (d, J=2.1 Hz, 3H), 2.90 (d, J=6.9 Hz, 3H), 1.66 (s, 3H), 1.05 (t, J=7.1 Hz, 3H), 0.79 (d, J=5.9 Hz, 3H).

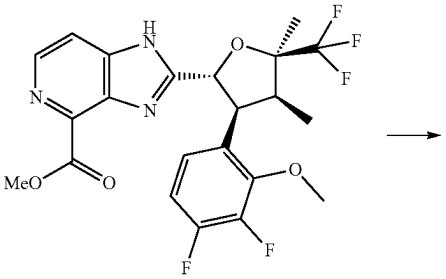
[0409] TM1-21. LCMS: m/z=542.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 9.28 (s, 1H), 8.33 (s, 1H), 7.85 (s, 1H), 7.10 (d, J=5.9 Hz, 2H), 5.94 (d, J=10.9 Hz, 1H), 4.75 (s, 1H), 3.96 (d, J=1.4 Hz, 3H), 2.89 (dd, J=26.9, 7.2 Hz, 5H), 1.66 (s, 3H), 1.00 (s, 6H), 0.79 (d, J=5.8 Hz, 3H).

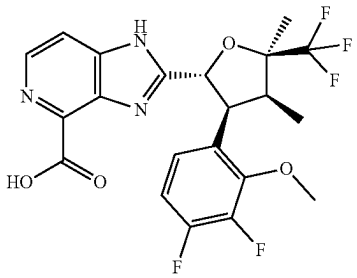
Example 1-21

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-N-methoxy-1H-imidazo[4,5-c]pyridine-4-carboxamide (TM1-22)



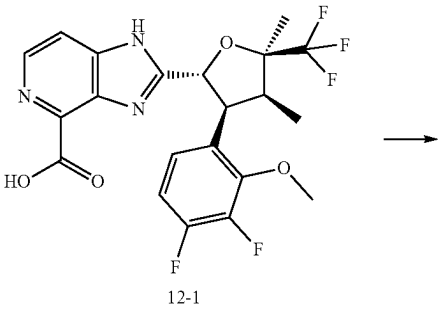
Step 1: General Procedure for Preparation of Intermediate 12-1





[0410] The previously synthesized compound 9-4 (shown in TM1-10; 200 mg, 0.41 mmol) was added to a solution of LiOH—H_2O (346 mg, 8.25 mmol) in MeOH (1 mL) and THF (1 mL) at 0° C. The reaction mixture was stirred rt for 16 h. The mixture was diluted with 1 N HCl solution, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) to get compound 12-1 (127 mg, 65% yield) as a white solid. LCMS: m/z=470.1$[M-H]^-$.

Step 2: General Procedure for Preparation of Compound TM1-22



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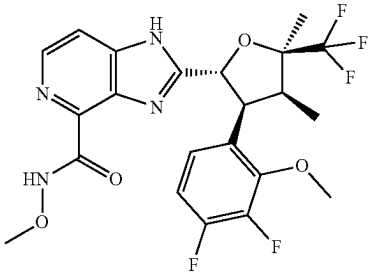
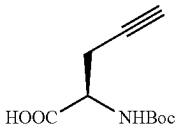


TM1-22

[0411] HATU (48 mg, 0.13 mmol) and DIEA (66 mg, 0.51 mmol) were added to a solution of compound 12-1 (60 mg, 0.12 mmol) and Hydroxylamine hydrochloride (21 mg, 0.25 mmol) in DMF (1 mL), and the reaction mixture was stirred at r.t. for overnight. The resulting mixture was concentrated, diluted with water (20 mL), extracted with EA (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product TM1-22 (17.81 mg, 27% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=501.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 12.21 (s, 1H), 8.31 (d, J=5.2 Hz, 1H), 7.84 (s, 1H), 7.12 (dd, J=18.1, 7.9 Hz, 2H), 5.94 (d, J=10.9 Hz, 1H), 4.73 (s, 1H), 3.96 (s, 3H), 3.76 (s, 3H), 2.97-2.83 (m, 1H), 1.66 (s, 3H), 0.79 (d, J=6.1 Hz, 3H).

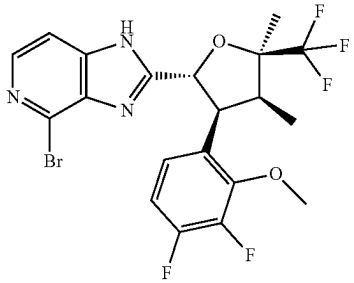
Example 1-22

5-(2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-yl)pyrrolidine-2-carboxamide (TM1-23)

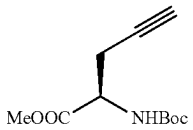


13-1

Step 1



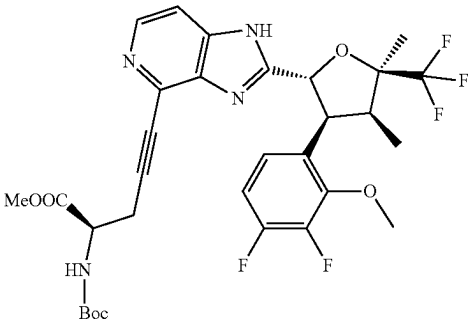
9-3



13-2

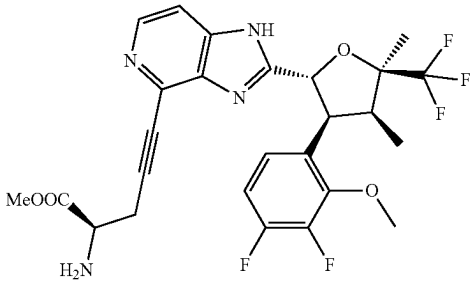
Step 2

-continued



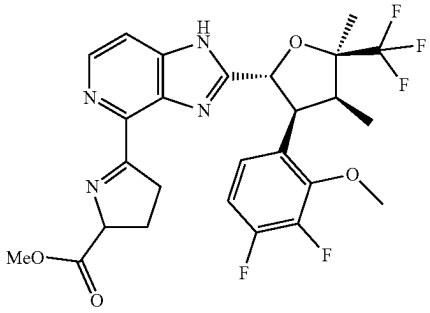
13-3

Step 3



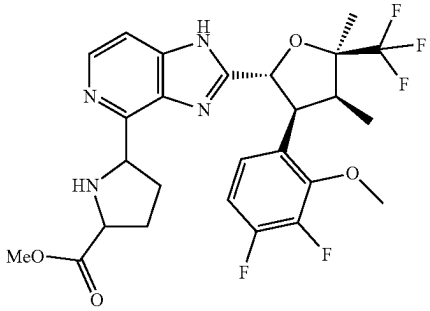
13-4

Step 4



13-5

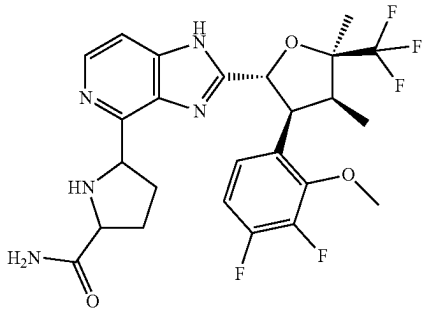
Step 5



13-6

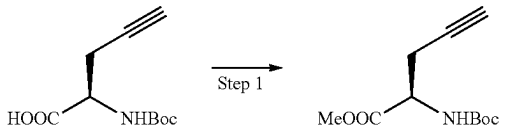
Step 6

-continued



TM1-23

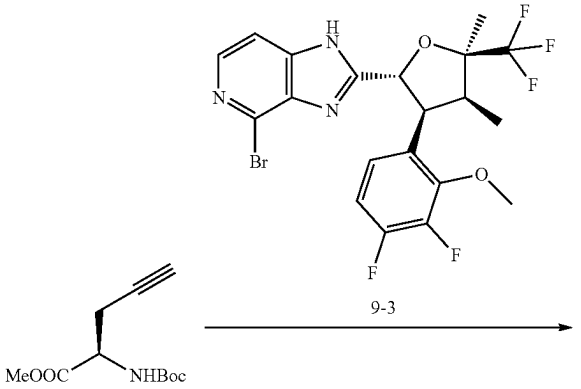
Step 1: General Procedure for Preparation of Intermediate 13-2



13-1 13-2

[0412] Cs_2CO_3 (9.2 g, 28.17 mmol) and CH_3I (1.3 g, 9.39 mmol) were added to a solution of compound 13-1 (2 g, 9.39 mmol) in EtOH (40 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with water (40 mL), extracted with EA (40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, concentrated to afford the desired product 13-2 (1.8 g, 84% yield) as a yellow oil. LCMS: m/z=128.1 $[M+H-100]^+$.

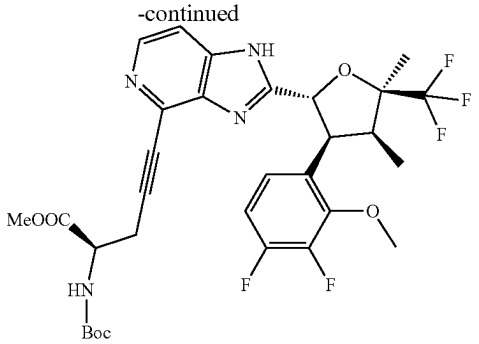
Step 2: General Procedure for Preparation of Intermediate 13-3



9-3

13-2

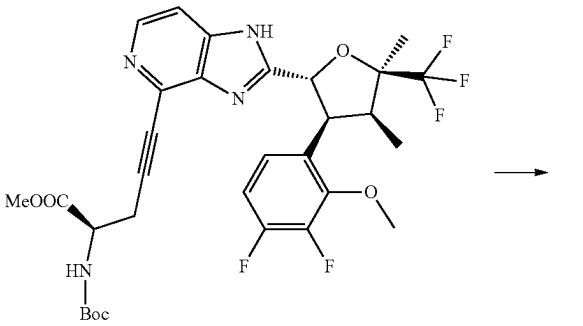
-continued



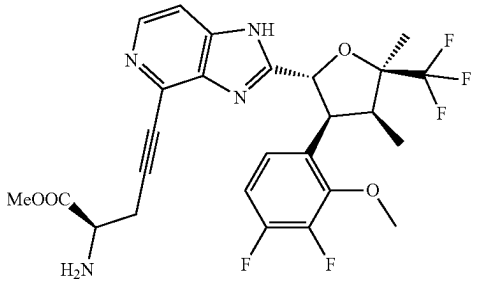
13-3

[0413] The previously synthesized compound 9-3 (shown in TM1-10; 500 mg, 0.99 mmol), compound 13-2 (337 mg, 1.49 mmol), $Pd(dppf)Cl_2$ (72 mg, 0.10 mmol), CuI (19 mg, 0.10 mmol), TEA (150 mg, 1.49 mmol) were added to THF (10 mL). The reaction mixture was stirred at 70° C. for 16 h. The resulting mixture was concentrated, diluted with water (40 mL), extracted with EA (40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, concentrated, purified by silica gel column chromatography, eluted with MeOH/DCM (10%) to get the desired product 13-3 (420 mg, 65% yield) as a white solid. LCMS: m/z=653.7 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 13-4



13-3

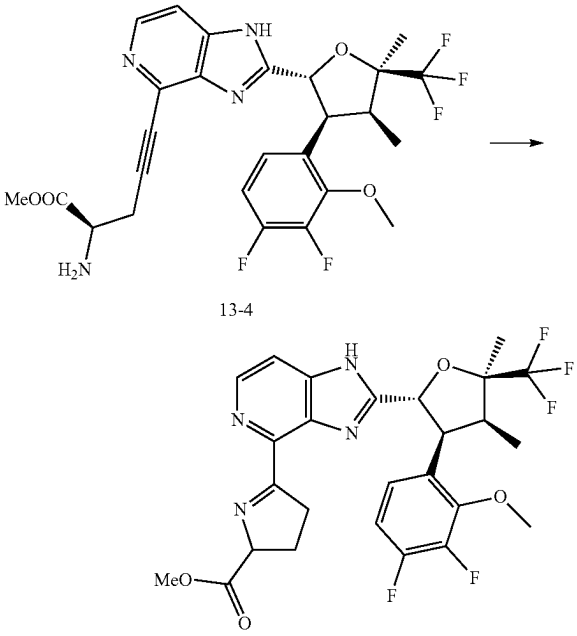


13-4

[0414] Compound 13-3 (420 mg, 0.64 mmol) was added to a solution of TFA (2 mL) and DCM (6 mL). The reaction mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated, purified by preparative liquid chromatography

(0.1% FA in H_2O/ACN=5%~95%) to afford compound 13-4 (240 mg, 67% yield) as a white solid. LCMS: m/z=553.7 $[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 13-5

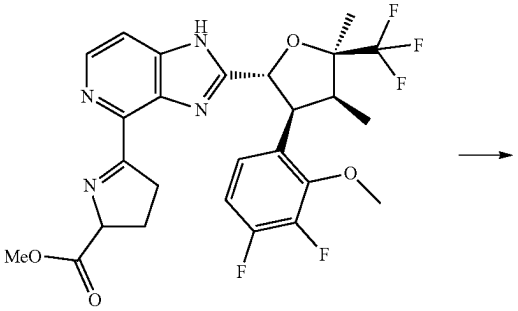


13-4

13-5

[0415] Compound 13-4 (240 mg, 0.04 mmol), AgOTf (22 mg, 0.09 mmol) were added to ACN (5 mL). The reaction mixture was stirred at 60° C. for 16 h. The reaction mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (10%) to afford compound 13-5 (120 mg, 50% yield) as a white solid. LCMS: m/z=553.7 $[M+H]^+$.

Step 5: General Procedure for Preparation of Intermediate 13-6



13-5

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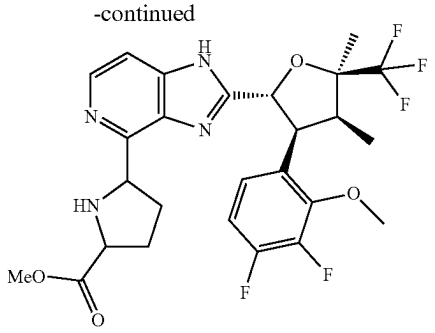
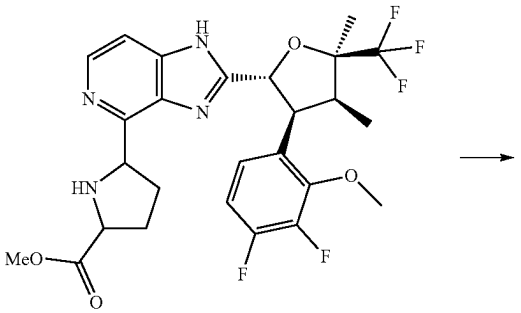


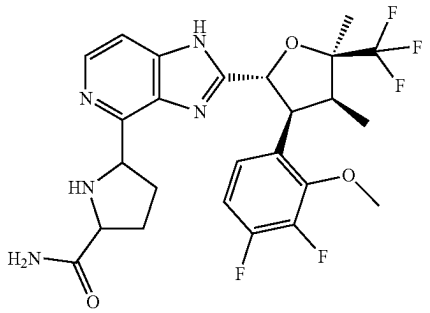
13-6

[0416] To a solution of compound 13-5 (50 mg, 0.09 mmol) in MeOH (1 mL) was added Pd/C (20 mg) under H2 atmosphere. The reaction mixture was stirred at r.t. for 2 h. The reaction mixture was filtered, the filtrate was concentrated to afford 13-6 (60 mg, 85% yield) as a white solid. LCMS: m/z=553.2 $[M+H]^+$.

Step 6: General Procedure for Preparation of Compound TM1-23



13-6



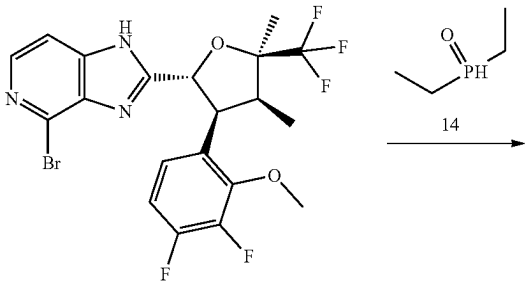
TM1-23

[0417] To a solution of NH_3 in MeOH (0.5 mL) was added the compound 13-6 (50 mg, 0.09 mmol) at r.t. The reaction

mixture was stirred rt for 16 h. Then the mixture was concentrated and purified through preparative liquid chromatography (0.1% FA in H_2O/ACN=5%~95%) to afford compound TM1-23 (3.95 mg, 8.12% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=540.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J=5.7 Hz, 1H), 7.48 (dd, J=5.7, 2.8 Hz, 1H), 7.20-6.99 (m, 2H), 5.70 (dd, J=11.4, 2.5 Hz, 1H), 4.80-4.53 (m, 2H), 3.92 (dd, J=13.9, 12.1 Hz, 4H), 2.99-2.83 (m, 1H), 2.22 (s, 2H), 1.88-1.63 (m, 5H), 0.81 (d, J=6.2 Hz, 3H).

Example 1-23

(2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-yl)diethylphosphine oxide (TM1-24)



9-3

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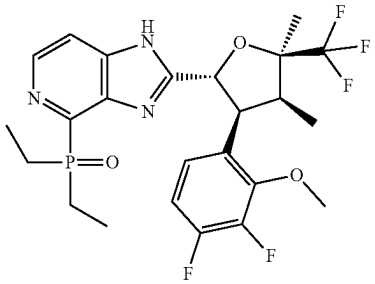
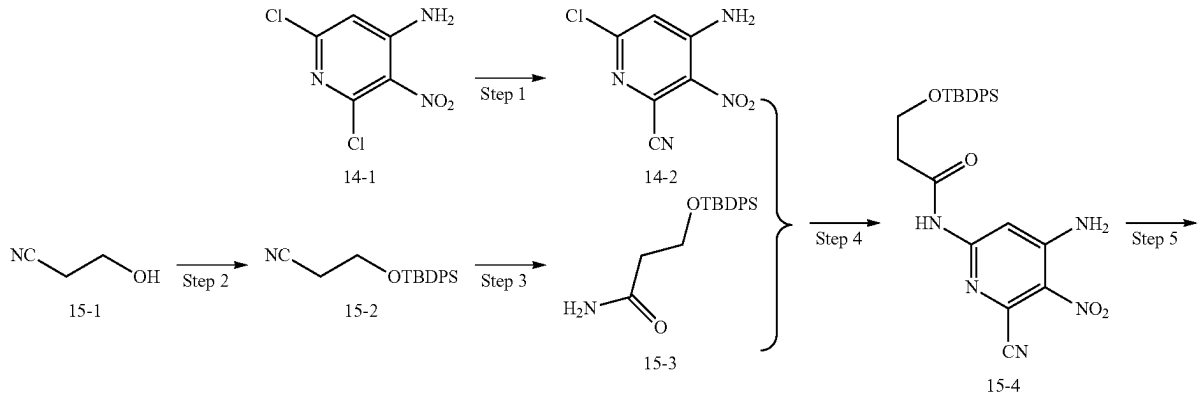


TM1-24

[0418] A mixture of the previously synthesized compound 9-3 (shown in TM1-10; 100 mg, 0.20 mmol), compound 14 (64 mg, 0.60 mmol), DIEA (125 mg, 1.00 mmol), DPPP (16 mg, 0.04 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) in DMF (0.3 mL) was stirred at 120° C. under argon for 16 h. The reaction was detected by LCMS. The resulting mixture was filtered and the filtrated was purified by prep-HPLC (ACN/0.1% FA=5%~60%) to afford TM1-24 (25.96 mg, 76% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=532.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.45 (d, J=5.4 Hz, 1H), 8.40 (s, 1H), 7.72 (d, J=3.2 Hz, 1H), 7.23-7.02 (m, 2H), 5.99 (d, J=11.0 Hz, 1H), 4.63 (s, 1H), 3.95 (d, J=1.9 Hz, 3H), 2.92-2.82 (m, 1H), 2.20-2.00 (m, 4H), 1.65 (s, 3H), 1.02-0.89 (m, 6H), 0.81 (d, J=6.1 Hz, 3H).

Example 1-24

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-(3-hydroxypropanamido)-1H-imidazo[4,5-c]pyridine-4-carboxamide (TM1-25)



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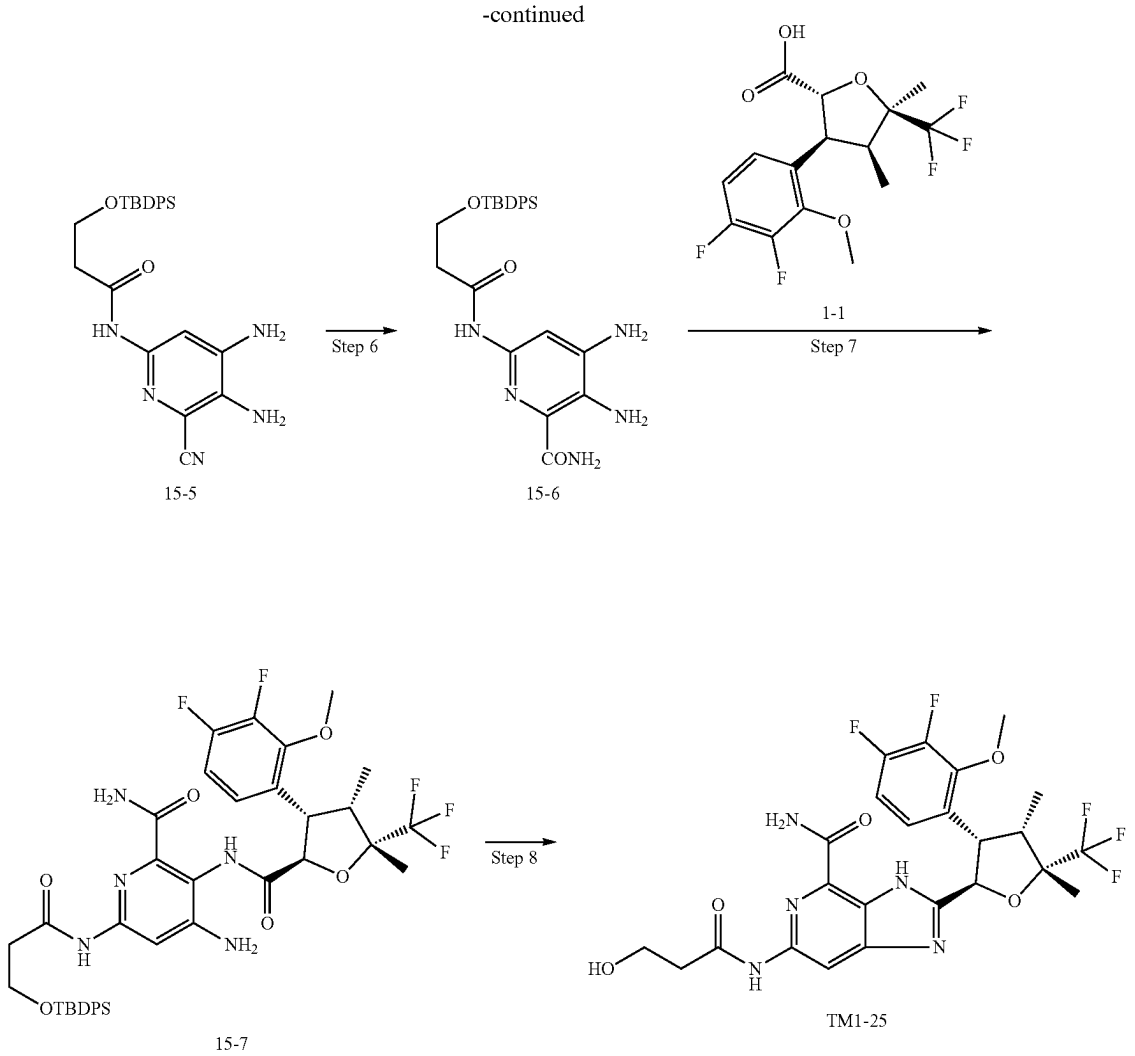
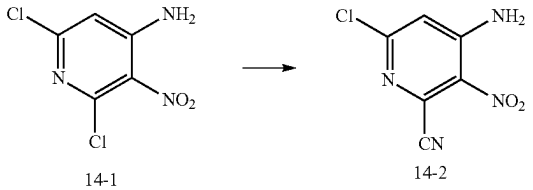
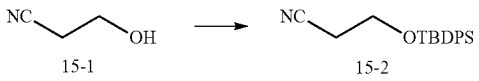


Step 1: General Procedure for Preparation of Intermediate 14-2



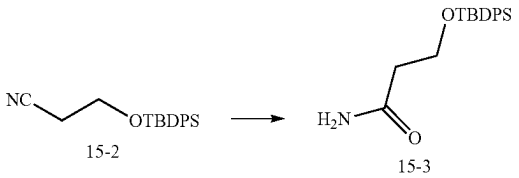
[0419] To a solution of compound 14-1 (10.0 g, 48.1 mmol) in NMP (80 mL) was added CuCN (8.6 g, 96.2 mmol) at r.t., then the whole mixture was stirred at 180° C. for 0.5 h under argon. The reaction was detected by LCMS. The mixture was diluted with EA, filtered and the filtrate washed with brine, dried and concentrated, the residue was purified by silica gel column chromatography (EA/PE=0%~40%) to afford compound 14-2 (6.8 g, 71.58% yield) as a yellow solid. LCMS: m/z=197.1 $[M-H]^-$.

Step 2: General Procedure for Preparation of Intermediate 15-2



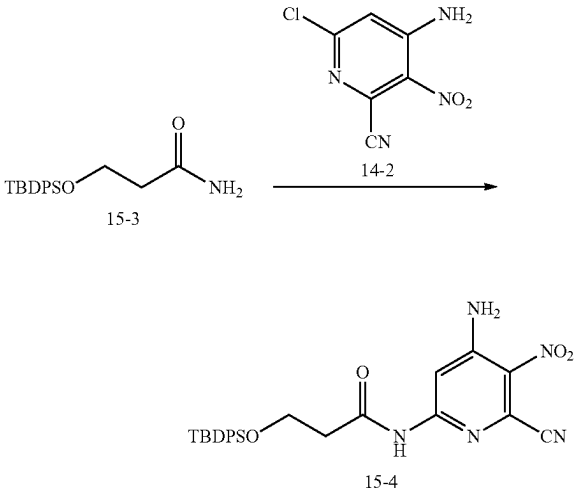
[0420] To a mixture of compound 15-1 (2.5 g, 35.2 mmol), DMAP (0.4 g, 3.5 mmol) and TEA (7.1 g, 70.4 mmol) in THF (75 mL) was added TBDPSCl (9.7 g, 35.2 mmol). Then the whole mixture was stirred at r.t. for 3 h. The reaction was detected by LCMS. The mixture was concentrated and poured into water (300 mL), extracted with EA (200 mL*2). The combined organic layers were washed with brine dried over sodium sulfate and concentrated, the residue was purified by silica gel column chromatography (EA/PE=0%~10%) to afford compound 15-2 (9.5 g, 87.16% yield) as a colorless oil.

Step 3: General Procedure for Preparation of Intermediate 15-3



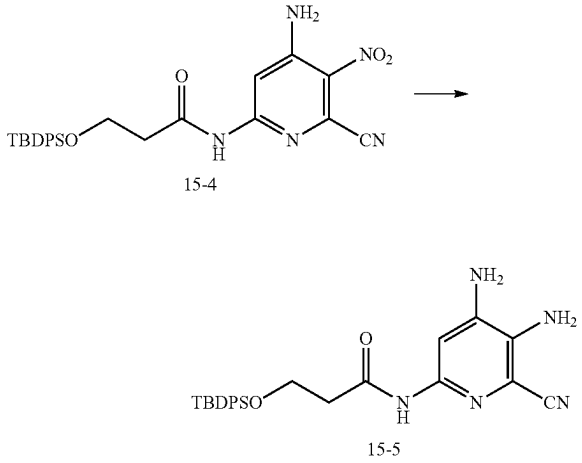
[0421] To a mixture of compound 15-2 (21.0 g, 27.8 mmol) and K_2CO_3 (7.7 g, 55.6 mmol) in DMSO (70 mL) was H_2O_2 (11 mL) at 0° C. Then the whole mixture was stirred at r.t. for 3 h. The reaction was detected by LCMS. The mixture was poured into water (300 mL), extracted with EA (2×30 mL). The combined organic layers were washed with brine dried over sodium sulfate and concentrated, the residue was purified by silica gel column chromatography (MeOH/DCM=0%~5%) to afford compound 15-3 (10.8 g, 49.09% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66-7.61 (m, 4H), 7.44 (d, J=7.1 Hz, 6H), 7.36 (s, 1H), 6.85 (s, 1H), 3.85 (t, J=6.4 Hz, 2H), 2.35 (t, J=6.4 Hz, 2H), 0.98 (s, 9H).

Step 4: General Procedure for Preparation of Intermediate 15-4



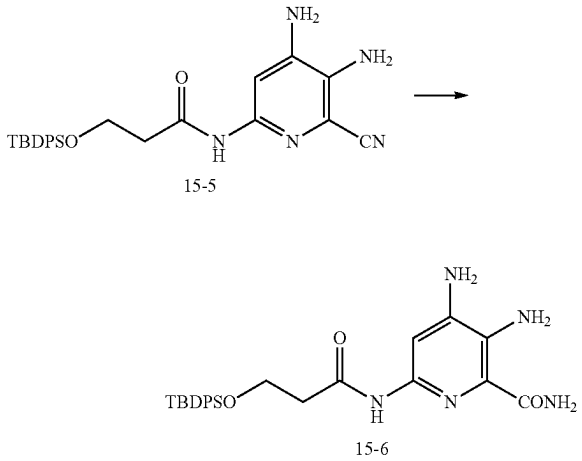
[0422] A mixture of compound 15-3 (2.0 g, 10.1 mmol), compound 14-2 (3.2 g, 10.1 mmol), Cs_2CO_3 (3.6 g, 11.1 mmol), XantPhos (810 mg, 1.4 mmol) and $Pd(OAc)_2$ (227 mg, 1.0 mmol) in Dioxane (120 mL) was stirred at 115° C. under argon for 16 h. The reaction was detected by LCMS. The mixture was filtered and washed with EA. Then the filtrate was concentrated and the residue was purified by silica gel column chromatography (EA/PE=0%~40%) to afford compound 15-4 (0.4 g, 8.16% yield) as a yellow solid. LCMS: m/z=490.1 $[M+H]^+$.

Step 5: General Procedure for Preparation of Intermediate 15-5



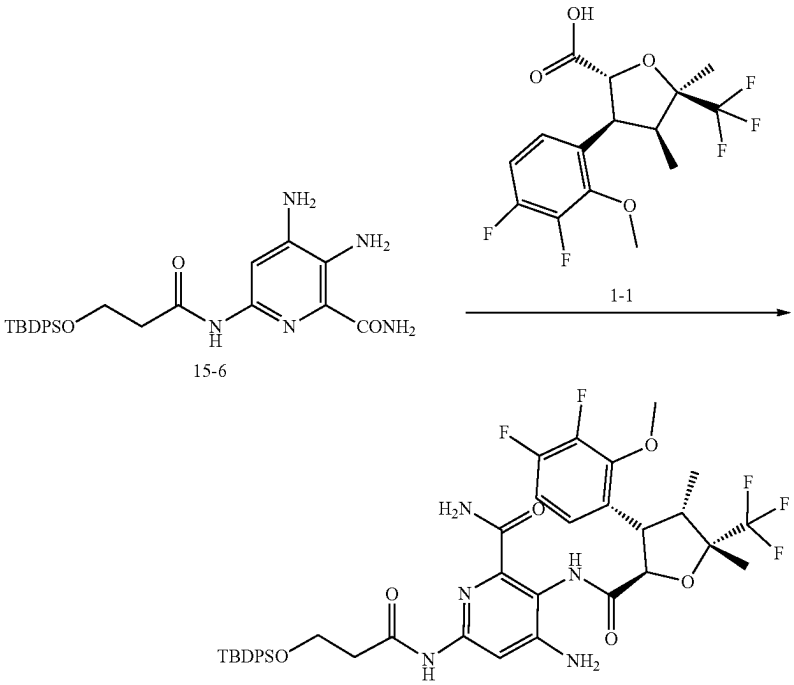
[0423] To a mixture of compound 15-4 (410 mg, 0.84 mmol) in EA (20 mL) was added Pd/C (10%, 80 mg). Then the mixture was stirred at r.t. under H2 atmosphere for 16 h. The reaction was detected by LCMS. The mixture was filtered and washed with EA, the filtrate was concentrated to afford compound 15-5 (360 mg, 93.75% yield) as a white solid. LCMS: m/z=460.1 $[M+H]^+$.

Step 6: General Procedure for Preparation of Intermediate 15-6



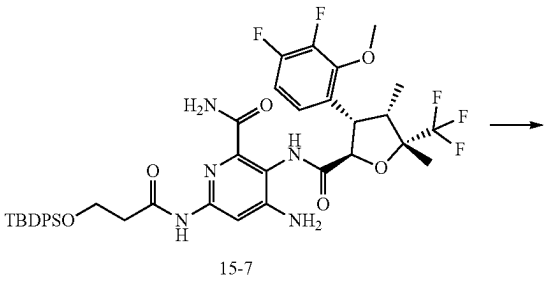
[0424] To a mixture of compound 15-5 (50 mg, 0.11 mmol) and K_2CO_3 (30 mg, 0.22 mmol) in DMSO (1 mL) was added H_2O_2 (50 mg) at 0° C. Then the whole mixture was stirred at r.t. for 3 h. The reaction was detected by LCMS. The mixture was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~70%) to afford compound 15-6 (46 mg, 88.46% yield) as a white solid. LCMS: m/z=478.2 $[M+H]^+$.

Step 7: General Procedure for Preparation of Intermediate 15-7



[0425] To a mixture of compound 15-6 (34 mg, 0.071 mmol), compound 1-1 (25 mg, 0.071 mmol) and NMI (23 mg, 0.284 mmol) in ACN (2 mL) was added TCFH (40 mg, 0.142 mmol) at r.t., then the whole mixture was stirred at r.t for 16 h. The reaction was detected by LCMS. The mixture was diluted with EA, washed with brine, dried and concentrated to afford compound 15-7 (58 mg, 100% yield) as a brown solid. LCMS: m/z=814.1 $[M+H]^+$.

Step 8: General Procedure for Preparation of Compound TM1-25



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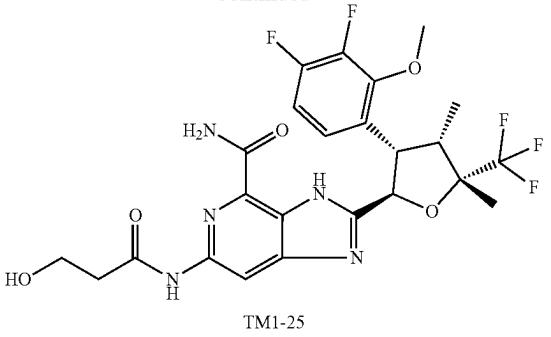
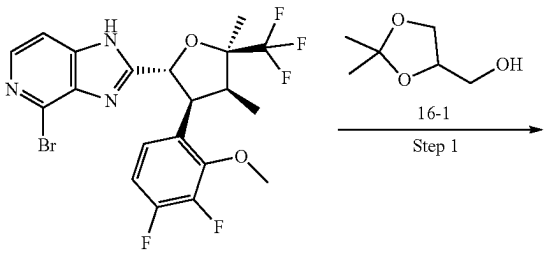


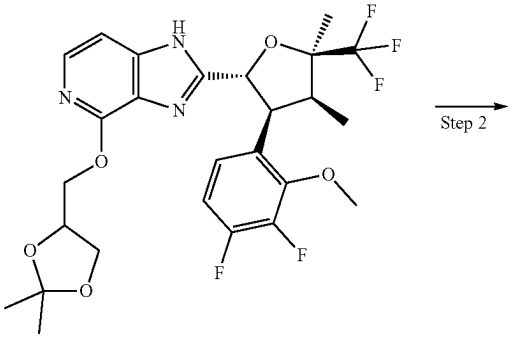
[0426] A solution of compound 15-7 (58 mg, 0.071 mmol) in AcOH (2 mL) was stirred at 80° C. for 16 h. The reaction was detected by LCMS. The mixture was concentrated under reduced pressure, diluted with EA, washed with aqueous $NaHCO_3$ and brine, dried and concentrated, the residue was purified by silica gel column chromatography (MeOH/DCM=0%~10%), then prep-HPLC (ACN/0.1% FA=5%~60%) to afford TM1-25 (9.30 mg, 23.43% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=558.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 10.29 (s, 1H), 8.38 (s, 1H), 7.91 (d, J=7.8 Hz, 2H), 7.11 (d, J=4.4 Hz, 2H), 5.87 (d, J=10.9 Hz, 1H), 4.71 (s, 2H), 3.96 (d, J=1.7 Hz, 3H), 3.72 (t, J=6.1 Hz, 2H), 2.89 (t, J=7.4 Hz, 1H), 2.55 (t, J=6.2 Hz, 2H), 1.66 (s, 3H), 0.79 (d, J=6.0 Hz, 3H).

Example 1-25

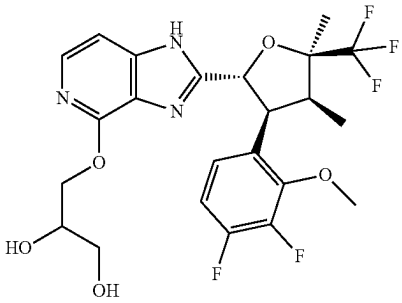
(±)-3-((2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-yl)oxy)propane-1,2-diol (TM1-26)



9-3

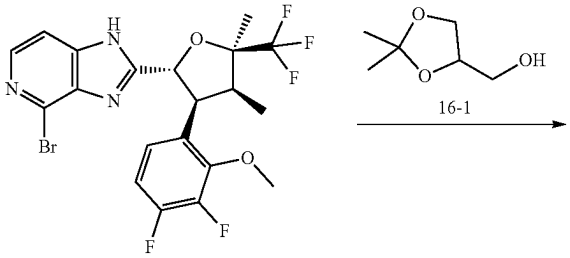


16-2



TM1-26

Step 1: General Procedure for Preparation of Intermediate 16-2



9-3

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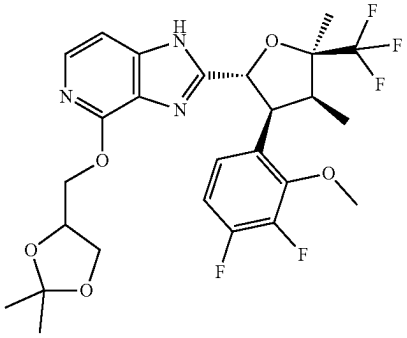
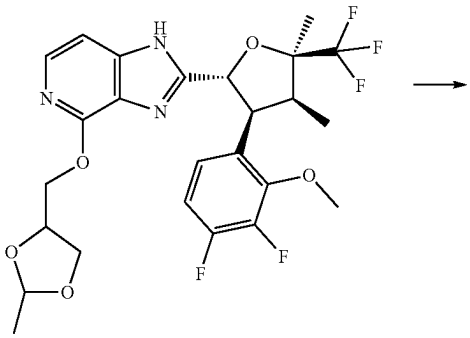


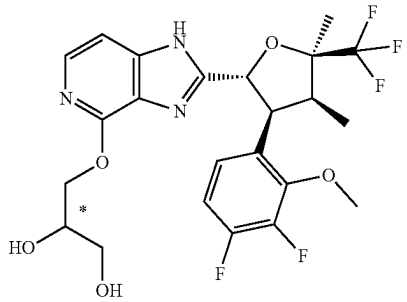
16-2

[0427] To a solution of NaH (60%, 72 mg, 1.78 mmol) in 1,4-dioxane (3 mL) was added (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (235 mg, 1.78 mmol) at 0° C. under N2, then the previously synthesized compound 9-3 (shown in TM1-10; 300 mg, 0.59 mmol) was added to the mixture at 0° C. The reaction mixture was stirred at 100° C. for 16 h. The reaction was diluted with water (20 mL), extracted with EA (20 mL). The combined organic phase washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified through preparative liquid chromatography (0.1% FA in H_2O/ACN=5%~95%) to afford compound 16-2 (110 mg, 33% yield) as a white solid. LCMS: m/z=558.2 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-26 (±)



16-2



TM1-26

[0428] The compound 16-2 (110 mg, 0.20 mmol) was added to HCl in EtOH (2M, 3 mL), and the reaction mixture

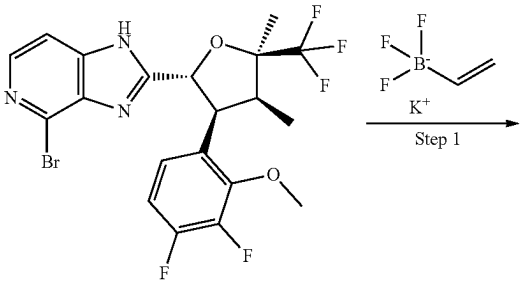
was stirred at r.t. for 2 h. The reaction was concentrated and purified by prep-HPLC and SFC to afford compound TM1-26a (2.28 mg, 2.23% yield, 90.57% purity at 214 nm) as a white solid, and TM1-26b (11.68 mg, 11.44% yield, 93.98% purity at 214 nm) as a white solid.

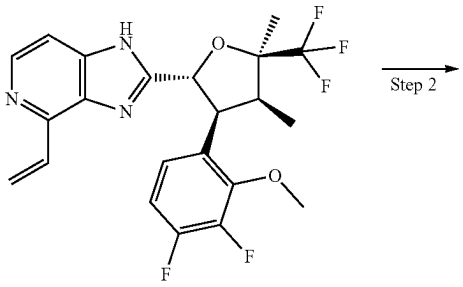
[0429] TM1-26a. LCMS: Rt=9.091 min, m/z=518.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 7.78 (d, J=5.6 Hz, 1H), 7.10 (d, J=7.8 Hz, 3H), 5.69 (d, J=11.2 Hz, 1H), 5.30 (s, 1H), 4.66 (d, J=100.9 Hz, 3H), 3.98 (s, 3H), 3.67 (s, 4H), 2.93-2.86 (m, 1H), 1.65 (s, 3H), 0.79 (d, J=6.5 Hz, 3H).

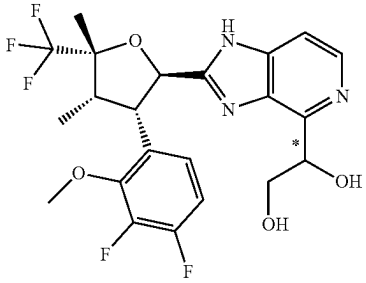
[0430] TM1-26b. LCMS: Rt=9.181 min, m/z=518.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 7.79 (d, J=5.7 Hz, 1H), 7.11 (s, 3H), 5.70 (d, J=11.4 Hz, 1H), 4.93 (s, 1H), 4.65 (s, 1H), 4.59-4.18 (m, 3H), 3.98 (d, J=1.9 Hz, 3H), 3.86 (s, 1H), 3.45 (s, 2H), 2.95-2.81 (m, 1H), 1.65 (s, 3H), 0.79 (d, J=6.1 Hz, 3H).

Example 1-26

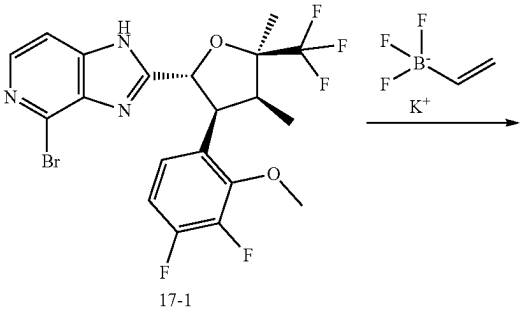
1-(2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4-yl)ethane-1,2-diol (TM1-27)

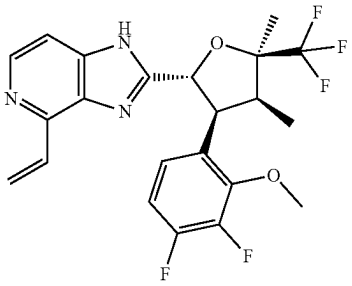






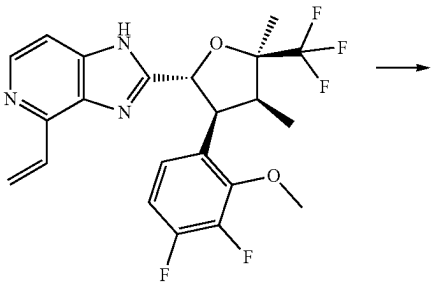
Step 1: General Procedure for Preparation of Intermediate 17-2





[0431] A mixture of compound 17-1 (200 mg, 0.40 mmol), potassium trifluoro(vinyl)borate (107 mg, 0.80 mmol), TEA (162 mg, 1.60 mmol) and Pd(dppf)Cl_2 (45 mg, 0.06 mmol) in IPA (10 mL) was stirred at 85° C. under argon for 16 h. The reaction was detected by LCMS. Then the mixture was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~70%) to afford compound 17-2 (75 mg, 43.60% yield) as a yellow solid. LCMS: m/z=454.1 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-27



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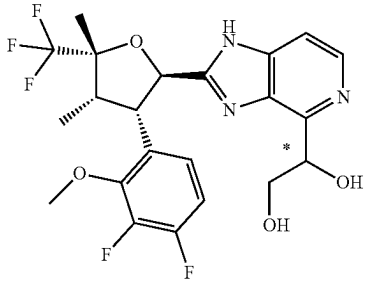


TM1-27

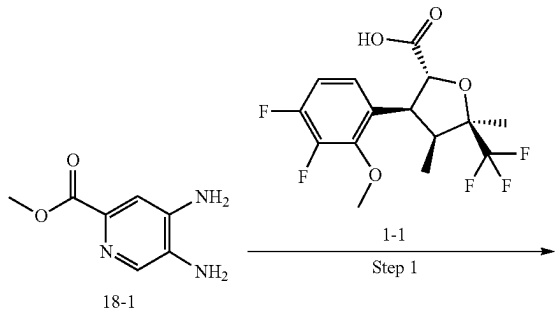
[0432] To a solution of compound 17-2 (40 mg, 0.088 mmol) in Acetone (0.5 mL) was added dropwise of a solution of MgSO4 (5 mg, 0.022 mmol) and $KMnO_4$ (14 mg, 0.088 mmol) in water (0.5 mL) at 0° C. Then the mixture was stirred at 0° C. for 5 h. The reaction was detected by LCMS. And the mixture was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~70%) to afford the isomer TM1-27a (1.57 mg, 3.67% yield, 100% purity at 214 nm) as a white solid and the isomer TM1-27b (2.33 mg, 5.41% yield, 100% purity at 214 nm) as a white solid.

[0433] TM1-27a. LCMS: Rt=8.164 min, m/z=488.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 8.20 (s, 1H), 7.47 (d, J=5.5 Hz, 1H), 7.09 (d, J=9.6 Hz, 2H), 5.82 (s, 1H), 4.83 (d, J=157.6 Hz, 4H), 3.97 (s, 3H), 3.82 (dd, J=10.8, 4.2 Hz, 1H), 3.71 (dd, J=10.8, 6.2 Hz, 1H), 2.93-2.84 (m, 1H), 1.65 (s, 3H), 0.80 (d, J=6.1 Hz, 3H).

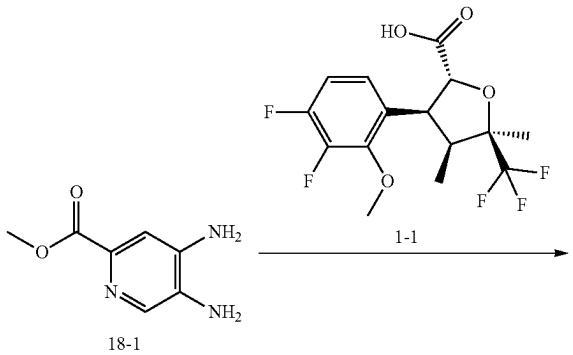
[0434] TM1-27b. LCMS: Rt=8.055 min, m/z=488.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.19 (s, 1H), 7.47 (d, J=5.6 Hz, 1H), 7.10 (d, J=9.3 Hz, 2H), 5.82 (d, J=10.0 Hz, 1H), 4.83 (d, J=160.0 Hz, 3H), 3.97 (d, J=1.6 Hz, 3H), 3.80 (dd, J=10.9, 4.4 Hz, 1H), 3.70 (dd, J=10.9, 6.2 Hz, 1H), 2.89 (t, J=7.5 Hz, 1H), 1.65 (s, 3H), 0.80 (d, J=6.4 Hz, 3H).

Example 1-27

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-6-carboxamide (TM1-28)



Step 1: General Procedure for Preparation of Intermediate 18-2



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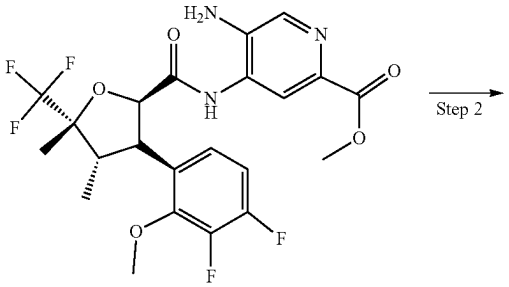
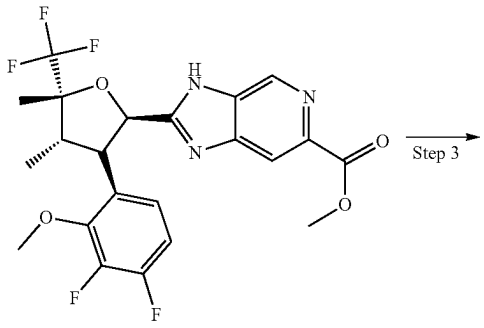
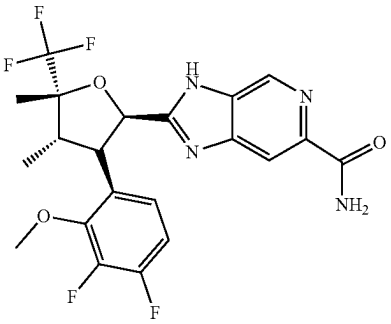


18-2

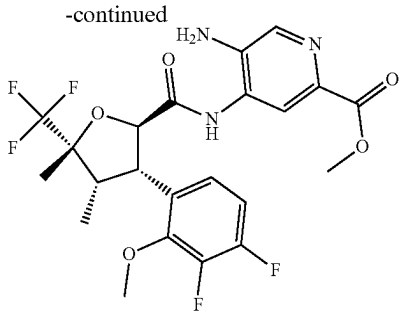


18-3



TM1-28

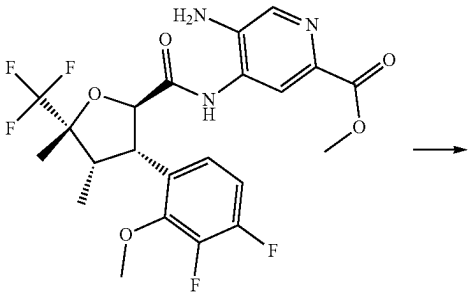
-continued



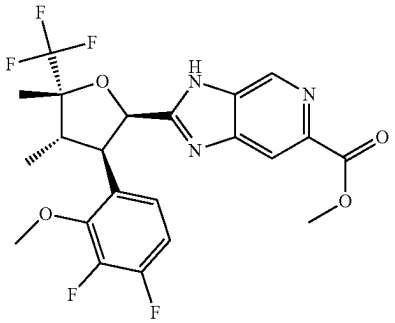
18-2

[0435] HATU (570 mg, 1.50 mmol) and DIPEA (0.26 mL, 2.50 mmol) were added to a solution of compound 18-1 (400 mg, 1.20 mmol) and compound 1-1 (354 mg, 1.00 mmol) in anhydrous dichloromethane (15 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was concentrated, then extracted with water (15 mL) and saturated saltwater solution (15 mL) before drying over anhydrous Na_2SO_4. Later the organic solution was concentrated and purified by column chromatography (PE/EA=10%~50%) to get the desired product 18-2 (212 mg, 42% yield) as a white solid. LCMS: m/z=504.24 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 18-3



18-2

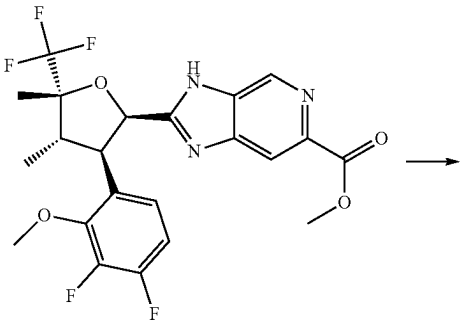


18-3

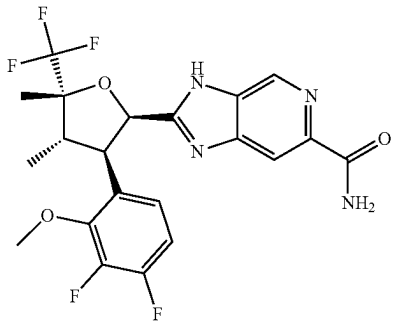
[0436] The compound 18-2 (100 mg, 0.20 mmol) was added to AcOH (5 mL) in a single-neck flask before the reaction mixture was stirred at 120° C. for 2 h. The resulting mixture was concentrated, diluted with $NaHCO_3$ solution (5 mL) to keep the pH value at 8-9 and the crude product was obtained before filtration. Later the product was purified by column chromatography (PE/EA=100/50) to get the pure product 18-3 (60 mg, 67% yield), as a pale yellow solid.

[0437] LCMS: m/z=486.24 $[M+H]^+$.

Step 3: General Procedure for Preparation of Compound TM1-28



18-3

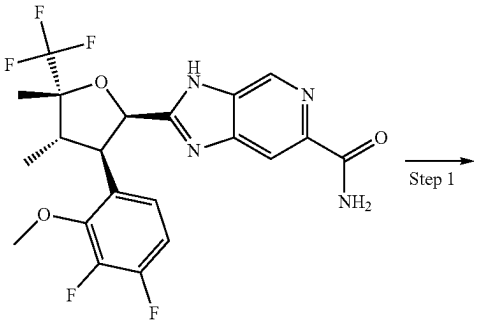


TM1-28

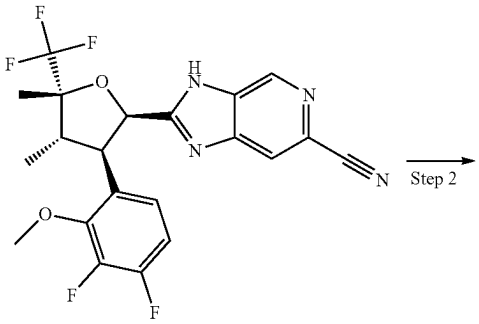
[0438] The compound 18-3 (60 mg, 0.12 mmol) was added to a solution of NH_3 in THF (0.4 M, 10 mL), and the reaction mixture was stirred at for 12 h under reflux condition. The resulting mixture was then diluted with water (5 mL) and extracted with EA (10 mL). The combined organic layers were washed with saturated salt water solution (10 mL), dried over anhydrous Na_2SO_4, concentrated and purified by preparative thin-layer chromatography to get the final product TM1-28 (39.01 mg, 67% yield, 95.96% purity at 214 nm), as a white solid. LCMS: m/z=471.25 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 11.67 (s, 1H), 8.90 (s, 1H), 8.42 (s, 1H), 8.09 (d, J=4.4 Hz, 1H), 7.09 (s, 1H), 6.85 (d, J=8.4 Hz, 1H), 5.91 (d, J=4.6 Hz, 1H), 5.78 (d, J=10.4 Hz, 1H), 4.46-4.37 (m, 1H), 3.98 (d, J=2.5 Hz, 3H), 2.88 (q, J=7.8 Hz, 1H), 1.72 (s, 6H).

Example 1-28

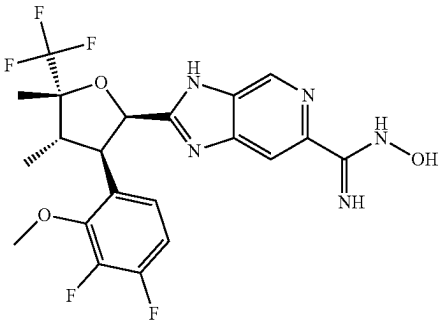
2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-yl)-N-hydroxy-1H-imidazo[4,5-c]pyridine-6-carboximidamide (TM1-29)



TM1-28

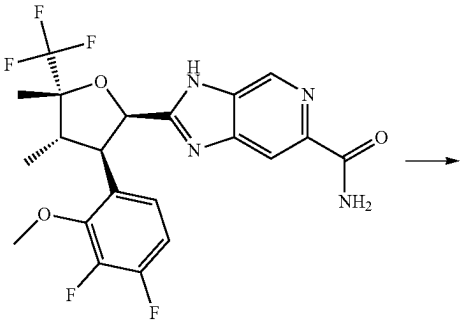


19-1

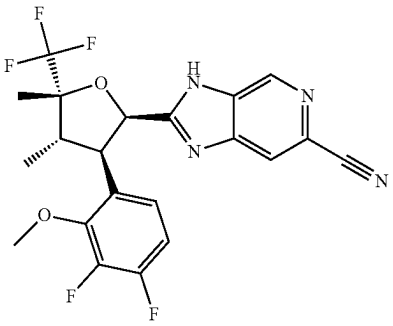


TM1-29

Step 1: General Procedure for Preparation of Intermediate 18-1



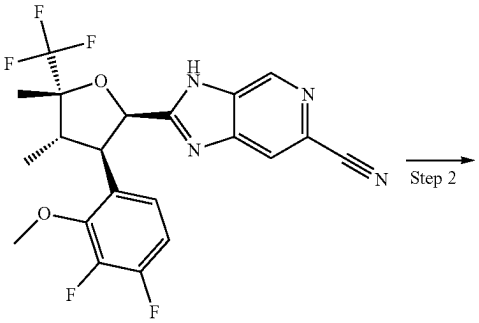
TM1-28



19-1

[0439] The previously synthesized compound TM1-28 (132 mg, 0.35 mmol) was added to a solution of $POCl_3$ (5 mL), and the reaction mixture was stirred at for 12 h under 110° C. The resulting mixture was quenched with ice water (20 mL), then extracted with EA (20 mL). Later, the combined organic layers were washed with saturated saltwater solution (10 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography to get the pure product 19-1 (75 mg, 56% yield), as a pale yellow solid. LCMS: m/z=453.23 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-29



19-1

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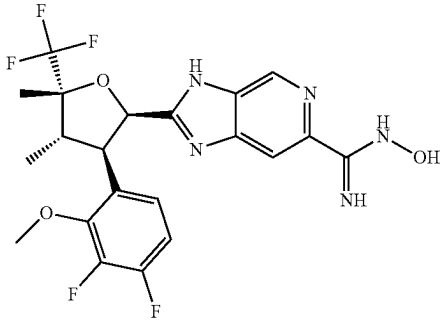
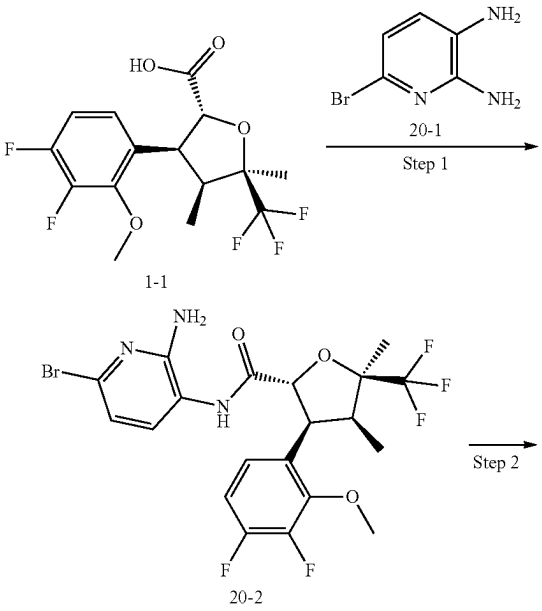


TM1-29

[0440] The compound 19-1 (75 mg, 0.24 mmol) was dissolved with absolute ethanol (5 mL) in a single-neck flask before the addition of hydroxylamine hydrochloride (33 mg, 0.48 mmol) and $NaHCO_3$ (40 mg, 0.48 mmol), and the reaction mixture was stirred at for 12 h under 40° C. Later, the filtrate was obtained, concentrated and purified by column chromatography to get the final product TM1-29 (38 mg, 37% yield, 93.27% purity at 214 nm), as a pale yellow solid. LCMS: m/z=467.32 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 10.33 (s, 1H), b 9.79 (s, 1H), 7.73 (s, 1H), 7.18 (m, 1H), 7.01 (m, 1H), 6.31 (d, J=12.0 Hz, 1H), 5.92 (s, 1H), 4.97 (s, 1H), 3.91 (s, 3H), 3.31-3.25 (m, 2H), 1.47 (s, 3H), 1.14 (s, 3H).

Example 1-29

2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-b]pyridine-5-carboxamide (TM1-30)



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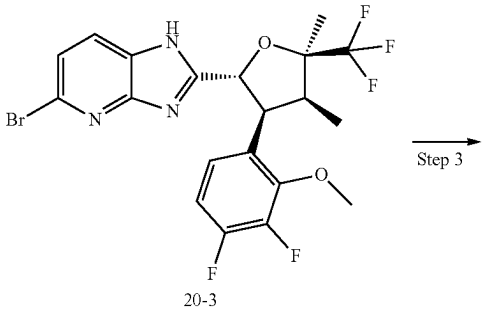
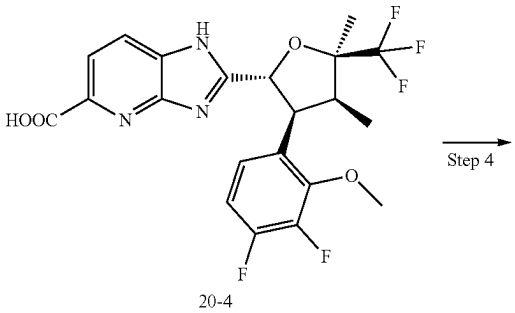
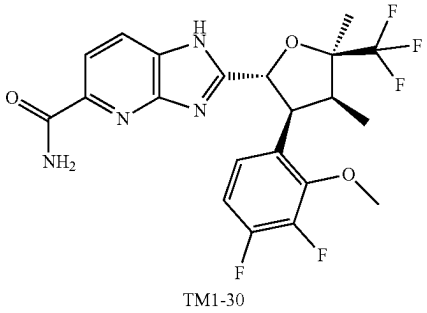


20-3

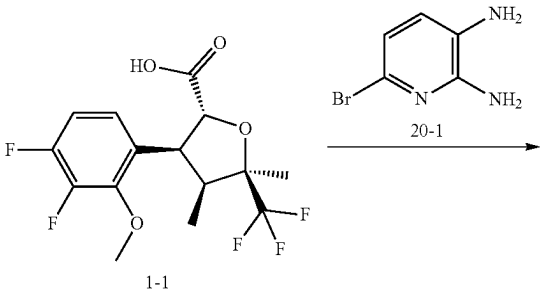


20-4



TM1-30

Step 1: General Procedure for Preparation of Intermediate 20-2



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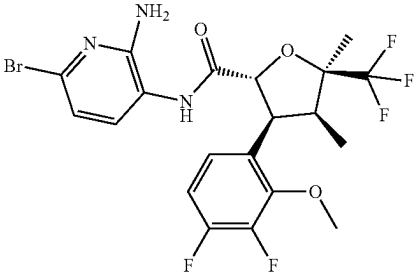
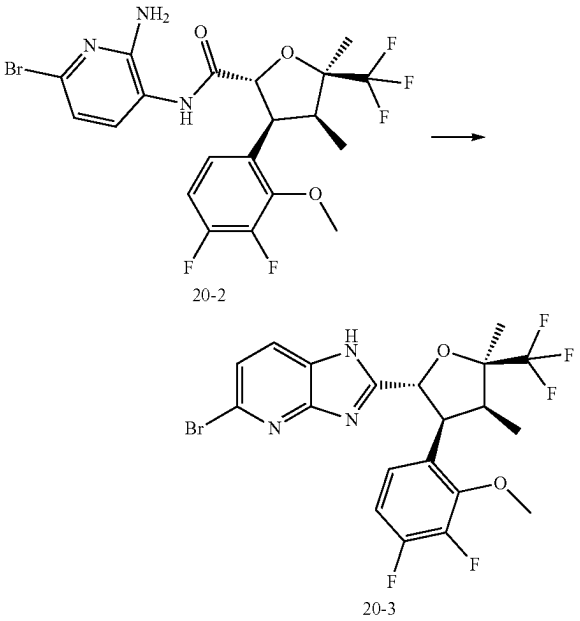


20-2

[0441] NMI (83 mg, 1.02 mmol) and TCFH (286 mg, 1.02 mmol) were added to a solution of compound 1-1 (180 mg, 0.51 mmol) and compound 20-1 (96 mg, 0.51 mmol) in ACN (4 mL), and the reaction mixture was stirred at r.t. for overnight. The resulting mixture was concentrated, diluted with water (20 mL), extracted with EA (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get compound 20-2 (189 mg, 70% yield) as a white solid

[0442] LCMS: m/z=526.0 $[M+H+2]^+$.

Step 2: General Procedure for Preparation of Intermediate 20-3

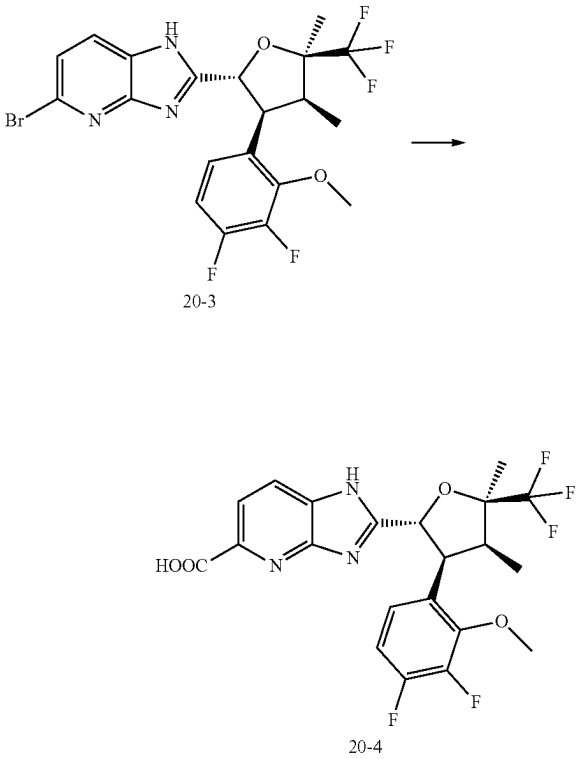


20-2

20-3

[0443] The compound 20-2 (190 mg, 0.36 mmol) was added to AcOH (4 mL), the reaction mixture was stirred at 80° C. for overnight. The resulting mixture was concentrated, diluted with $NaHCO_3$ solution (20 mL), extracted with EA (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product 20-3 (135 mg, 73% yield) as a white solid. LCMS: m/z=507.8 $[M+H+2]^+$.

Step 3: General Procedure for Preparation of Intermediate 20-4

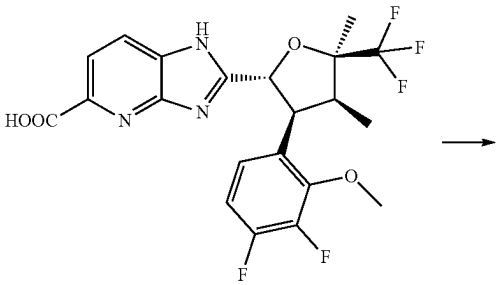


20-3

20-4

[0444] The compound 20-3 (130 mg, 0.26 mmol), DCPP (79 mg, 0.13 mmol), K_2CO_3 (106 mg, 0.77 mmol), and $Pd(OAc)_2$ (12 mg, 0.05 mmol) were added to a solution of DMSO (2.6 mL) and H_2O (0.26 mL), and the reaction mixture was stirred at 100° C. under CO for 16 h. The mixture was diluted with H_2O, filtered, the filtrate was adjusted to pH=3, then extrated with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford compound 20-4 (78 mg, 64% yield) as a white solid. LCMS: m/z=472.1 $[M+H]^+$.

Step 4: General Procedure for Preparation of Compound TM1-30



20-4

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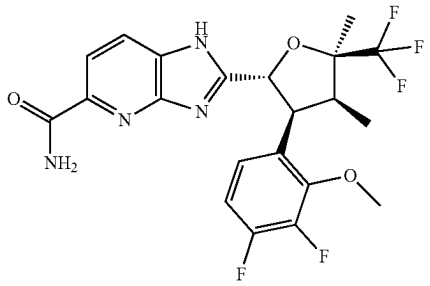
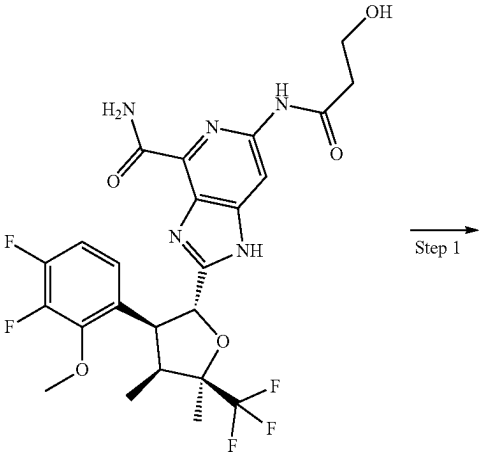


TM1-30

[0445] The compound 20-4 (90 mg, 0.19 mmol), NH_4Cl (24 mg, 0.45 mmol), HATU (85 mg, 0.22 mmol), and DIEA (96 mg, 0.74 mmol) were added to DMF (15 mL). The reaction mixture was stirred rt for 16 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) to get compound TM1-30 (20.46 mg, 22.78% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=471.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.37 (d, J=192.0 Hz, 1H), 8.30-7.40 (m, 4H), 7.32-6.99 (m, 2H), 5.81 (s, 1H), 4.51 (s, 1H), 3.96 (d, J=2.1 Hz, 3H), 2.90 (p, J=7.5 Hz, 1H), 1.67 (s, 3H), 0.81 (d, J=6.4 Hz, 3H).

Example 1-30

6-(3-aminopropanamido)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-4-carboxamide (TM1-31)



TM1-25

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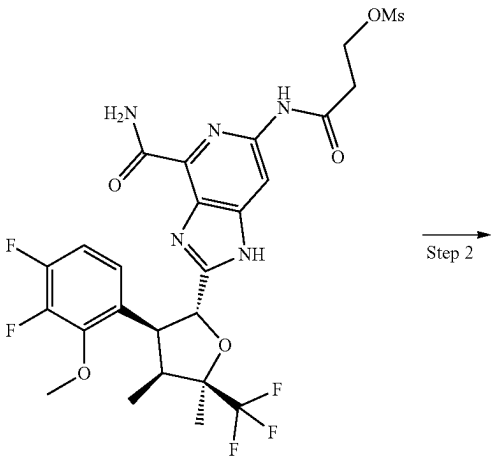
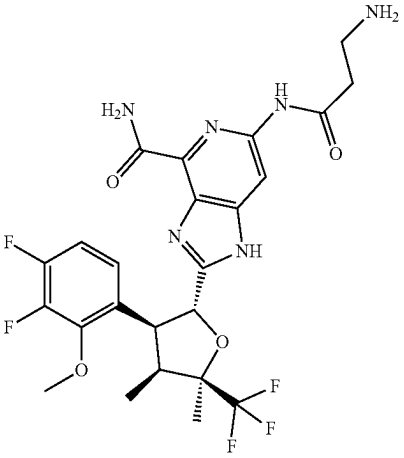
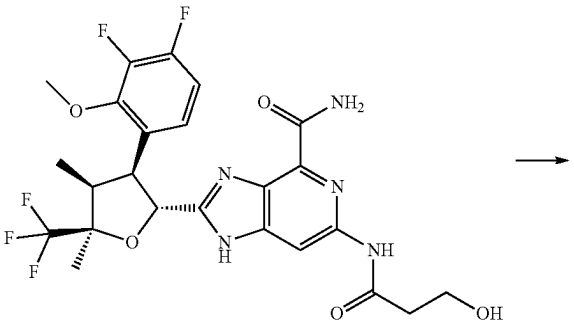


21-1



TM1-31

Step 1: General Procedure for Preparation of Intermediate 21-1



TM1-25

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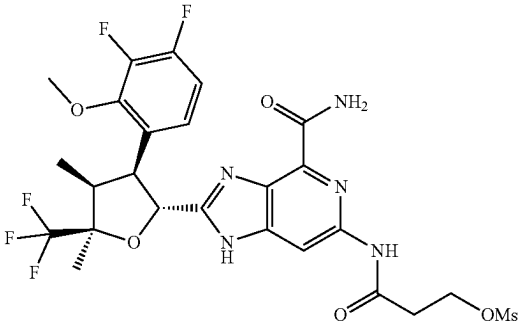
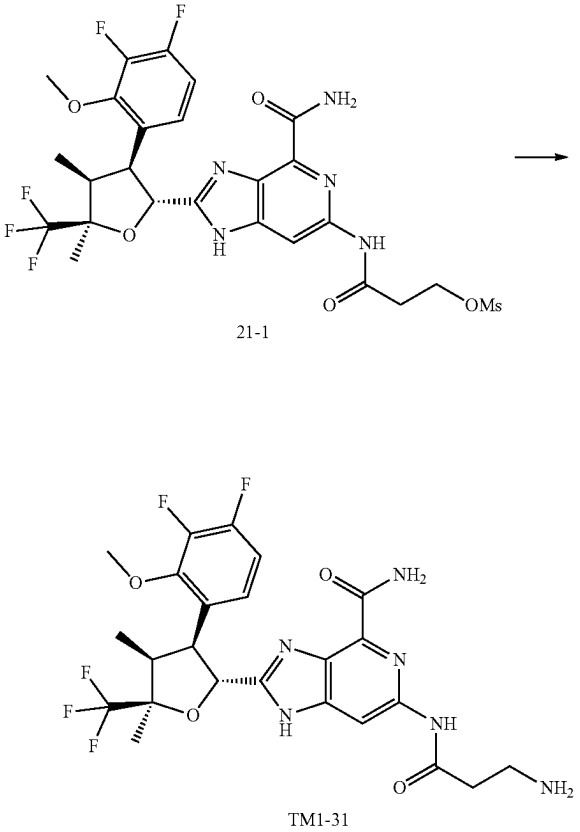


21-1

[0446] To a mixture of TM1-25 (75 mg, 0.13 mmol) and DIEA (110 mg, 0.85 mmol) in DCM (3 mL) was added MsCl (60 mg, 0.52 mmol) at −10° C. under argon. Then the mixture was stirred at 0° C. for 2 h. The reaction was detected by LCMS. The resulting mixture was quenched with H_2O, extracted with DCM, dried and concentrated to afford 21-1 (100 mg, 116.96% yield) as a colorless oil, which was used in next step without further purification. LCMS: m/z=636.6 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-31



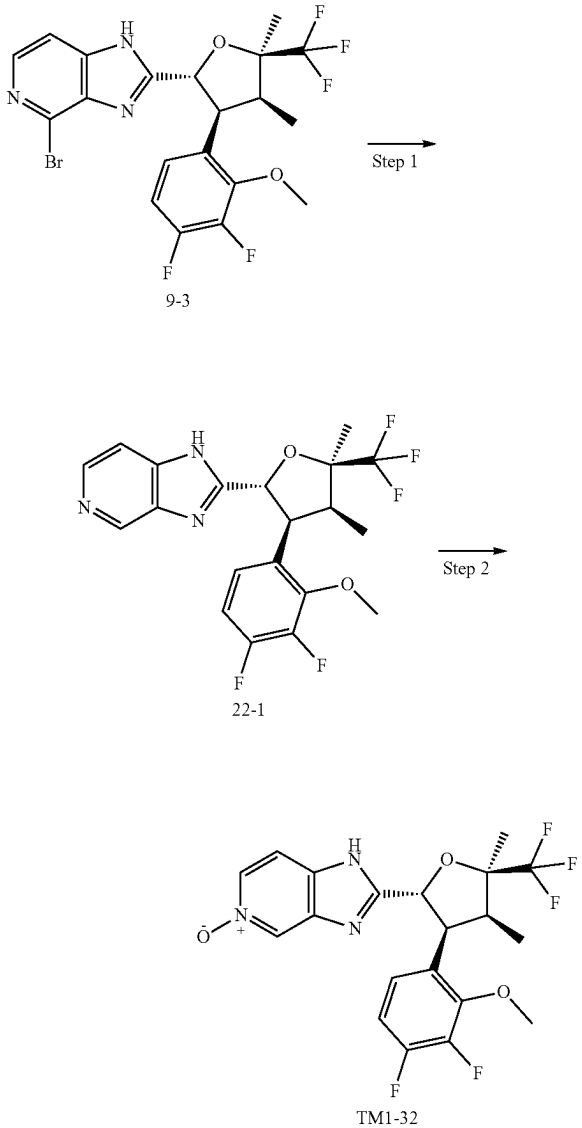
21-1

TM1-31

[0447] A solution of compound 21-1 (100 mg, 0.13 mmol) in 7.0M MeOH/NH_3 (5 mL) was stirred at r.t. for 48 h. The reaction was detected by LCMS. The resulting mixture was concentrated, the residue was purified by silica gel column chromatography (MeOH/DCM=0%~10%), then further purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~60%) to afford TM1-31 (5.75 mg, 6.61% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=557.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.52 (s, 1H), 7.12-7.05 (m, 1H), 6.91 (dd, J=17.0, 9.3 Hz, 1H), 5.81 (d, J=11.1 Hz, 1H), 4.60 (dd, J=11.0, 8.0 Hz, 1H), 3.99 (d, J=2.3 Hz, 3H), 3.00 (dt, J=15.3, 7.0 Hz, 3H), 2.66 (t, J=6.3 Hz, 2H), 1.70 (s, 3H), 0.88 (d, J=5.7 Hz, 3H).

Example 1-31

6-(3-aminopropanamido)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine-4-carboxamide (TM1-32)

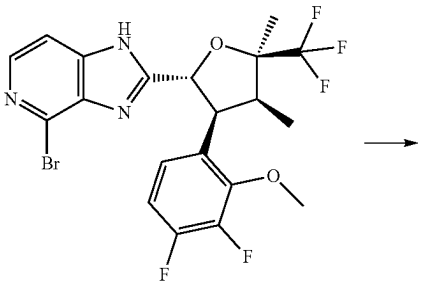


9-3

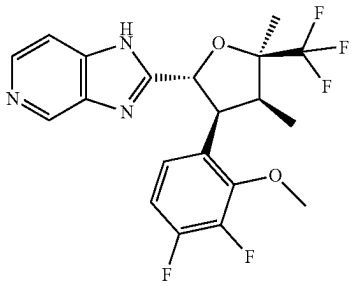
22-1

TM1-32

Step 1: General Procedure for Preparation of Intermediate 22-1



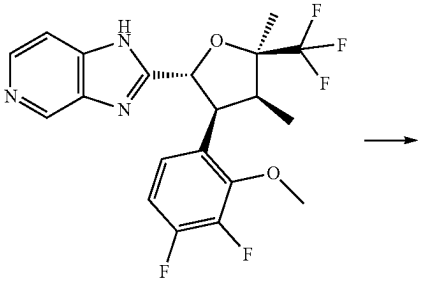
9-3



22-1

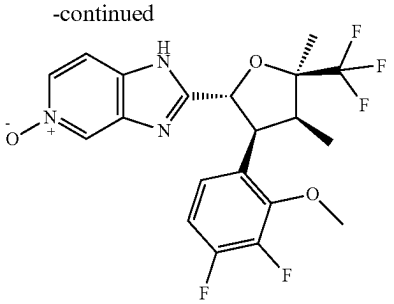
[0448] To a mixture of previously synthesized compound 9-3 (shown in TM1-10; 110 mg, 0.22 mmol) in MeOH (10 mL) was added Pd/C (30 mg) at r.t. The reaction mixture was stirred at r.t. under H2 atmosphere for 2 h. The reaction was detected by LCMS. The resulting mixture was filtered and washed with MeOH, the filtrate was concentrated to afford compound 22-1 (100 mg, 100% yield) as a white solid. LCMS: m/z=428.1 $[M+H]^+$.

Step 2: General Procedure for Preparation of Compound TM1-32



22-1

-continued

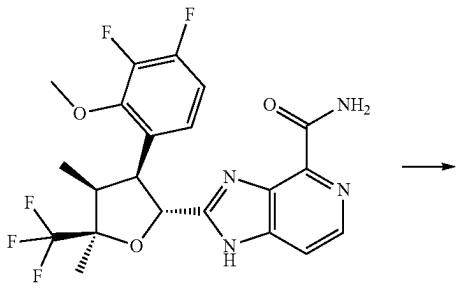


TM1-32

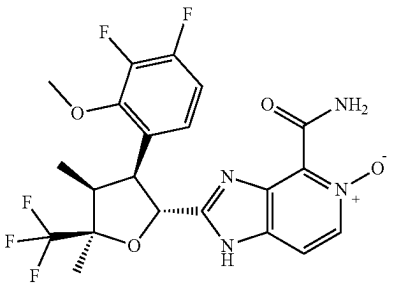
[0449] To a mixture of compound 22-1 (90 mg, 0.21 mmol) in DCM (1 mL), $CHCl_3$ (1 mL) and MeOH (0.2 mL) was added m-CPBA (85%, 85 mg, 0.42 mmol) at r.t. The reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. The mixture was concentrated, the residue was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~50%) to afford TM1-32 (36.08 mg, 38.71% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=444.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.20 (d, J=58.3 Hz, 1H), 8.59 (d, J=1.1 Hz, 1H), 7.99 (dd, J=7.0, 1.7 Hz, 1H), 7.55 (d, J=7.0 Hz, 1H), 7.18-7.06 (m, 2H), 5.75 (d, J=11.1 Hz, 1H), 4.46 (dd, J=11.0, 7.6 Hz, 1H), 3.95 (d, J=2.2 Hz, 3H), 2.87 (p, J=7.4 Hz, 1H), 1.64 (s, 3H), 0.79 (d, J=6.1 Hz, 3H).

Example 1-32

4-carbamoyl-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridine 5-oxide (TM1-33)



TM1-10



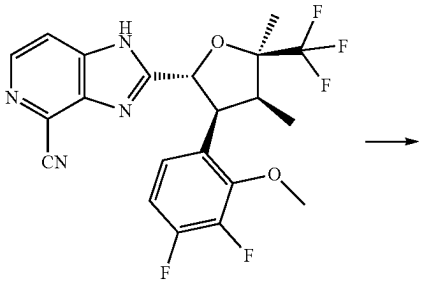
TM1-33

[0450] To a solution of TM1-10 (30 mg, 0.06 mmol) in DCM (0.4 mL) was added m-CPBA (11 mg, 0.06 mmol).

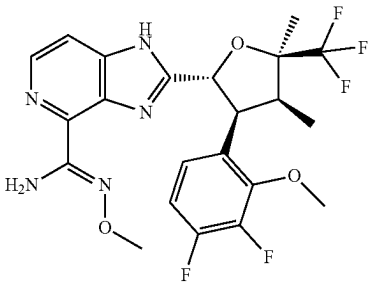
The reaction mixture was stirred at 40° C. for 16 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by HPLC to afford the target compound TM1-33 (3.22 mg, 10.38% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=487.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.25 (s, 1H), 7.78 (s, 1H), 7.05 (s, 1H), 6.92 (s, 1H), 5.89 (d, J=8.0 Hz, 1H), 4.66 (s, 1H), 4.00 (s, 3H), 2.93 (s, 1H), 1.65 (d, J=24.1 Hz, 3H), 0.88 (s, 3H).

Example 1-33

(Z)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-N'-methoxy-1H-imidazo[4,5-c]pyridine-4-carboximidamide (TM1-34)



10-1



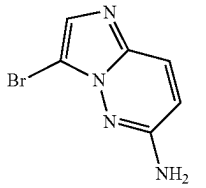
TM1-34

[0451] The previously synthesized compound 10-1 (shown in TM1-11; 30 mg, 0.06 mmol), NH_2OMe-HCl (11 mg, 0.13 mmol), DIEA (17 mg, 0.13 mmol), 2-mercaptoacetic acid (7 mg, 0.09 mmol) were added to IPA (2 mL), the reaction mixture was stirred at 80° C. under N2 for 16 h. The reaction mixture was diluted with water, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by HPLC to afford compound TM1-34 (8.65 mg, 26% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=500.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.31 (d, J=5.5 Hz, 1H), 7.70 (d, J=5.5 Hz, 1H), 7.14 (t, J=5.3 Hz, 2H), 6.29 (s, 2H), 6.09 (d, J=10.8 Hz, 1H), 4.80-4.64 (m, 1H), 4.06-3.94 (m, 6H), 2.99-2.86 (m, 1H), 1.65 (s, 3H), 0.82 (d, J=6.1 Hz, 3H).

General Scheme Provides a Process of the Synthesis for Preparing TM2-1-TM2-16

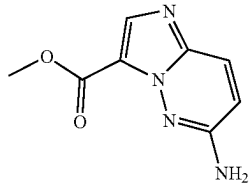
Example 2-1

6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxamido)imidazo[1,2-b]pyridazine-3-carboxamide (TM2-1)



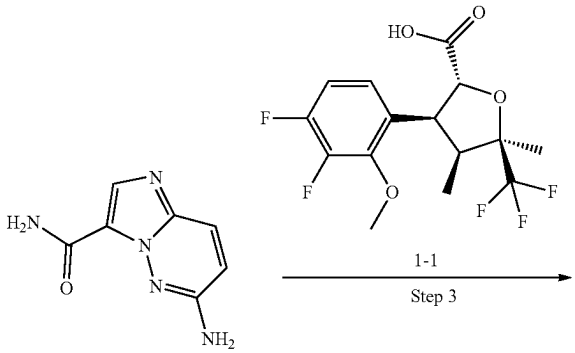
Step 1

23-1



Step 2

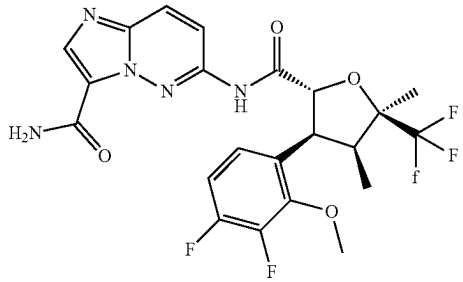
23-2



1-1

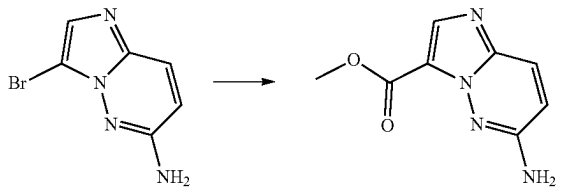
Step 3

23-3



TM2-1

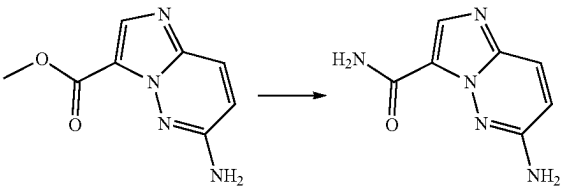
Step 1: General Procedure for Preparation of Intermediate 23-2



23-1 23-2

[0452] To a solution of the starting material 23-1 (2.0 g, 9.4 mmol) in MeOH/ACN=1:1 (30 mL) was added Pd(dppf) Cl_2 (760 mg, 0.94 mmol) and TEA (2.8 g, 28.2 mmol). The reaction mixture was degassed and purged with CO (4 MPa) and stirring was continued at 100° C. for 48 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/MeOH=0%~8%) to afford 23-2 (2.0 g, 27.7% yield) as a yellow solid. LCMS: m/z=193.0 $[M+H]^+$.

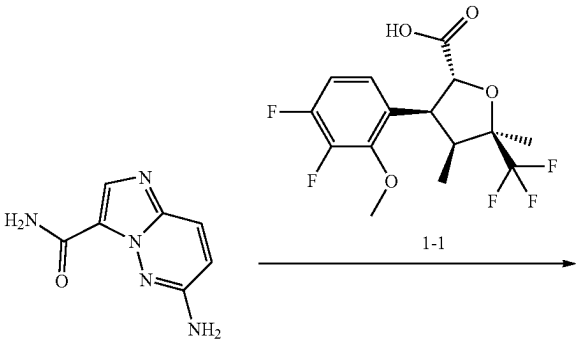
Step 2: General Procedure for Preparation of Intermediate 23-3



23-2 23-3

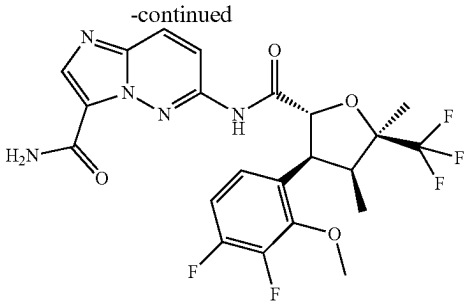
[0453] To a solution of dissolve intermediate 23-2 (100 mg, 0.52 mmol) in NH_3-MeOH (4 mL) and stir the mixture at r.t. for 48 h. The reaction was detected by LCMS. Filter the reaction solution and recover the filter cake to obtain the intermediate 23-3 (46 mg, 44.91% yield) as a yellow solid, which can be directly used for the next step without further purification. LCMS: m/z=178.0 $[M+H]^+$.

Step 3: General Procedure for Preparation of TM2-1



23-3

-continued

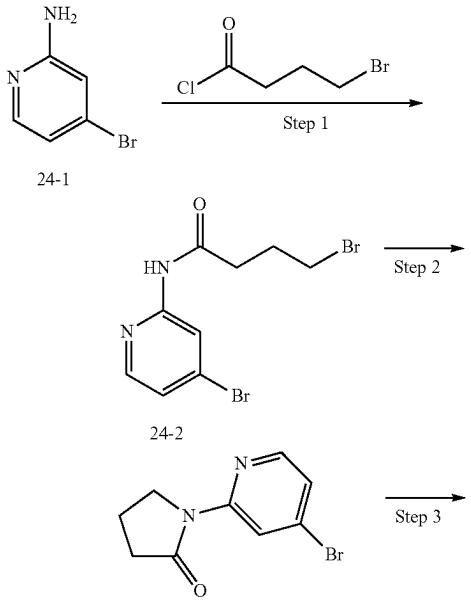


TM2-1

[0454] To a stirred solution of dissolve intermediate 23-3 (36.0 mg, 0.20 mmol) and the compound 1-1 (70.8 mg, 0.20 mmol) in DMF:ACN=1:1 (1 mL), add TCFH (168.0 mg, 0.60 mmol) and NMI (49.2 mg, 0.40 mmol) sequentially at r.t., and stir the mixture at r.t. for 16 h. The reaction was detected by LCMS. The mixture was concentrated, the residue was purified by prep-HPLC (0.1% Ammonium hydroxide in H_2O/ACN=5%~95%) to afford the target compound TM2-1 (4.28 mg, 13.51% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=514.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.34 (s, 1H), 8.28 (d, J=9.9 Hz, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.90 (d, J=9.9 Hz, 1H), 7.23-7.12 (m, 2H), 5.19 (d, J=10.0 Hz, 1H), 4.38-4.28 (m, 1H), 3.96 (d, J=2.1 Hz, 3H), 2.85-2.76 (m, 1H), 1.61 (s, 3H), 0.75 (d, J=6.1 Hz, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ −69.20 (s), −71.03--71.16 (m), −73.28 (s), −137.85--138.28 (m), −154.86 (s), −154.92 (s).

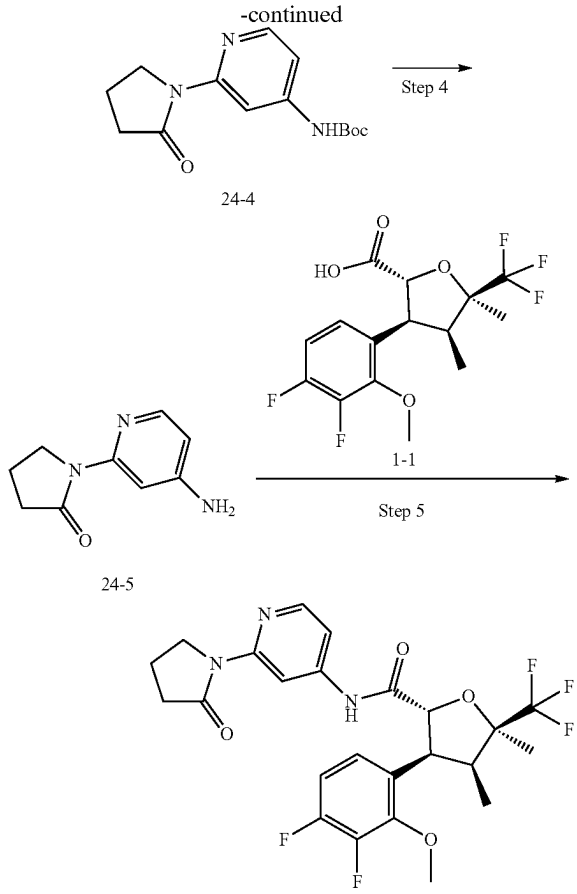
Example 2-2

(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(2-(2-oxopyrrolidin-1-yl)pyridin-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-2)

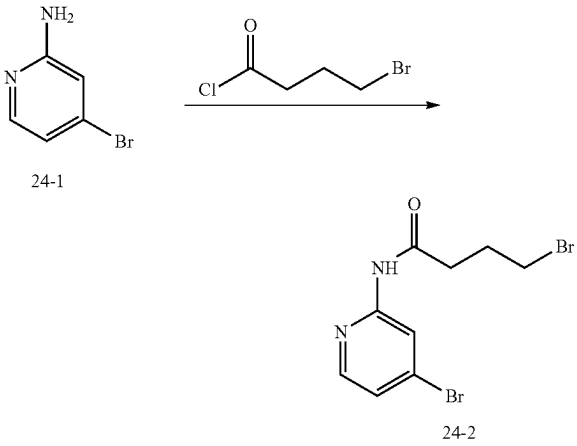


24-1 24-2 24-3

-continued

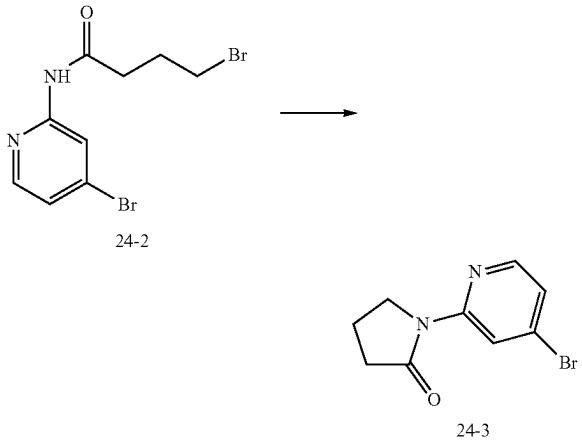


Step 1: General Procedure for Preparation of Intermediate 24-2



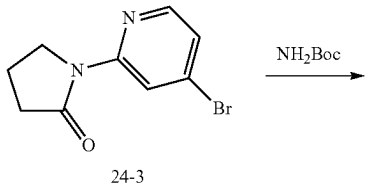
[0455] To a solution of the starting material 24-1 (4.5 g, 26.2 mmol) in ACN (45 mL) was added Pyridine (3.1 g, 39.3 mmol) at −15° C. for 30 min. To this reaction was added 4-bromobutanoyl chloride (5.81 g, 31.4 mmol). The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The reaction mixture was added EA (20 mL). The resulting mixture was extracted with EA (3×30 mL). The organic phases were combined, washed with NaCl (20 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (20%~100%) to give the desired product intermediate 24-2 (6.2 g, 67.0% yield) as a yellow solid. LCMS: m/z=322.8 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 24-3



[0456] To a solution of intermediate 24-2 (2.0 g, 6.2 mmol) in DMF (20 mL) was added Cs_2CO_3 (2.2 g, 6.8 mmol) at 25° C. The reaction mixture was degassed and purged with N2 and stirring was continued at 65° C. for 16 h. LCMS detected the desired product. The reaction mixture was added EA (20 mL). The resulting mixture was extracted with EA (3×30 mL). The organic phases were combined, washed with NaCl (20 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (20%~100%) to give the desired product intermediate 24-3 (1.0 g, 67.2% yield) as a white solid. LCMS: m/z=243.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J=1.6 Hz, 1H), 8.16 (d, J=5.4 Hz, 1H), 7.19 (dd, J=5.4, 1.7 Hz, 1H), 4.11-4.05 (m, 2H), 2.67 (dd, J=10.3, 5.9 Hz, 2H), 2.18-2.10 (m, 2H).

Step 3: General Procedure for Preparation of Intermediate 24-4



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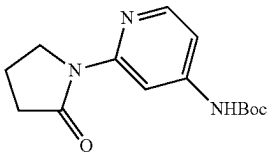
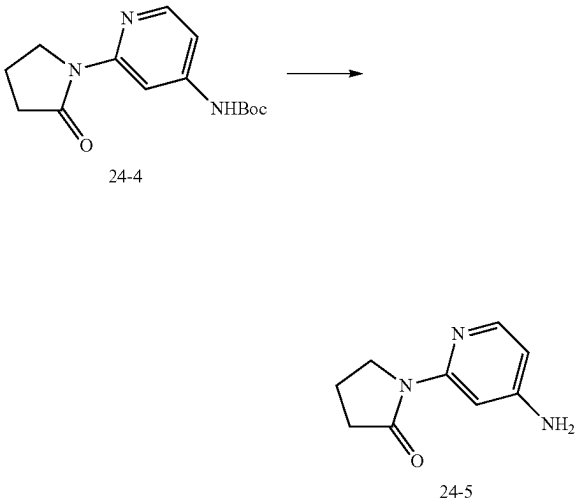


24-4

[0457] To a solution of intermediate 24-3 (800 mg, 3.33 mmol) in dioxane (8 mL) was added NH_2Boc (584.9 mg, 5.0 mmol), $BrettPhosPdG_4$ (153.3 mg, 0.16 mmol) and Cs_2CO_3 (1082 mg, 3.33 mmol) at r.t. The reaction mixture was degassed and purged with N2 and stirring was continued at 100° C. for 12 h. LCMS detected the desired product. The reaction mixture was added EA (20 mL). The resulting mixture was extracted with EA (3×30 mL). The organic phases were combined, washed with NaCl (20 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (20%~40%) to give the desired product intermediate 24-4 (1 g, 24.6% yield) as a yellow solid. LCMS: m/z=278.1$[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 24-5

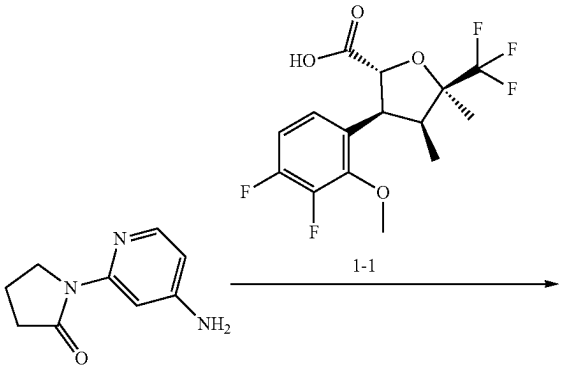


24-4

24-5

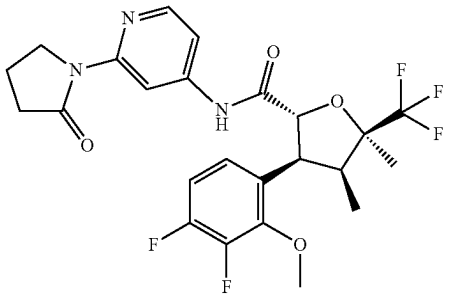
[0458] To a solution of intermediate 24-4 (200 mg, 0.72 mmol) in 4 N HCl in dioxane (2 mL). The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 2 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get the crude product intermediate 24-5 (150 mg, 117% yield) as a white solid. LCMS: m/z=178.1 $[M+H]^+$

Step 5: General Procedure for Preparation of TM2-2



24-5

1-1

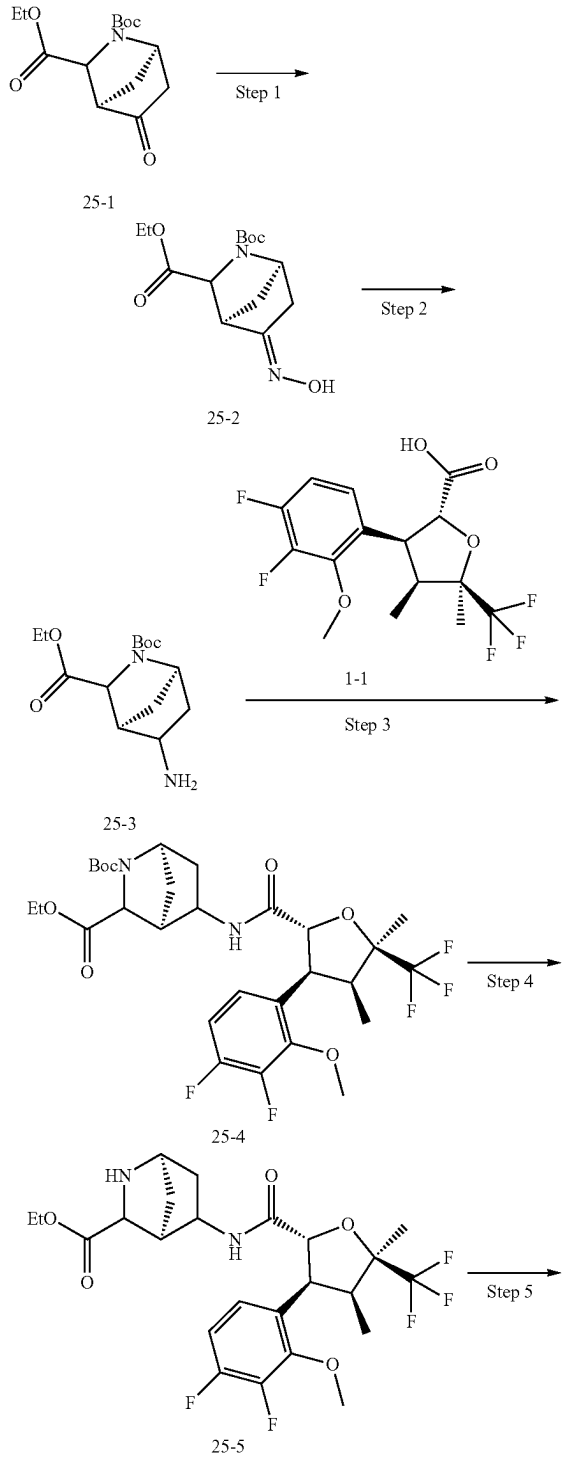


TM2-2

[0459] To a solution of intermediate 24-5 (50 mg, 0.28 mmol) in dry DMF (2 mL) was added compound 1-1 (100 mg, 0.28 mmol), NMI (92 mg, 1.12 mmol). To this reaction was added TCFH (157 mg, 0.56 mmol). The reaction mixture was degassed and purged with N2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product TM2-2 (37.05 mg, 25.8% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=514.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) b 10.73 (s, 1H), 8.49 (d, J=1.7 Hz, 1H), 8.23 (d, J=5.6 Hz, 1H), 7.52 (dd, J=5.7, 1.9 Hz, 1H), 7.22-7.08 (m, 2H), 5.09 (d, J=10.3 Hz, 1H), 4.29-4.22 (m, 1H), 3.99-3.92 (m, 5H), 2.77 (t, J=7.5 Hz, 1H), 2.56 (t, J=8.1 Hz, 2H), 2.07-1.97 (m, 2H), 1.59 (s, 3H), 0.72 (d, J=5.7 Hz, 3H).

Example 2-3

(1R,4S)-5-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-carboxamido)-2-azabicyclo[2.2.1] heptane-3-carboxamide (TM2-3)



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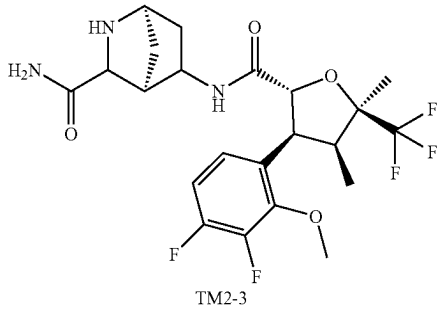
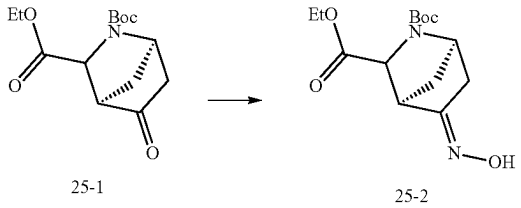
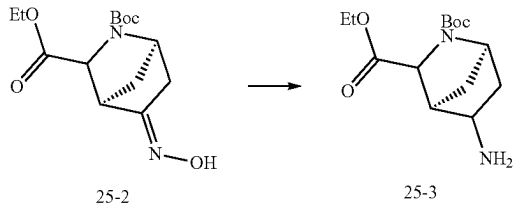


Step 1: General Procedure for Preparation of Intermediate 25-2



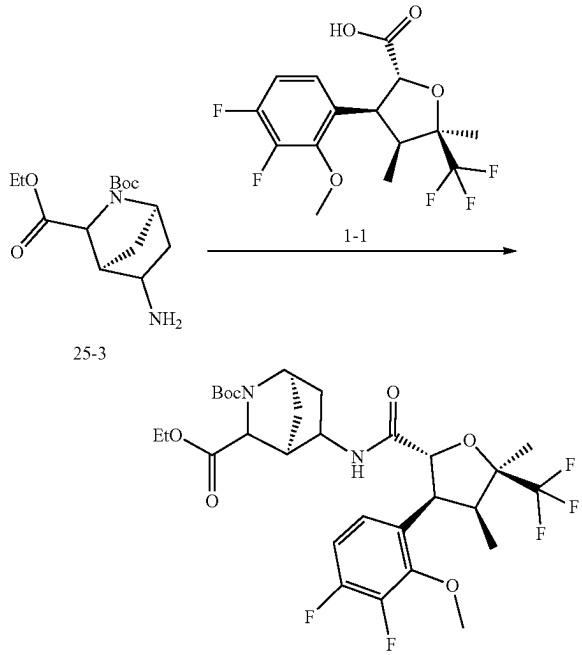
[0460] To a solution of the starting material 25-1 (280 mg, 0.98 mmol) and HO—NH_{2n}Cl (81 mg, 1.17 mmol) in EtOH (5 mL) was added a solution of AcONa (96 mg, 1.17 mmol) in H_2O (3.4 mL), and the reaction mixture was stirred at 80° C. for 2 h. The resulting mixture was concentrated, diluted with water, adjusted to PH=5 with 1M HCl, extracted with EA (10 mL), concentrated to get the desired product intermediate 25-2 (242 mg, 82% yield) as an oil. LCMS: m/z=243.1 $[M+H-56]^+$.

Step 2: General Procedure for Preparation of Intermediate 25-3



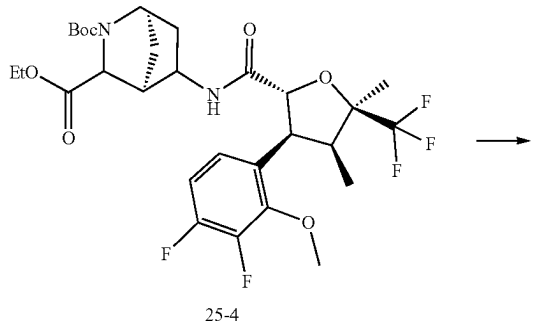
[0461] To a solution of intermediate 25-2 (240 mg, 0.81 mmol) in EtOH (5 mL) and NH_3—H_2O (0.5 mL) was added Raney Ni (20 mg), and the reaction mixture was stirred at r.t. under H2 atmosphere for 16 h. The resulting mixture was filtered, concentrated to get the desired product intermediate 25-3 (184 mg, 88% yield) as an oil. LCMS: m/z=285.11 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 25-4



[0462] NMI (115 mg, 1.41 mmol) and TCFH (396 mg, 1.41 mmol) were added to a solution of the intermediate 25-3 (200 mg, 0.70 mmol) and intermediate 1-1 (249 mg, 0.70 mmol) in ACN (5 mL), and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with H_2O (20 mL). The resulting mixture was extracted with EA (3×20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) and was performed to get the desired product intermediate 25-4 (200 mg, 45% yield) as a white solid. LCMS: m/z=521.2 $[M+H-100]^+$.

Step 4: General Procedure for Preparation of Intermediate 25-5



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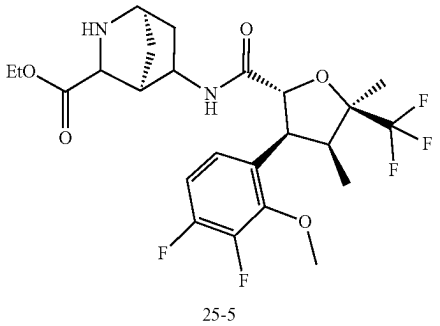
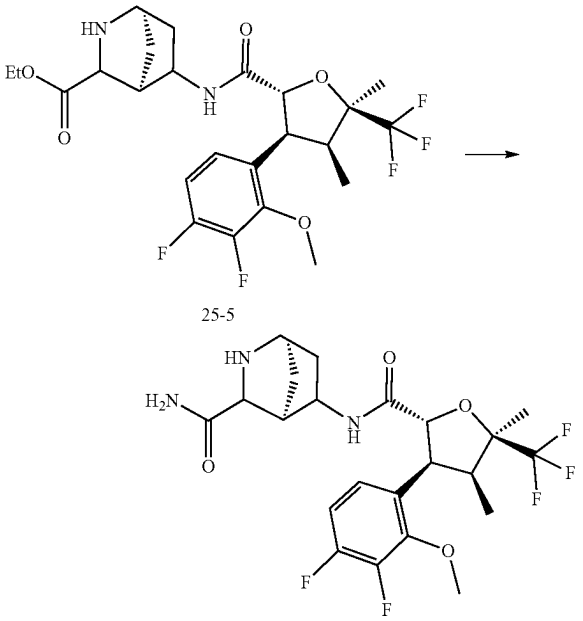


[0463] Intermediate 25-4 (80 mg, 0.13 mmol) was added to a solution of HCl in 1,4-dioxane (4M, 0.5 mL), and the reaction mixture was stirred at r.t. for 2 h. The resulting mixture was concentrated to get intermediate 25-5 (64 mg, 95% yield) as an oil. LCMS: m/z=521.3 $[M+H]^+$.

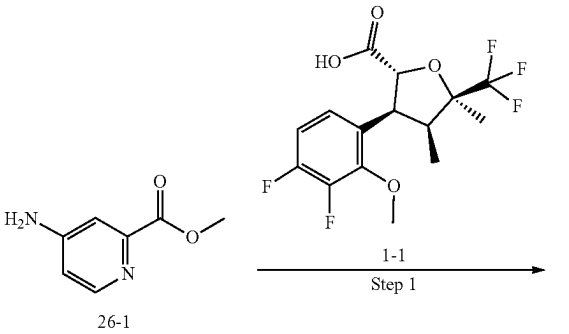
Step 5: General Procedure for Preparation of TM2-3

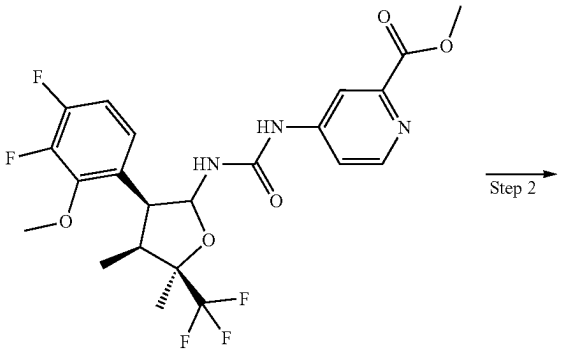


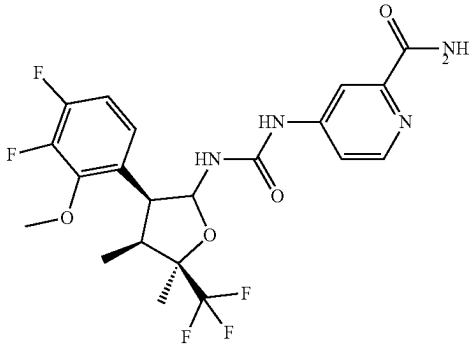
[0464] Intermediate 25-5 (80 mg, 0.15 mmol was added to a solution of NH_3 in MeOH (7M, 1.5 mL), and the reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. The resulting mixture was concentrated and purified by HPLC to get TM2-3 (25.19 mg, 33% yield, 97.03% purity at 214 nm) as a white solid. LCMS: m/z=492.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (t, J=6.0 Hz, 1H), 7.38-7.00 (m, 4H), 4.87 (d, J=10.4 Hz, 1H), 4.19-3.87 (m, 5H), 3.30 (s, 1H), 2.98 (s, 1H), 2.74-2.64 (m, 1H), 2.38 (s, 1H), 1.98-1.69 (m, 1H), 1.54 (s, 3H), 1.38-1.09 (m, 3H), 0.70 (d, J=7.6 Hz, 3H).

Example 2-4

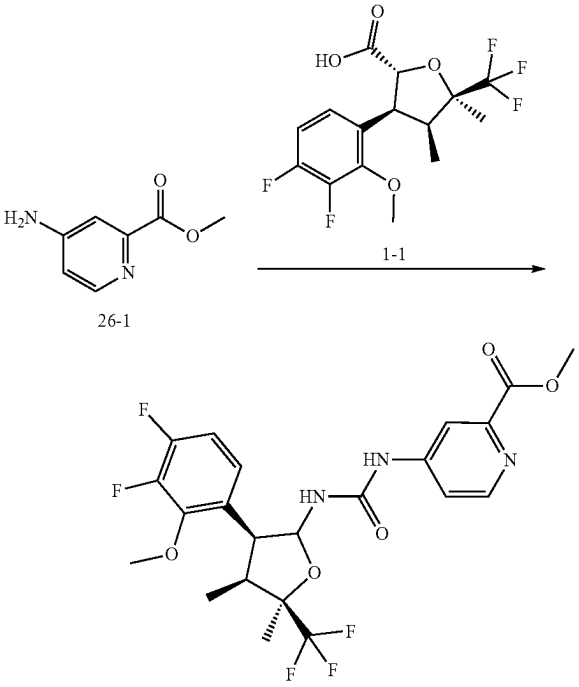
4-(3-((3S,4 S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)ureido)picolinamide (TM2-4)





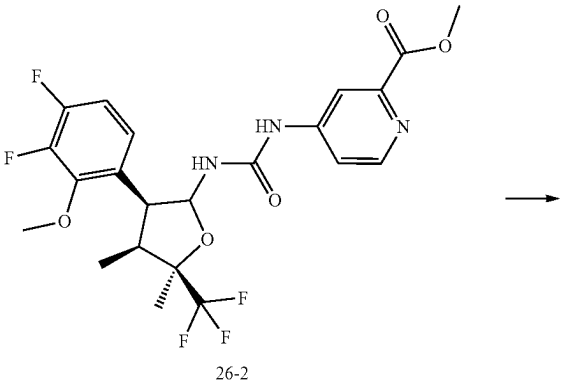


Step 1: General Procedure for Preparation of Intermediate 26-2



[0465] The intermediate 2 (200 mg, 0.56 mmol), DPPA (190 mg, 0.68 mmol), and TEA (80 mg, 0.68 mmol), to ultra-dry TOL (5 mL) at 95° C. and stir for 30 minutes. Then, add intermediate 26-1 (92 mg, 0.62 mmol) under nitrogen protection and stir the mixture for 2 h at 115° C. The reaction was detected by LCMS. This reaction solution washed with saturated sodium carbonate, extracted with EA, concentrated and dried, and the crude product was purified through a silica gel column to get the intermediate 26-2 (200 mg, 49.26% yield) as a yellow oil. LCMS: m/z=504.1 $[M+H]^+$.

Step 1: General Procedure for Preparation of TM2-4



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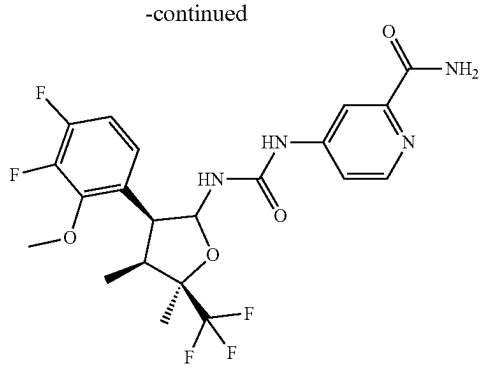
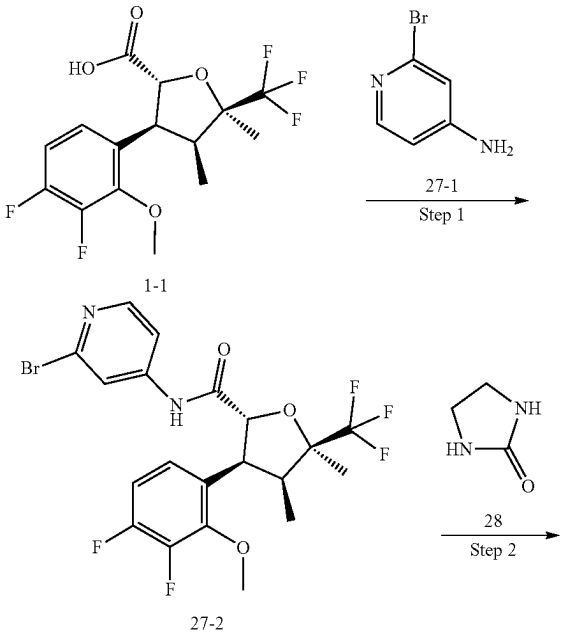


TM2-4

[0466] Dissolve intermediate 26-2 (180 mg, 0.36 mmol) in NH_3-MeOH (10 mL) and stir the mixture at r.t. for 48 h. The reaction was detected by LCMS. Filter the reaction solution and recover the filter cake to obtain the target product, which can be directly used for the next step without further purification to the target compound TM2-4 (15.42 mg, 8.38% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=489.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.37 (d, J=5.6 Hz, 1H), 8.06-7.99 (m, 2H), 7.59 (dt, J=24.8, 6.1 Hz, 3H), 7.18 (dd, J=17.9, 8.8 Hz, 1H), 6.99-6.90 (m, 1H), 6.11 (t, J=9.9 Hz, 1H), 3.99 (d, J=2.0 Hz, 4H), 2.73-2.67 (m, 1H), 1.56 (s, 3H), 0.71 (d, J=6.1 Hz, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ −73.93 (s), −138.21 (s), −138.25 (d, J=21.1 Hz), −154.97 (s), −155.03 (s).

Example 2-5

(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(2-(2-oxoimidazolidin-1-yl)pyridin-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-5)



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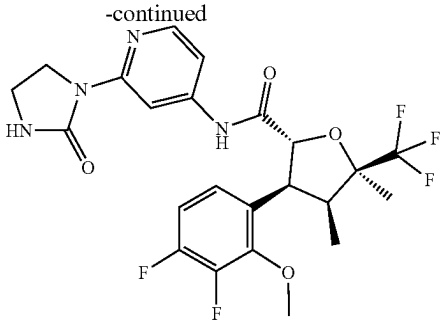
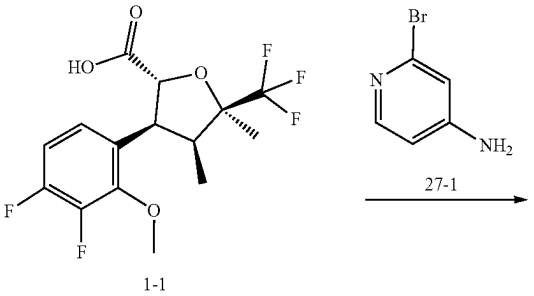
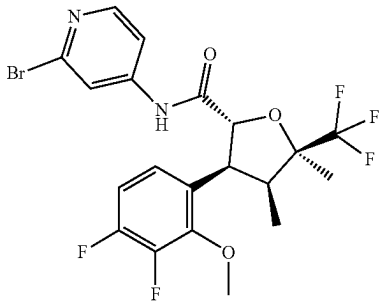


TM2-5

Step 1; General Procedure for Preparation of Intermediate 27-2

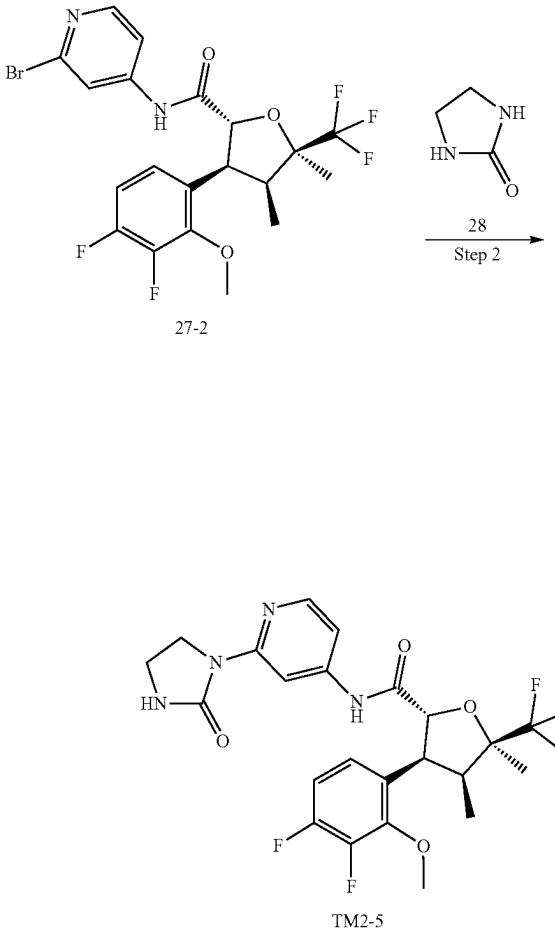




27-2

[0467] TCFH (230.0 mg, 0.84 mmol) and NMI (46 mg, 0.56 mmol) were added to a solution of intermediate 1-1 (100 mg, 0.28 mmol) and intermediate 27-1 (48 mg, 0.28 mmol) in DMF (3 mL), and the reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. Concentrate the reaction solution and purify the residue through a silica gel column to obtain the intermediate 27-2 (70 mg, 48.7% yield) as a white solid. LCMS: m/z=509.1 $[M+H]^+$.

Step 2: General Procedure for Preparation of TM2-5

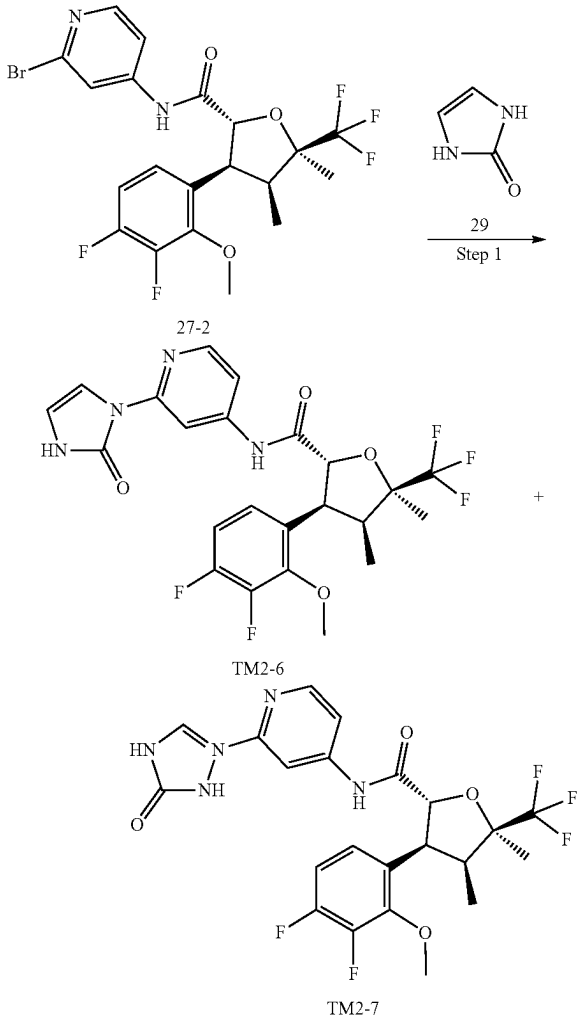


[0468] To a stirred solution of the intermediate 27-2 (60 mg, 0.12 mmol) in DMF (2 ml) was added compound 28 (103.2 mg, 1.2 mmol) and Cs_2CO_3 (117.4 mg, mmol) at r.t. under N2 atmosphere. The resulting reaction mixture was degassed with argon for 15 min. Then Xantphos-pd-g3 (3 mg, 0.001 mmol) were added and the resulting reaction mixture was stirred at 100° C. for 16 h. The reaction was monitored by LCMS. Concentrate on the reaction solution and purify the residue through a silica gel column to obtain the target product. And TM2-5 (8.88 mg, 14.52% yield, 100% purity at 214 nm) was eventually got as a white solid. LCMS: m/z=515.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.30 (s, 1H), 8.14 (d, J=5.8 Hz, 1H), 7.39 (dd, J=5.8, 1.9 Hz, 1H), 7.31-7.14 (m, 2H), 7.12-7.07 (m, 1H), 5.09 (d, J=10.3 Hz, 1H), 4.24 (dd, J=10.3, 7.8 Hz, 1H), 3.98-3.93 (m, 5H), 3.40 (s, 2H), 2.77 (t, J=7.5 Hz, 1H), 1.58 (s, 3H), 0.72 (d, J=6.1 Hz, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ −73.40 (s), −137.99 (s), −138.05 (s), −154.79 (s), −154.85 (s).

Example 2-6

(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(2-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)pyridin-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-6)

(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(2-(2-oxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-7)



Step 1: General Procedure for Preparation of TM2-6 and TM2-7

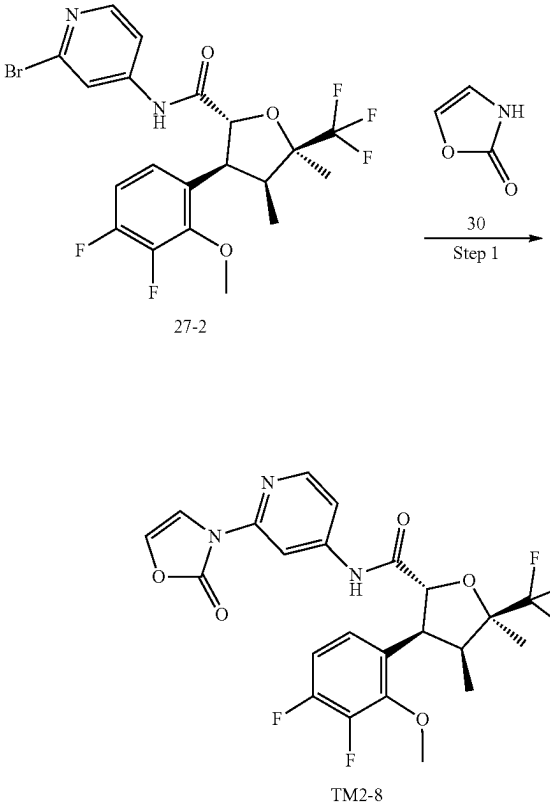
[0469] To a stirred solution of the intermediate 27-2 (80 mg, 0.16 mmol) in DMF (2 ml) was added compound 29 (137.6 mg, 1.6 mmol) and Cs_2CO_3 (156.5 mg, 0.48 mmol) at r.t. under N2 atmosphere. The resulting reaction mixture was degassed with argon for 15 min. Then Xantphos-pd-g3 (19.0 mg, 0.02 mmol) were added and the resulting reaction mixture was stirred at 100° C. for 16 h. The reaction was monitored by LCMS. Concentrate the reaction solution and

purify the residue through a silica gel column to obtain the target product. And TM2-6 (5.65 mg, 6.99% yield, 100% purity at 214 nm) was eventually got as a yellow solid. LCMS: Rt=1.931 min, m/z=513.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 10.44 (s, 1H), 8.57 (d, J=1.8 Hz, 1H), 8.27 (d, J=5.6 Hz, 1H), 7.59 (dd, J=5.6, 1.9 Hz, 1H), 7.23-7.09 (m, 3H), 6.60 (d, J=3.1 Hz, 1H), 5.11 (d, J=10.2 Hz, 1H), 4.30-4.21 (m, 1H), 3.96 (d, J=2.2 Hz, 3H), 2.78 (t, J=7.6 Hz, 1H), 1.59 (s, 3H), 0.73 (d, J=5.8 Hz, 3H). ^{19}F NMR (377 MHz, DMSO-d_6) δ −73.40 (s), −137.99 (s), −138.05 (s), −154.79 (s), −154.85 (s).

[0470] With the same procedure, TM2-7 (5.65 mg, 6.99% yield, 100% purity at 214 nm) was got as a pink solid. LCMS: Rt=9.286 min, m/z=513.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.35 (d, J=5.7 Hz, 1H), 7.85 (d, J=1.5 Hz, 1H), 7.39 (dd, J=5.7, 2.0 Hz, 1H), 7.16-7.09 (m, 1H), 7.05-6.93 (m, 2H), 5.07 (s, 1H), 4.34-4.29 (m, 1H), 4.00 (d, J=2.3 Hz, 3H), 2.85-2.74 (m, 1H), 1.66 (s, 3H), 0.82 (d, J=5.4 Hz, 3H). ^{19}F NMR (377 MHz, MeOD) δ −75.64 (s), −140.13 (d, J=19.5 Hz), −156.87 (d, J=18.7 Hz).

Example 2-7

(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(2-(2-oxooxazol-3(2H)-yl)pyridin-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-8)

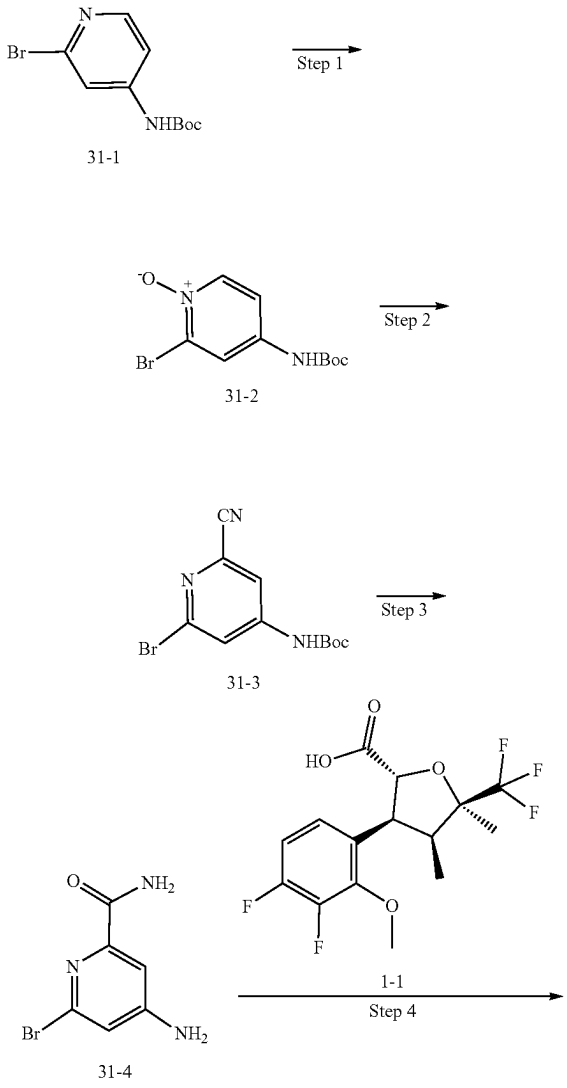


Step 1: General Procedure for Preparation of TM2-8

[0471] The compound 27-2 (50 mg, 0.10 mmol), compound 30 (83 mg, 0.98 mmol), t-Buxphos-Pd-G3 (8 mg, 0.01 mmol), and Cs_2CO_3 (96 mg, 0.29 mmol) were added to DMA (5 mL). The reaction mixture was stirred at 100° C. under N2 for overnight. The reaction mixture was diluted with water, extracted with EA (10 mL). The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by prep-HPLC to afford compound TM2-8 (6.6 mg, 13.09% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=514.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.44 (s, 1H), 8.33 (d, J=5.6 Hz, 1H), 7.79 (s, 1H), 7.62 (d, J=5.6 Hz, 1H), 7.42 (s, 1H), 7.26-7.04 (m, 2H), 5.11 (d, J=10.0 Hz, 1H), 4.33-4.20 (m, 1H), 3.96 (s, 3H), 2.84-2.74 (m, 1H), 1.60 (s, 3H), 0.73 (d, J=6.5 Hz, 3H).

Example 2-8

4-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxamido)-6-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)picolinamide (TM2-9)



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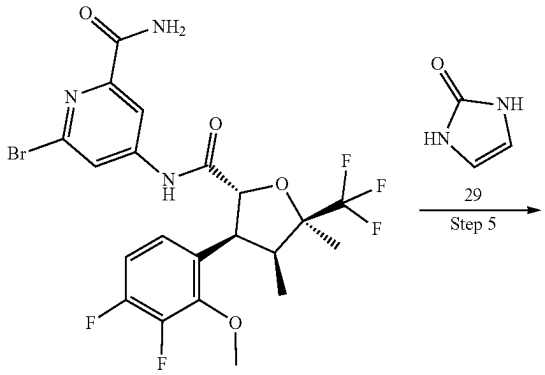
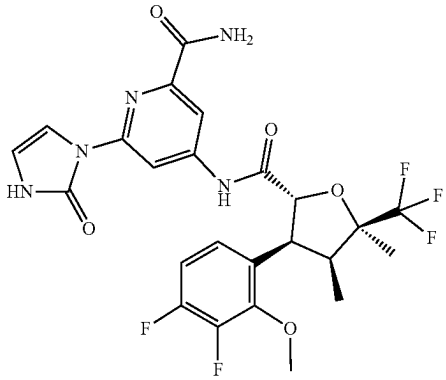
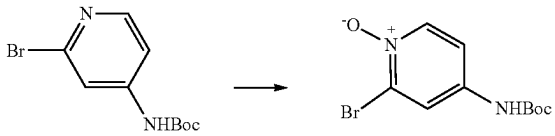


31-5



TM2-9

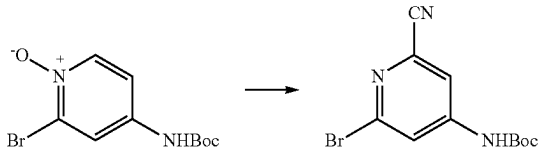
Step 1: General Procedure for Preparation of Intermediate 31-2



31-1 31-2

[0472] To a mixture of compound 31-1 (3 g, 11.03 mmol) in DCM (60 mL) was added m-CPBA (3.8 g, 22.06 mmol), then the whole mixture was stirred at r.t for 16 h. The reaction mixture was diluted with H_2O, extracted with DCM. The combined organic phase washed with $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (0%~100% EA/hexanes) to afford compound 31-2 (1.8 g, 56% yield) as a yellow solid. LCMS: m/z=291.0 $[M+H+2]^+$.

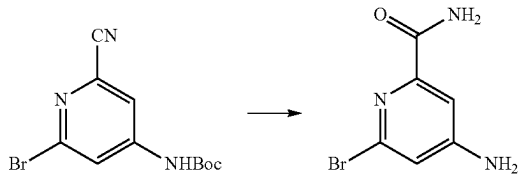
Step 2: General Procedure for Preparation of Intermediate 31-3



31-2 31-3

[0473] To a mixture of compound 31-2 (1.8 g, 6.23 mmol) and TMSCN (1.8 g, 18.69 mmol) in ACN (27 mL) was added TEA (1.3 g, 12.46 mmol), then the whole mixture was stirred at 90° C. for 16 h. The reaction mixture was diluted with water, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (0%~50% EA/hexanes) to afford 31-3 (1.5 g, 80% yield) as a white solid. LCMS: m/z=299.9 $[M+H+2]^+$.

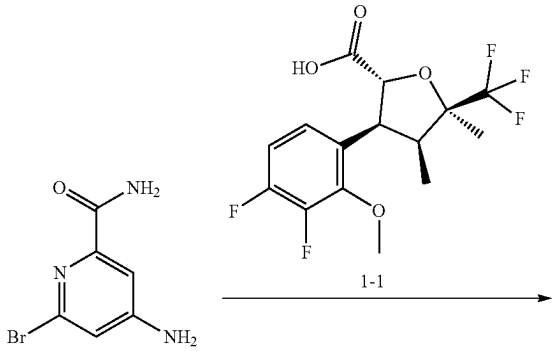
Step 3: General Procedure for Preparation of Intermediate 31-4



31-3 31-4

[0474] Compound 31-3 (1.5 g, 5.05 mmol) was added to HCl in 1,4-dioxane (2M, 15 mL), then the whole mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (0%~100% EA/hexanes) to afford compound 31-4 (0.8 g, 73% yield) as a white solid. LCMS: m/z=218.0 $[M+H+2]^+$.

Step 4: General Procedure for Preparation of Intermediate 31-5



31-4

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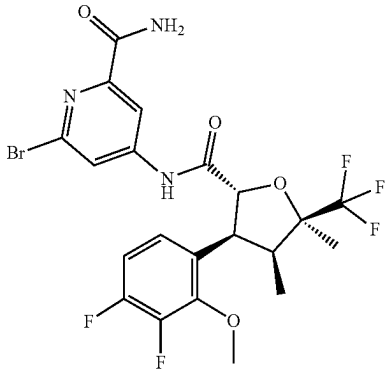

31-5

[0475] NMI (74 mg, 0.90 mmol) and TCFH (254 mg, 0.90 mmol) were added to a solution of compound 1-1 (160 mg, 0.45 mmol) and compound 31-4 (98 mg, 0.45 mmol) in ACN (3.2 mL), and the reaction mixture was stirred at r.t. for overnight. The resulting mixture was concentrated, diluted with water (40 mL), extracted with EA (40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, concentrated, purified by Reversed phase column (ACN/0.01% FA in H_2O=0%~50%) to get the desired product 31-5 (130 mg, 51% yield) as a white solid. LCMS: min m/z=554.3 $[M+H+2]^+$.

Step 5: General Procedure for Preparation of TM2-9

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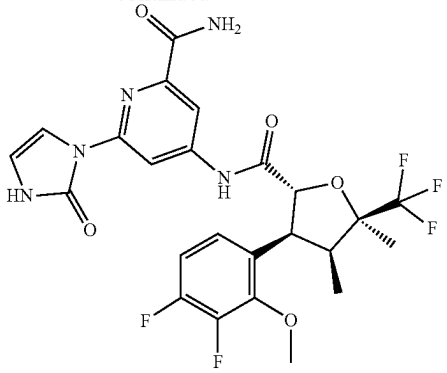
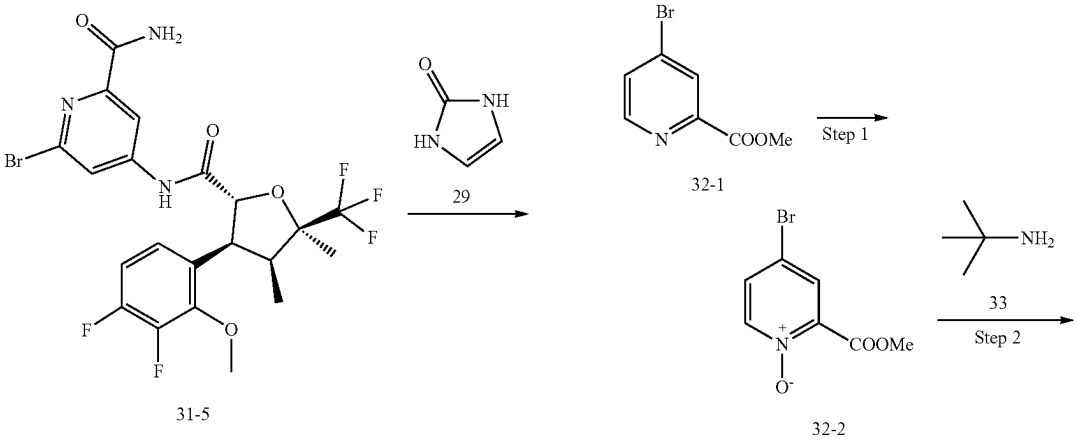


TM2-9

[0476] Compound 31-5 (90 mg, 0.16 mmol), 1,3-dihydro-2h-imidazol-2-one (29; 137 mg, 1.63 mmol), t-Buxphos-Pd-G3 (13 mg, 0.02 mmol), Cs_2CO_3 (159 mg, 0.49 mmol) were added to DMA (4.5 mL). The reaction mixture was stirred at 70° C. under N2 for 1 h. The reaction mixture was diluted with water and EA and the aqueous layer extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford compound TM2-9 (23.94 mg, 26% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=556.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.45 (s, 1H), 8.84 (d, J=1.8 Hz, 1H), 8.32 (s, 1H), 8.22 (d, J=1.8 Hz, 1H), 7.87-7.76 (m, 1H), 7.63 (s, 1H), 7.24-7.08 (m, 2H), 6.66-6.59 (m, 1H), 5.11 (d, J=10.2 Hz, 1H), 4.26 (dd, J=10.2, 7.8 Hz, 1H), 3.96 (d, J=2.1 Hz, 3H), 2.78 (dd, J=15.1, 7.6 Hz, 1H), 1.61 (s, 3H), 0.73 (d, J=5.7 Hz, 3H).

Example 2-9

6-(3-aminopropanamido)-4-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxamido)picolinamide (TM2-10)



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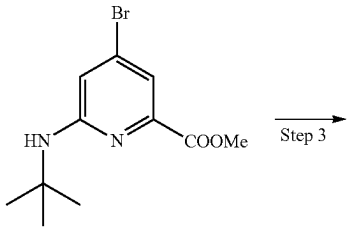
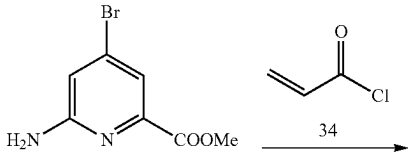
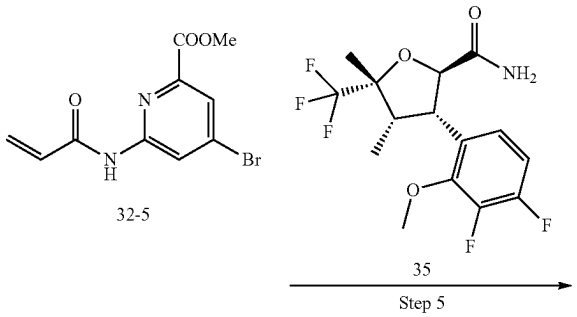


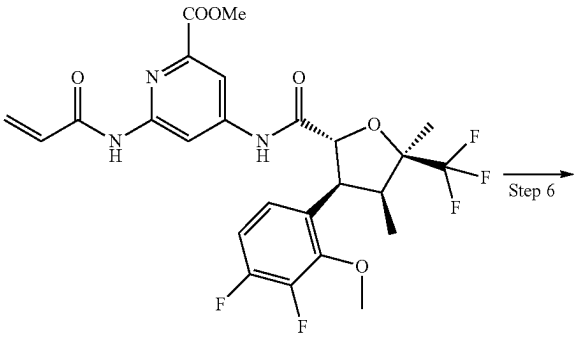
32-3



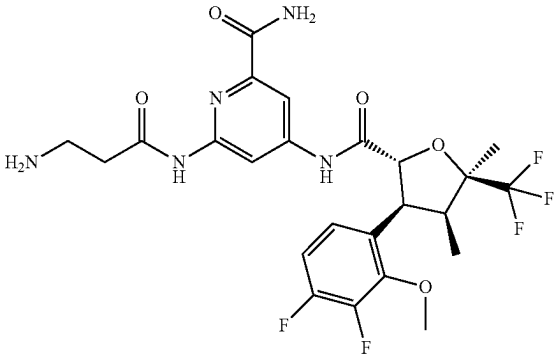
32-4



32-5

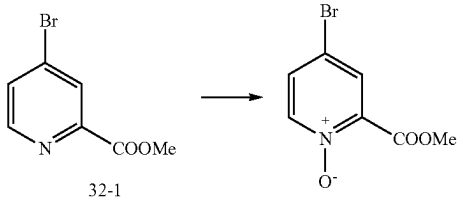


32-6



TM2-10

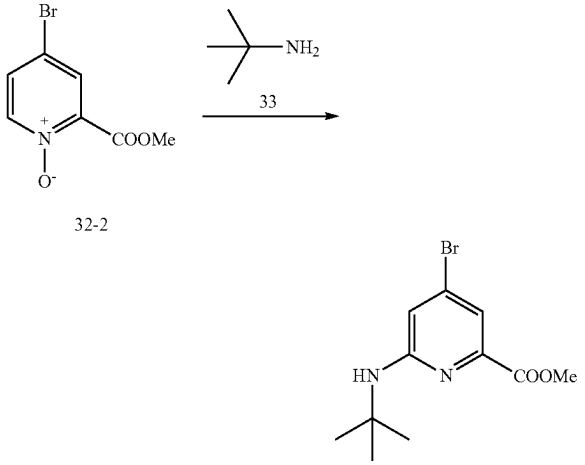
Step 1: General Procedure for Preparation of Intermediate 32-2



32-1 32-2

[0477] To a solution of compound 32-1 (5 g, 23.1 mmol) in DCM (100 mL) was added 85% m-CPBA (12 g, 69.4 mmol) at r.t. The reaction mixture was degassed and purged with N_2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The reaction mixture was added DCM (100 mL). The resulting mixture was extracted with DCM (3×120 mL). The organic phases were combined, washed with NaCl (30 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, MeOH/DCM (0%~10%) to give the desired product 32-2 (3.5 g, 65.59% yield) as a yellow solid. LCMS: m/z=233.9 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 32-3

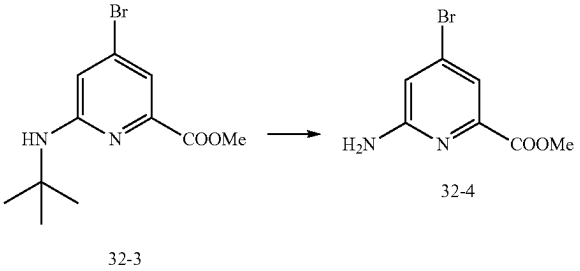


32-2 32-3

[0478] To a solution of compound 32-2 (3 g, 12.99 mmol) in $CHCl_3$ (30 mL) was added 2-methylpropan-2-amine (33; 8.5 g, 116.88 mmol) and Ts_2O (19.1 g, 58.45 mmol) at r.t. The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The reaction mixture was added EA (20 mL). The resulting mixture was extracted with EA (3×20 mL). The organic phases were combined, washed with NaCl (15 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column

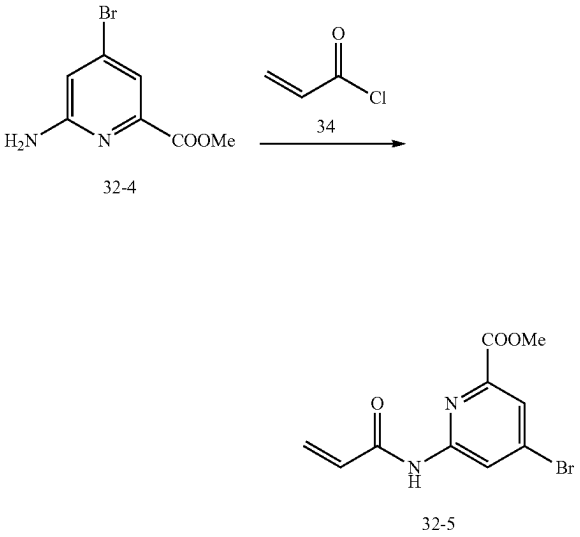
chromatography, EA/PE (0%~20%) to give the desired product intermediate 32-3 (800 mg, 19.98% yield) as a yellow oil. LCMS: m/z=287.0 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 32-4



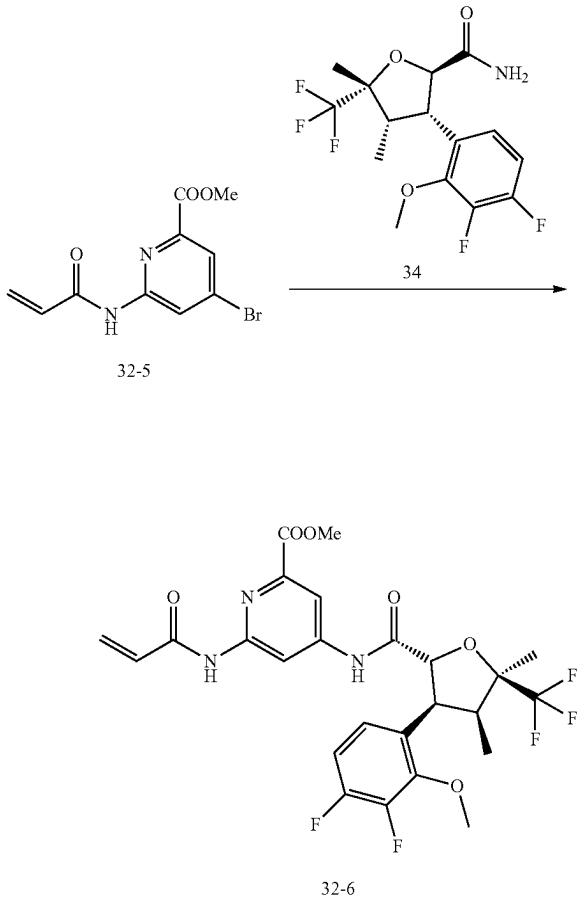
[0479] To a mixture of compound 32-3 (750 mg, 2.62 mmol) in TFA (8 mL), then the whole mixture was stirred at 70° C. for 16 h under argon. LCMS detected the desired product. The mixture was adjusted to pH 8 with Na_2CO_3. The resulting mixture was extracted with EA (3×20 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, EA/PE (40%~60%) to give the desired product 32-4 (600 mg, 93.5% yield) as a yellow solid. LCMS: m/z=233.0 $[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 32-5



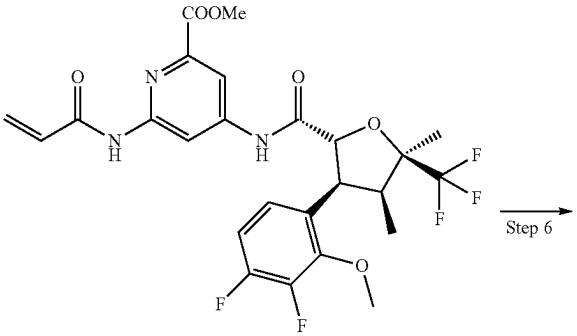
[0480] To a solution of compound 32-4 (300 mg, 1.3 mmol) in DCM (5 mL) was added acryloyl chloride (34; 141.67 mg, 1.56 mmol) and TEA (197 mg, 1.95 mmol) at r.t. The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The reaction mixture was added EA (10 mL). The resulting mixture was extracted with EA (3×10 mL). The organic phases were combined, washed with NaCl (15 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, EA/PE (0%~30%) to give the desired product 32-5 (130 mg, 35.21% yield) as a white solid. LCMS: m/z=287.0 $[M+H]^+$.

Step 5: General Procedure for Preparation of Intermediate 32-6

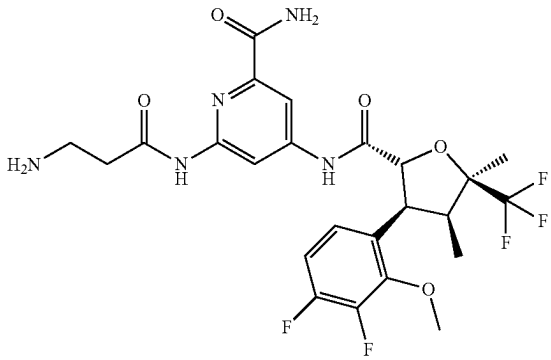


[0481] To a solution of compound 32-5 (128.7 mg, 0.45 mmol) in dioxane (5 mL) was added compound 35 (200 mg, 0.57 mmol), Cs_2CO_3 (33.5 mg, 1.03 mmol) and $Pd(OAc)_2$ (15.5 mg, 0.068 mmol), xantphos (49.5 mg, 0.085 mmol), then the whole mixture was stirred at 100° C. for 16 h. LCMS detected the desired product. The reaction mixture was added EA (10 mL). The resulting mixture was extracted with EA (3×10 mL). The organic phases were combined, washed with NaCl (15 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, EA/PE (0%~30%) to give the desired product 32-6 (50 mg, 19.95% yield) as a yellow oil. LCMS: m/z=558.2 $[M+H]^+$.

Step 6: General Procedure for Preparation of TM2-10



32-6

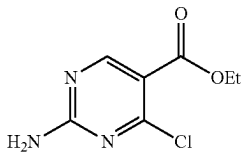


TM2-10

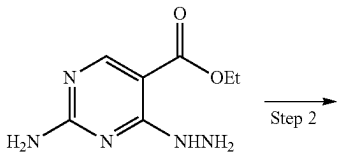
[0482] To a solution of compound 32-6 (45 mg, 0.08 mmol) in NH_3 in MeOH (7 M, 2 mL). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 16 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product TM2-10 (6.80 mg, 15.20% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=560.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.66-8.29 (m, 2H), 8.05 (t, J=5.9 Hz, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 7.22-7.12 (m, 2H), 5.11 (d, J=10.2 Hz, 1H), 4.28-4.22 (m, 1H), 3.95 (d, J=2.0 Hz, 3H), 3.24 (s, 2H), 2.95 (s, 2H), 2.81-2.74 (m, 1H), 2.60 (s, 2H), 1.60 (s, 3H), 0.73 (d, J=5.8 Hz, 3H).

Example 2-10

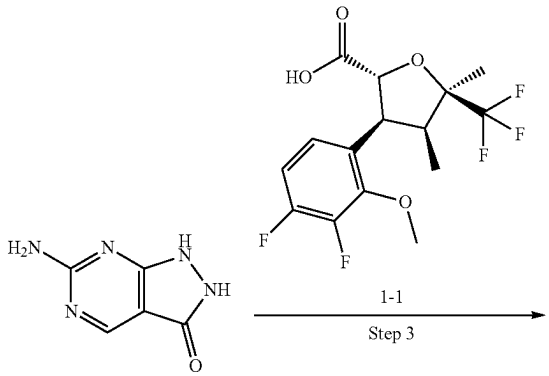
(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-(trifluoromethyl)tetrahydro-furan-2-carboxamide (TM2-11)



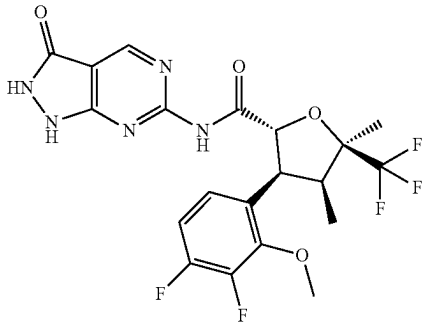
36-1



36-2

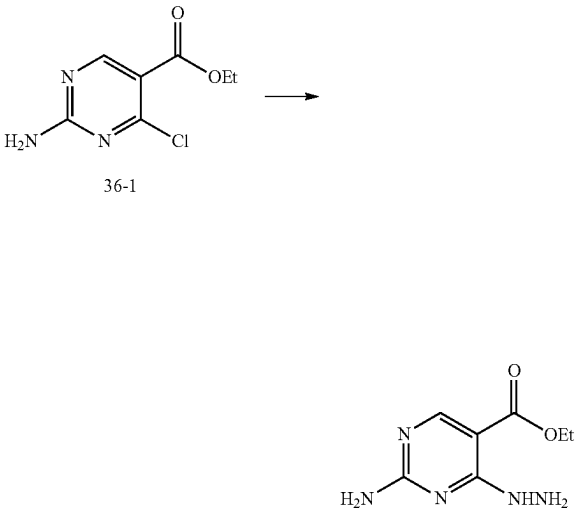


36-3



TM2-11

Step 1: General Procedure for Preparation of Intermediate 36-2

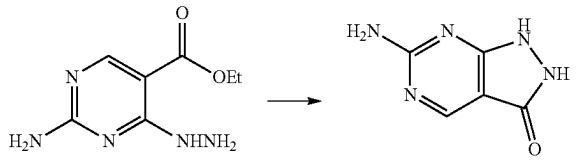


36-1

36-2

[0483] To a solution of compound 36-1 (200 mg, 0.99 mmol)) in THF (2 mL) was slowly added NH_2NH_2—H_2O (2 mL). The reaction mixture was stirred at r.t. for 16 h. The resulting mixture was diluted with water (5 mL), extracted with EA (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated to get the intermediate 36-2 (140 mg, 71% yield) as a white solid. LCMS: m/z=198.1 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 36-3

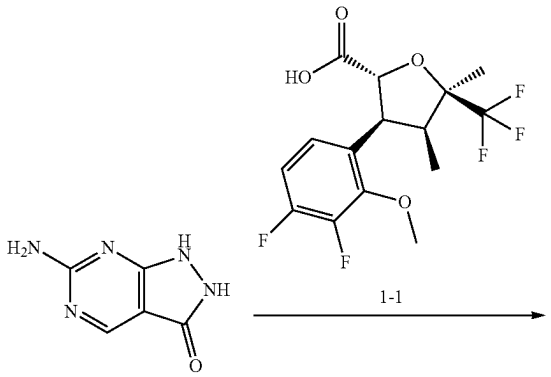


36-2

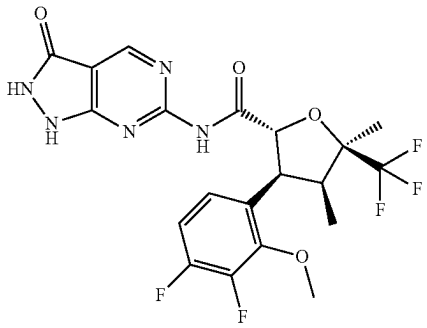
36-3

[0484] Compound 36-2 (140 mg, 0.71 mmol) was added a solution of MeONa (77 mg, 1.42 mmol) in MeOH (2 mL), and the reaction mixture was stirred at 65° C. under N2 for 4 h. After completion of reaction, 1 M HCl was added to adjust pH to 4, and then purified by Reversed phase column (ACN/0.01% FA in H_2O=5%) to get the desired product 36-3 (70 mg, 65% yield) as a yellow solid. LCMS: m/z=152.1 $[M+H]^+$.

Step 3: General Procedure for Preparation of TM2-11



36-3

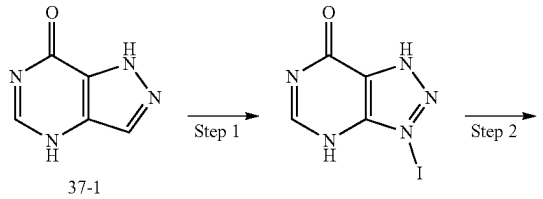


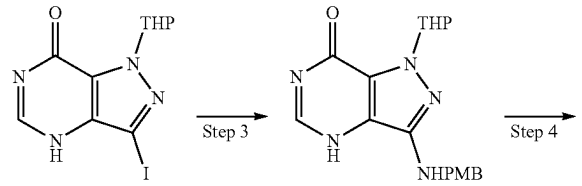
TM2-11

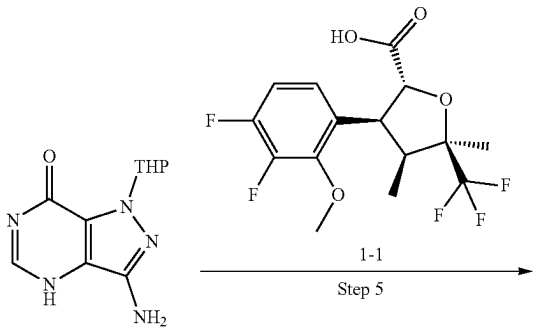
[0485] $(COCl)_2$ (126 mg, 0.99 mmol) was added to a solution of compound 2 (117 mg, 0.33 mmol) and DMF (2 mg, 0.03 mmol) in DCM (1 mL) at 0° C. under N2, and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was concentrated, redissolved in THF (1 mL) and added to a mixture of NaH (30%, 80 mg, 0.99 mmol) and intermediate 36-3 (50 mg, 0.33 mmol) in THF (1 mL). The reaction mixture was stirred at r.t. for 1 h. The reaction was diluted with water, extracted with EA. The combined organic phase washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by HPLC to afford compound TM2-11 (3.57 mg, 2.2% yield, 100% purity at 214 nm) as a yellow solid. LCMS: m/z=488.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 10.80 (s, 1H), 8.88 (s, 1H), 7.19 (d, J=5.6 Hz, 3H), 5.25 (d, J=10.4 Hz, 1H), 4.27-4.21 (m, 1H), 3.94 (d, J=2.0 Hz, 3H), 2.79-2.72 (m, 1H), 1.60 (s, 3H), 0.72 (d, J=6.8 Hz, 3H).

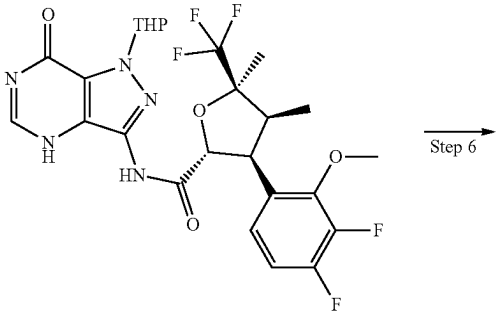
Example 2-11

(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(7-oxo-4,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-12)









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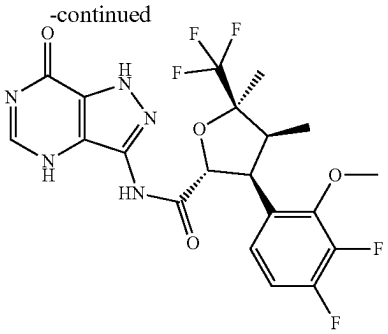
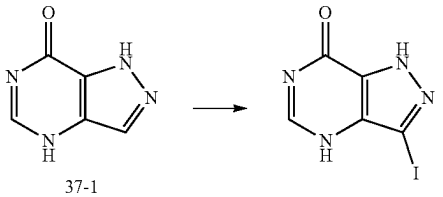


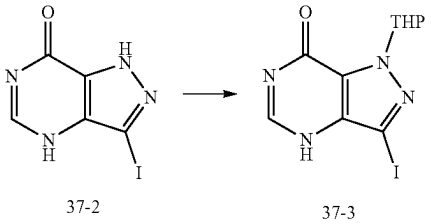
TMS2-12

Step 1: General Procedure for Preparation of Intermediate 37-2



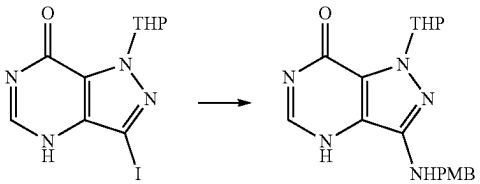
[0486] To a mixture of compound 37-1 (2 g, 14.71 mmol) in DMF (40 mL) was added NIS (6.6 g, 29.41 mmol), then the whole mixture was stirred at r.t for 16 h. The reaction mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (0%~100% EA/hexanes) to afford compound 37-2 (2.5 g, 64% yield) as a yellow solid. LCMS: m/z=262.9 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 37-3



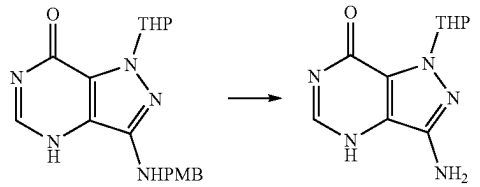
[0487] TsOH (1.3 g, 7.63 mmol) was added to a solution of compound 37-2 (2 g, 7.63 mmol) and DHP (1.3 g, 15.27 mmol) in DMSO (24 mL), the reaction mixture was stirred at 65° C. for overnight. The resulting mixture was concentrated, diluted with H_2O (50 mL), extracted with EA (50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated, purified by silica gel column chromatography, eluting with a gradient of MeOH/DCM (0%~25%) to get the desired product 37-3 (1.6 g, 60% yield) as a white solid. LCMS: min m/z=346.9 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 37-4



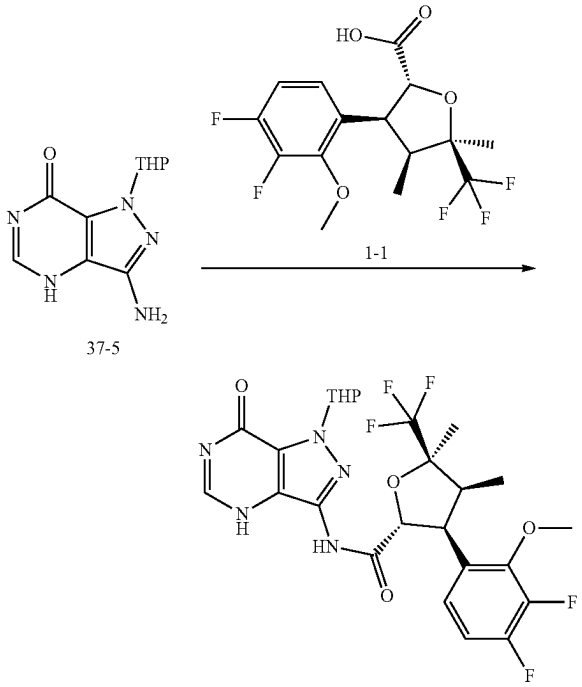
[0488] To a solution of 37-3 (800 mg, 2.31 mmol), $PMBNH_2$ (297 mg, 2.77 mol), L-proline (106 mg, 0.92 mol), and K_2CO_3 (1.6 g, 11.56 mmol) in DMSO (16 mL) was added CuI (88 mg, 0.46 mmol), then the whole mixture was stirred at 100° C. for 16 h under argon. The reaction mixture was diluted with water and EA and the aqueous layer extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by preparative liquid chromatography (0.1% FA in H_2O/ACN=5%~95%) to afford the compound 37-4 (200 mg, 19% yield) as a white solid. LCMS: m/z=356.2 $[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 37-5



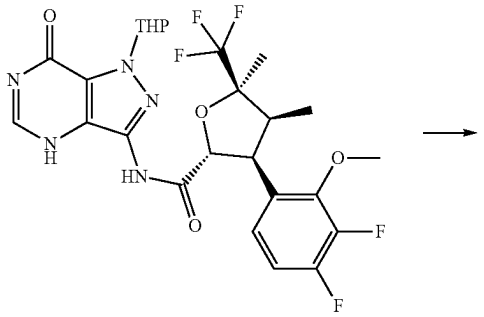
[0489] To a solution of 37-4 (200 mg, 0.56 mmol) in MeOH (4 mL) were added Pd/C (10%, 100 mg), $Pd(OH)_2$/C (10%, 100 mg), AcOH (20 mg). The reaction mixture was stirred at r.t. for 16 h. The mixture was filtered and the filtrate was concentrated to afford compound 37-5 as a white solid. LCMS: m/z=236.1 $[M+H]^+$.

Step 5: General Procedure for Preparation of Intermediate 37-6



[0490] Compound 37-5 (110 mg, 0.47 mmol), compound 2 (166 mg, 0.47 mmol), HATU (267 mg, 0.70 mmol), and DIEA (302 mg, 2.34 mmol) were added to DMF (2 mL). The reaction mixture was stirred rt for 16 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~60%) to get the compound 37-6 (180 mg, 67% yield) as a white solid. LCMS: m/z=572.2 $[M+H]^+$.

Step 6: General Procedure for Preparation of TM2-12



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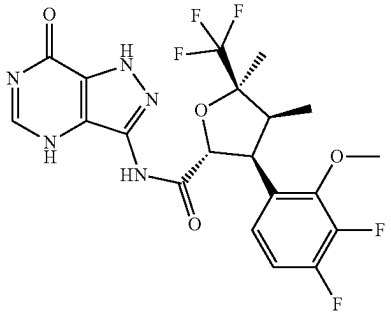
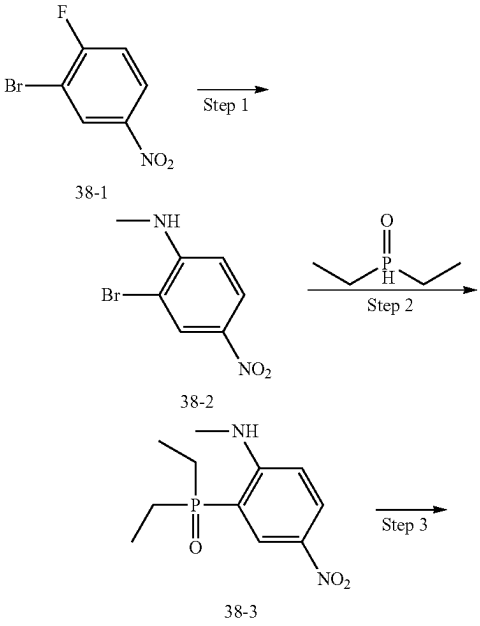


TMS2-12

[0491] To a solution of compound 37-6 (150 mg, 0.26 mmol) in ACN (3 mL) was added TMSI (105 mg) at 0° C. The reaction mixture was stirred rt for 2 h. The reaction mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by prep-HPLC to afford compound TM2-12 (2.06 mg, 1.5% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=488.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) b 8.04 (s, 1H), 7.24-7.14 (m, 1H), 6.97 (dd, J=17.2, 9.1 Hz, 1H), 5.20 (d, J=10.5 Hz, 1H), 4.43-4.29 (m, 1H), 4.00 (s, 3H), 2.83 (dd, J=16.9, 9.3 Hz, 1H), 1.70 (s, 3H), 0.82 (d, J=5.4 Hz, 3H).

Example 2-12

(2R,3S,4S,5R)—N-(3-(diethylphosphoryl)-4-(methylamino)phenyl)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-13)



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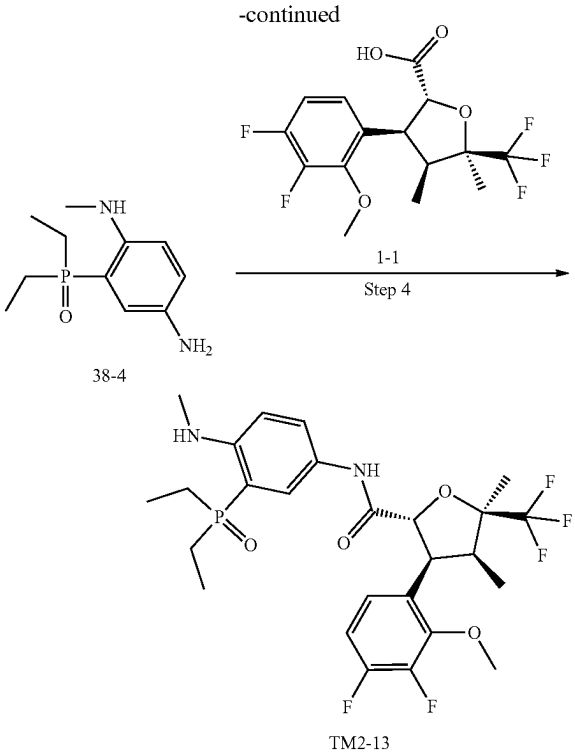
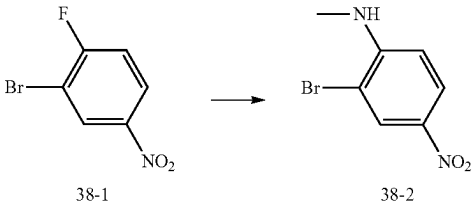


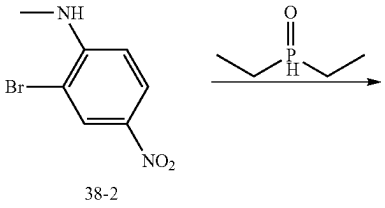
TM2-13

Step 1: General Procedure for Preparation of Intermediate 38-2



[0492] To a solution of compound 38-1 (5 g, 22.73 mmol) and NH_2—HCl (3.1 g, 45.45 mmol) in DMSO (50 mL) was added K_2CO_3 (6.3 g, 45.45 mmol) at r.t. The reaction mixture was stirred at r.t. for 16 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated to get compound 38-2 (4.3 g, 81% yield) as a yellow solid. LCMS: m/z=230.9 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 38-3



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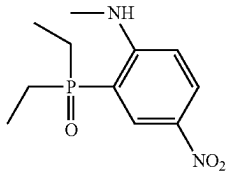
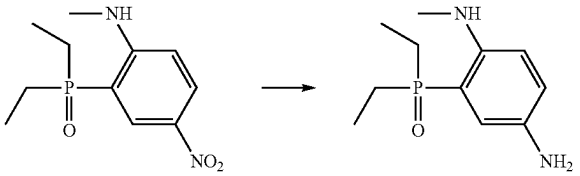


38-3

[0493] A mixture of compound 38-2 (300 mg, 1.30 mmol), diethylphosphine oxide (413 mg, 3.90 mmol), DIEA (812 mg, 6.49 mmol), DPPP (107 mg, 0.26 mmol) and $Pd(OAc)_2$ (2 mg, 0.01 mmol) in 1,4-dioxane (6 mL) was stirred at 100° C. under argon for 16 h. The resulting mixture was filtered and the filtrated was purified by prep-HPLC (ACN/0.1% FA=5%~60%) to give the intermediate compound 38-3 (80 mg, 22% yield) as a white solid. LCMS: min m/z=257.1 $[M+H]^+$.

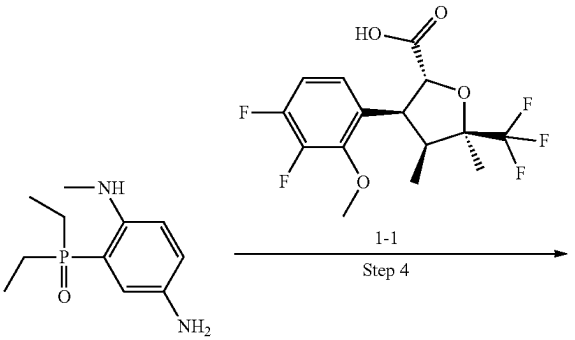
Step 3: General Procedure for Preparation of Intermediate 38-4



38-3 38-4

[0494] To a solution of compound 38-3 (80 mg, 0.31 mmol) in MeOH (0.5 mL) was added Pd/C (30 mg). The mixture was stirred at r.t. under H2 atmosphere for 16 h. The reaction mixture filtered, and the filtrate was concentrated to afford the intermediate compound 38-4 (60 mg, 84% yield) as a white solid. LCMS: m/z=227.1 $[M+H]^+$.

Step 4: General Procedure for Preparation of TM2-13



38-4

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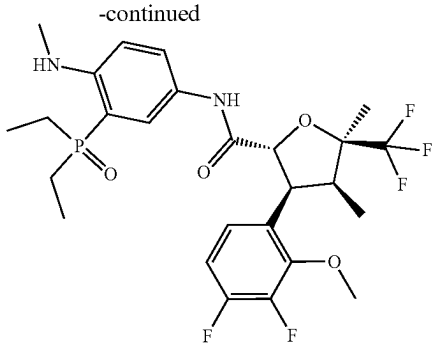
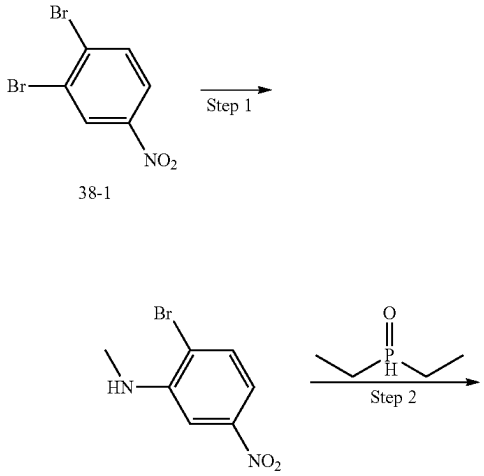


TM2-13

[0495] A mixture of compound 38-4 (60 mg, 0.27 mmol), compound 1-1 (94 mg, 0.27 mmol), DIEA (171 mg, 1.33 mmol), and HATU (303 mg, 0.80 mmol) in DMF (1 mL) was stirred at r.t. for 16 h. The reaction mixture was diluted with water and EA and the aqueous layer extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford the title compound TM2-13 (80.95 mg, 54% yield, 93.45% purity at 214 nm) as a white solid. LCMS: m/z=563 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.50-7.36 (m, 2H), 7.29 (d, J=5.1 Hz, 1H), 7.21-7.10 (m, 2H), 6.56 (dd, J=8.9, 4.8 Hz, 1H), 4.99 (d, J=10.5 Hz, 1H), 4.21 (dd, J=10.5, 7.7 Hz, 1H), 3.95 (d, J=2.1 Hz, 3H), 3.32 (s, 3H), 2.71 (t, J=10.5 Hz, 4H), 2.00-1.78 (m, 4H), 1.58 (s, 3H), 0.99 (dtd, J=17.0, 7.6, 1.9 Hz, 6H), 0.71 (d, J=5.8 Hz, 3H).

Example 2-13

(2R,3S,4S,5R)—N-(4-(diethylphosphoryl)-3-(methylamino)phenyl)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-14)



38-1 39-2

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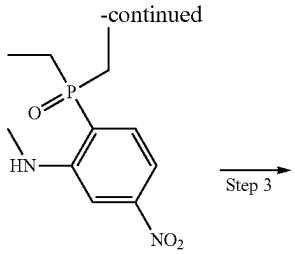
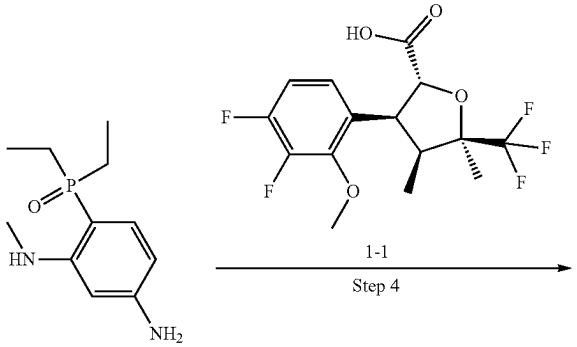
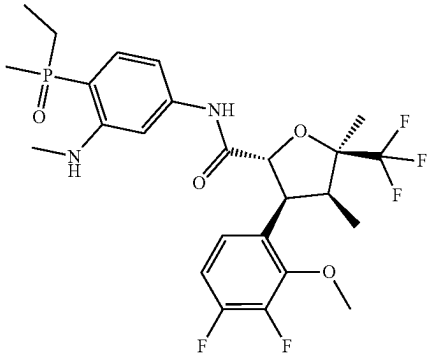
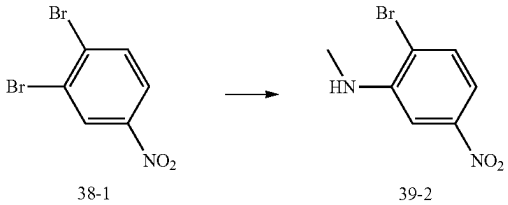




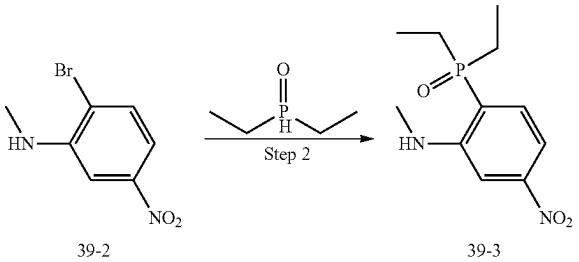


Step 1: General Procedure for Preparation of Intermediate 39-2



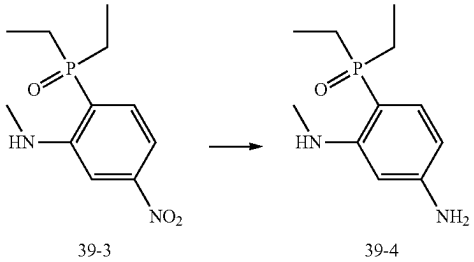
[0496] To a solution of compound 39-1 (2 g, 4.84 mmol) and $(CHO)_n$ (211 mg, 7.26 mmol) in MeOH (20 mL) was added MeONa (654 mg, 12.11 mmol) at 0° C. The reaction mixture was stirred at 60° C. for 2 h. Then $NaBH_4$ (460 mg, 12.11 mmol) was added to the mixture at 0° C., and the mixture was stirred at r.t. for 2 h. The mixture was diluted with H_2O, extracted with EA. The combined organic phase washed with brine, dried over anhydrous Na_2SO_4, and concentrated to get compound 18-2 (1.4 g, 65% yield) as a yellow solid. LCMS: m/z=233.0 $[M+H+2]^+$.

Step 2: General Procedure for Preparation of Intermediate 39-3



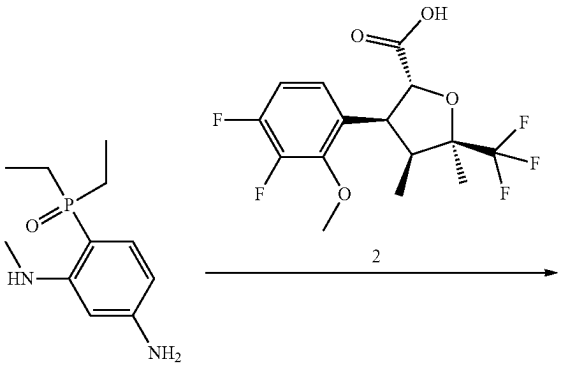
[0497] A mixture of compound 39-2 (700 mg, 3.03 mmol), diethylphosphine oxide (964 mg, 9.09 mmol), DIEA (1.9 g, 15.15 mmol), DPPP (250 mg, 0.61 mmol) and $Pd(OAc)_2$ (69 mg, 0.30 mmol) in 1,4-dioxane (14 mL) was stirred at 100° C. under argon for 16 h. The resulting mixture was filtered and the filtrated was purified by prep-HPLC (ACN/0.1% FA=5%~60%) to give the compound 39-3 (160 mg, 14% yield) as a white solid. LCMS: m/z=257.1 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 39-4

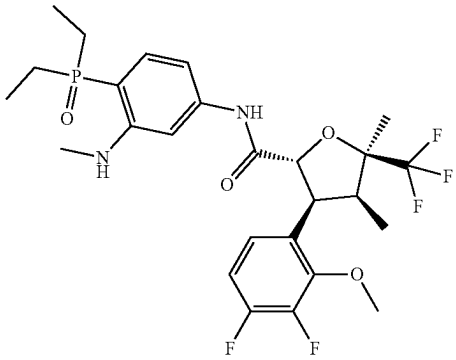


[0498] A mixture of compound 39-3 (140 mg, 0.55 mmol), Fe(153 mg, 2.73 mmol), NH_4Cl (145 mg, 2.73 mmol), H_2O (1.4 mL) in EtOH (0.2.8 mL) was stirred at 80° C. for 1 h. The reaction mixture was diluted with water and EA and the aqueous layer extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by Reversed phase column (ACN/0.01% FA in H_2O=5%~50%) to afford the compound 39-4 (90 mg, 72% yield) as a yellow solid. LCMS: m/z=227.1$[M+H]^+$.

Step 4: General Procedure for Preparation of TM2-14



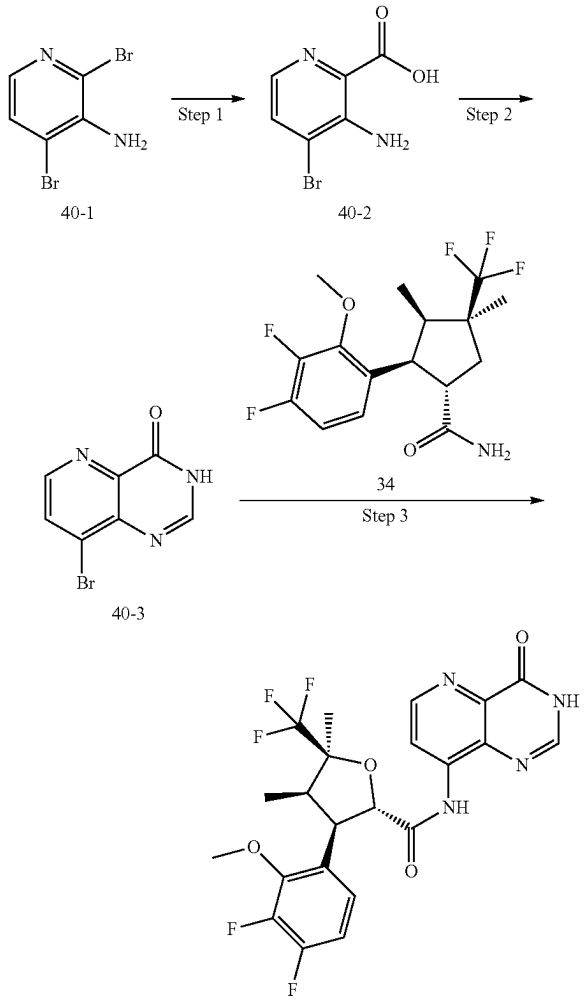
18-4



TM2-14

Example 2-14

(2S,3R,4R,5S)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-N-(4-oxo-3,4-dihydropyrido[3,2-d]pyrimidin-8-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxamide (TM2-15)



40-1

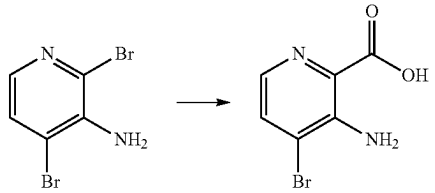
40-2

40-3

TM2-15

[0499] A mixture of compound 39-4 (90 mg, 0.40 mmol), compound 2 (141 mg, 0.40 mmol), DIEA (257 mg, 1.99 mmol), and HATU (454 mg, 1.19 mmol) in DMF (3 mL) was stirred at r.t. for 16 h. The reaction mixture was diluted with water and EA and the aqueous layer extracted with EA. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford TM2-14 (76.43 mg, 34% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=563.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.56 (d, J=5.1 Hz, 1H), 7.31-7.04 (m, 3H), 7.00-6.72 (m, 2H), 5.06 (dd, J=10.3, 5.2 Hz, 1H), 4.35-4.17 (m, 1H), 3.96 (s, 3H), 3.32 (s, 3H), 2.72 (dt, J=10.1, 5.9 Hz, 4H), 2.00-1.76 (m, 4H), 1.59 (s, 3H), 0.96 (ddd, J=16.4, 12.9, 7.3 Hz, 6H), 0.73 (s, 3H).

Step 1: General Procedure for Preparation of Intermediate 40-2



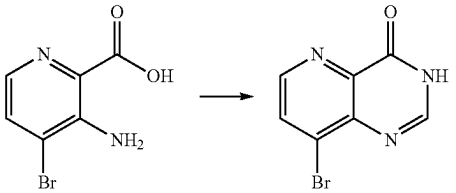
40-1

40-2

[0500] To a solution of compound 40-1 (2.5 g, 9.92 mmol), DCPP (3.04 g, 4.96 mmol) in DMSO (25 mL) and

water (2.5 mL) was added K_2CO_3 (4.1 g, 29.76 mmol) and $Pd(OAc)_2$ (449.4 mg, 1.98 mmol), then the whole mixture was stirred at 100° C. under CO atmosphere for 7 h. LCMS detected the desired product. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product 40-2 (100 mg, 4.67% yield) as a yellow solid. LCMS: m/z=217.1 $[M-H]^+$.

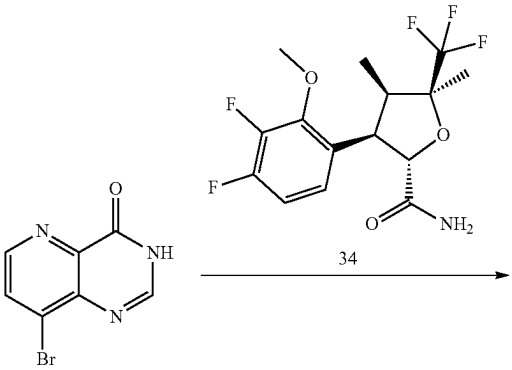
Step 2: General Procedure for Preparation of Intermediate 40-3



40-2 40-3

[0501] To a solution of compound 40-2 (100 mg, 0.5 mmol) in DMSO (2 mL) was added Formamidine acetate (72 mg, 0.7 mmol) at r.t. The reaction mixture was degassed and purged with N2 and stirring was continued at 160° C. for 2.5 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the crude product 40-3 (15 mg, 13.33% yield) as a yellow solid. LCMS: m/z=224.1 $[M-H]^+$.

Step 3: General Procedure for Preparation of TM2-15



40-3

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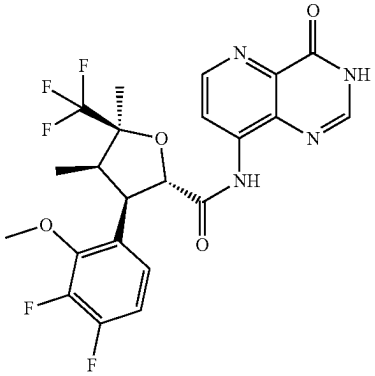
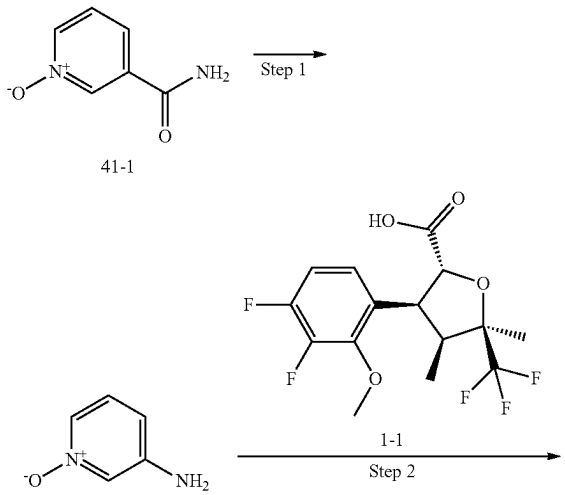


TM2-15

[0502] To a solution of 40-3 (12.5 mg, 0.055 mmol) in dioxane (0.5 mL) was added compound 34 (24.3 mg, 0.068 mmol), Cs_2CO_3 (39.8 mg, 0.122 mmol) and $Pd(OAc)_2$ (1.85 mg, 0.0082 mmol), xantphos (5.9 mg, 0.01 mmol), then the whole mixture was stirred at 100° C. for 3 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product TM2-15 (2.38 mg, 7.24% yield, 100% purity at 214 nm) as a yellow solid. LCMS: m/z=499.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 8.11 (d, J=5.5 Hz, 1H), 7.68 (d, J=5.5 Hz, 1H), 7.33-7.27 (m, 1H), 7.03-6.96 (m, 1H), 5.22 (d, J=10.7 Hz, 1H), 4.28 (dd, J=10.6, 8.0 Hz, 1H), 3.96 (d, J=2.3 Hz, 3H), 2.81 (p, J=7.5 Hz, 1H), 1.78 (s, 3H), 0.83 (d, J=5.3 Hz, 3H).

Example 2-15

3-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxamido)pyridine 1-oxide (TM2-16)



41-1 41-2

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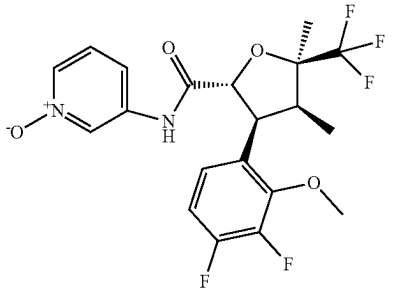
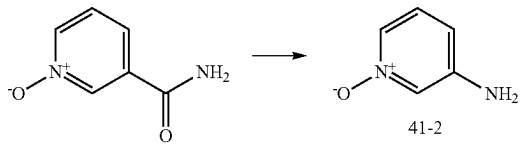


TM2-16

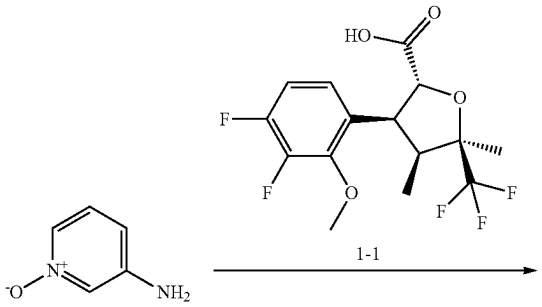
Step 1: General Procedure for Preparation of Intermediate 41-2



41-1 41-2

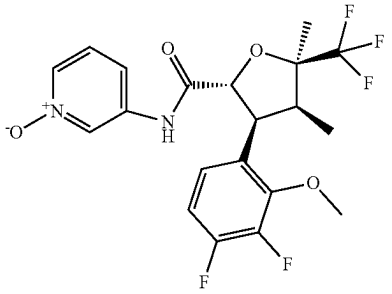
[0503] Under an ice bath, sodium hydroxide (4.70 g, 115.80 mmol) was added slowly into a single-neck flask containing 50 mL of a 9% sodium hypochlorite solution. After stirring for 10 min, compound 41-1 (4.00 g, 28.90 mmol) was added to the reaction mixture, which was then allowed to proceed under reflux conditions for 2 h. Then the resulting mixture was cooled and the pH was adjusted to 2 with 2M HCl. The reaction mixture was concentrated and the crude product, 41-2 (2.71 g, 86% yield), was directly used for next reaction without further purification. LCMS: m/z=111.06 $[M+H]^+$.

Step 2: General Procedure for Preparation of TM2-16



41-2

-continued



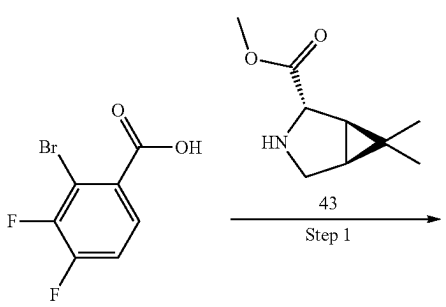
TM2-16

[0504] TCFH (300 mg, 1.05 mmol) and NMI (181 mg, 1.80 mmol) were added to a solution of compound 41-2 (100 mg, 0.90 mmol) and compound 1-1 (354 mg, 1.00 mmol) in anhydrous dichloromethane (15 mL), and the reaction mixture was stirred at r.t. for 2 h. The resulting mixture was concentrated, then extracted with water (15 mL) and brine (15 mL) before drying over anhydrous Na_2SO_4. Later the organic solution was concentrated and purified by column chromatography (PE/EA=1/1-1/5) to get the desired product, namely TM2-16 (122 mg, 15% yield, 92.95% purity at 214 nm), as a brown solid. LCMS: m/z=447.30 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (t, J=1.4 Hz, 1H), 8.16-8.10 (m, 1H), 7.86-7.80 (m, 1H), 7.55-7.48 (m, 1H), 7.14-7.08 (m, 1H), 7.06-6.98 (m, 1H), 4.87-4.82 (m, 1H), 3.87 (s, 3H), 3.40-3.33 (m, 1H), 2.47-2.38 (m, 1H), 1.33 (s, 3H), 1.09 (d, J=6.0 Hz, 3H).

General Scheme Provides a Process of the Synthesis for Preparing TM3-1~TM3-

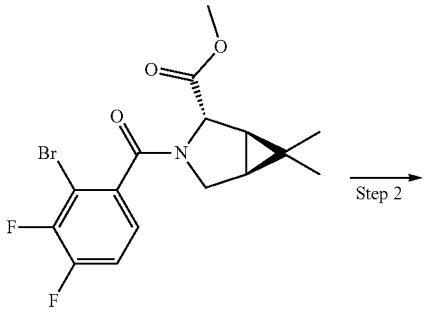
Example 3-1

carboxamide(1R,2S,5S)-3-(2-carbamoyl-3,4-difluorobenzoyl)-N-(2-carbamoylpyridin-4-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (TM3-1)



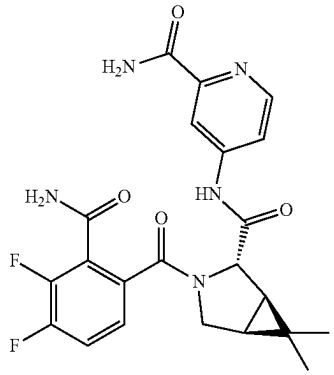
42-1

-continued

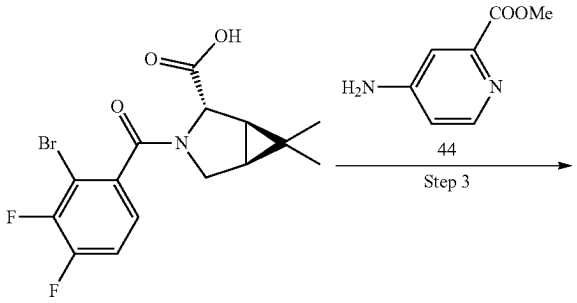


42-2

-continued

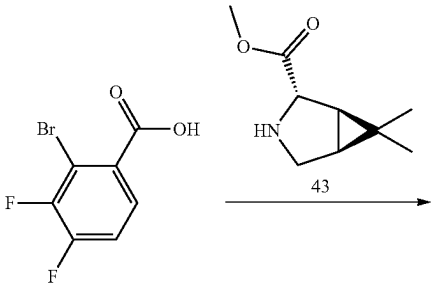


TM3-1

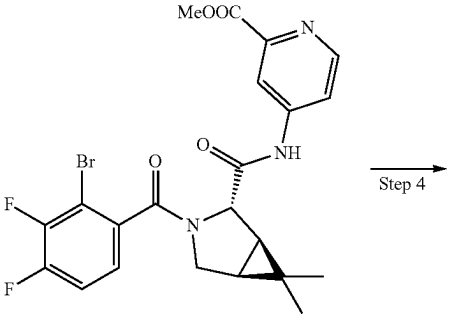


42-3

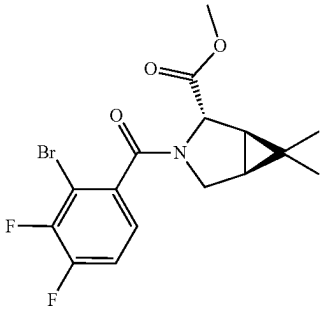
Step 1: General Procedure for Preparation of Intermediate 42-1



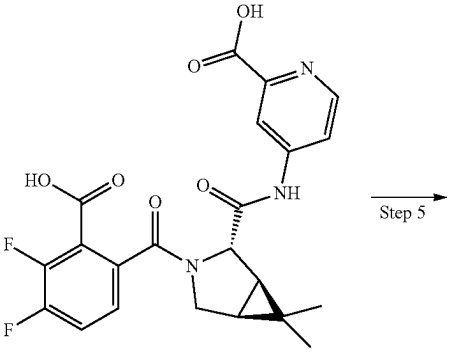
42-1



42-4



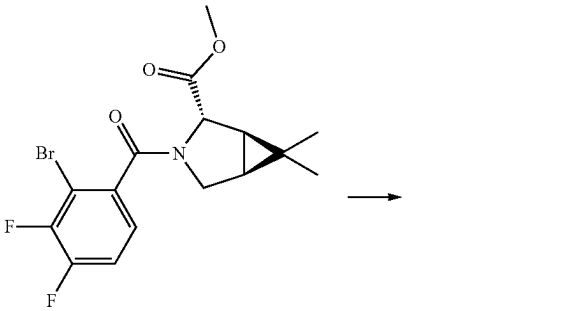
42-2



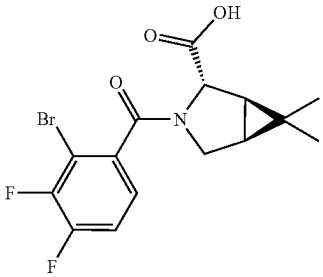
42-5

[0505] To a solution of compound 42-1 (3 g, 12.7 mmol) in dry DCM (30 mL) and dry DMF (0.01 mL) was added $(CO)_2Cl_2$ (6.45 g, 50.8 mmol) at 0° C. for 20 min. To this reaction was added compound 43 (2.87 g, 14.0 mmol), TEA (2.56 g, 25.4 mmol) in at 0° C. The reaction mixture was degassed and purged with N2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The resulting mixture was extracted with DCM (3×30 mL). The organic phases were combined, washed with NaCl (15 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (10%~30%) to give the desired product 42-2 (3.6 g, 63% yield) as a yellow oil. LCMS: m/z=387.9 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 42-3



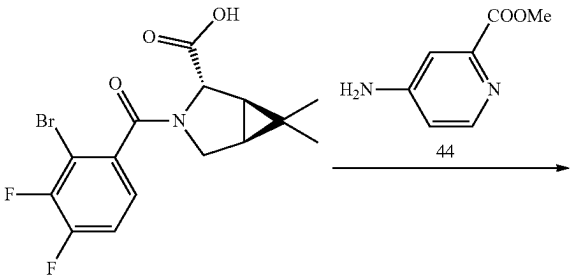
42-2



42-3

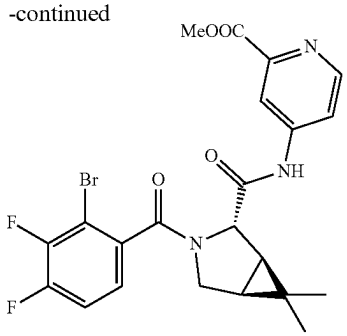
[0506] To a solution of compound 42-2 (3.5 g, 0.26 mmol) in THF/MeOH (50%, 35 mL) was added LiOH (1M, 27 mL, 27.1 mmol) at 0° C. The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The mixture was adjusted to pH=4 with 1 M HCl. The resulting mixture was extracted with EA (3×50 mL). The organic phases were combined, washed with NaCl (20 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get the crude product 42-3 (3 g, 89% yield) as a yellow oil. LCMS: m/z=375.9 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 42-4



42-3

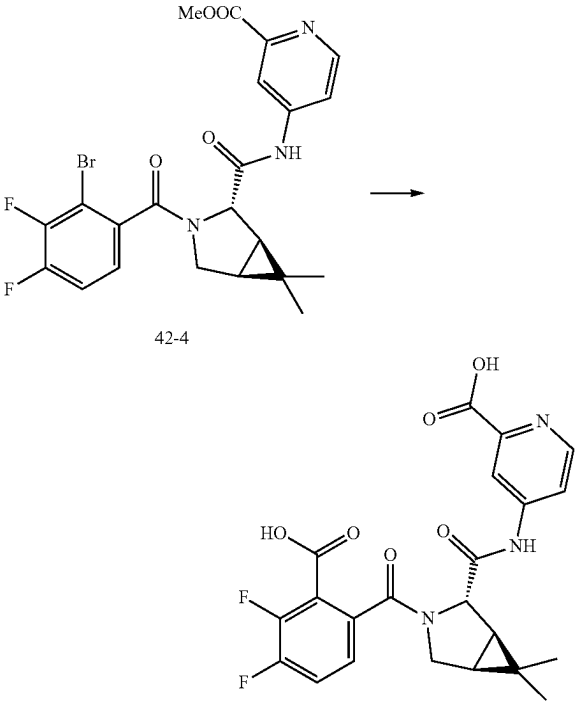
-continued



42-4

[0507] To a solution of compound 42-3 (3.3 g, 8.85 mmol) in dry DMF (33 mL) was added compound 44 (1.4 g, 8.85 mmol), and NMI (2.9 g, 35.4 mmol). To this reaction was added TCFH (4.96 g, 17.7 mmol). The reaction mixture was degassed and purged with N2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with 0.1% FA in H_2O/ACN (5%~95%) to give the product 42-4 (3 g, 66% yield) as a yellow oil. LCMS: m/z=510.2 $[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 42-5



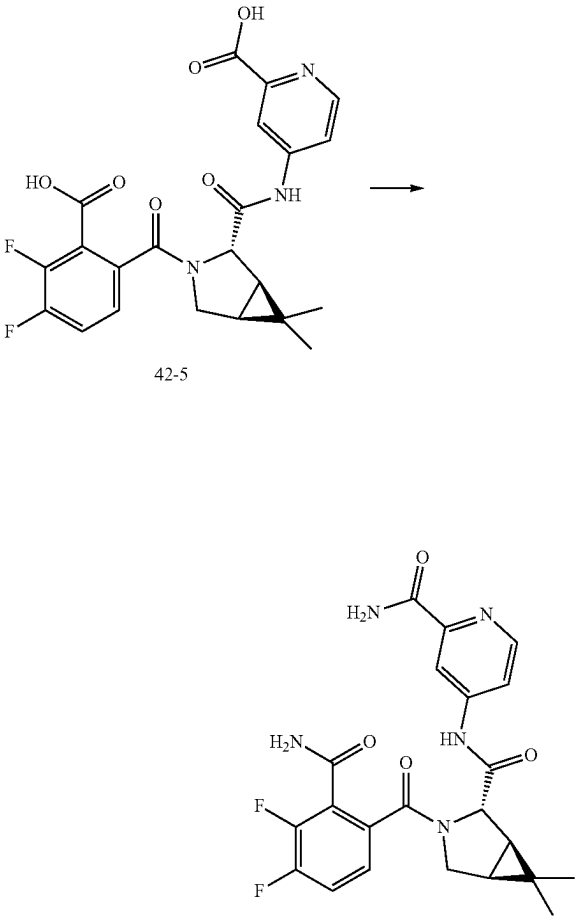
42-4

42-5

[0508] To a solution of compound 42-4 (500 mg, 0.98 mmol), DCPP (301.8 mg, 0.5 mmol) in DMSO (5.0 mL) and water (0.5 mL) was added K_2CO_3 (405.7 mg, 2.94 mmol) and $Pd(OAc)_2$ (44.4 mg, 0.2 mmol), then the whole mixture

was stirred at 100° C. under CO atmosphere for 5 h. The reaction was detected by LCMS, then filtered. And the filtrate was adjusted to pH=6 with 1N HCl, purified by prep-HPLC (ACN/0.1% FA=5%~95%) to afford desired product 42-5 (55 mg, 12%) as a yellow solid. LCMS: m/z=460.1 $[M+H]^+$.

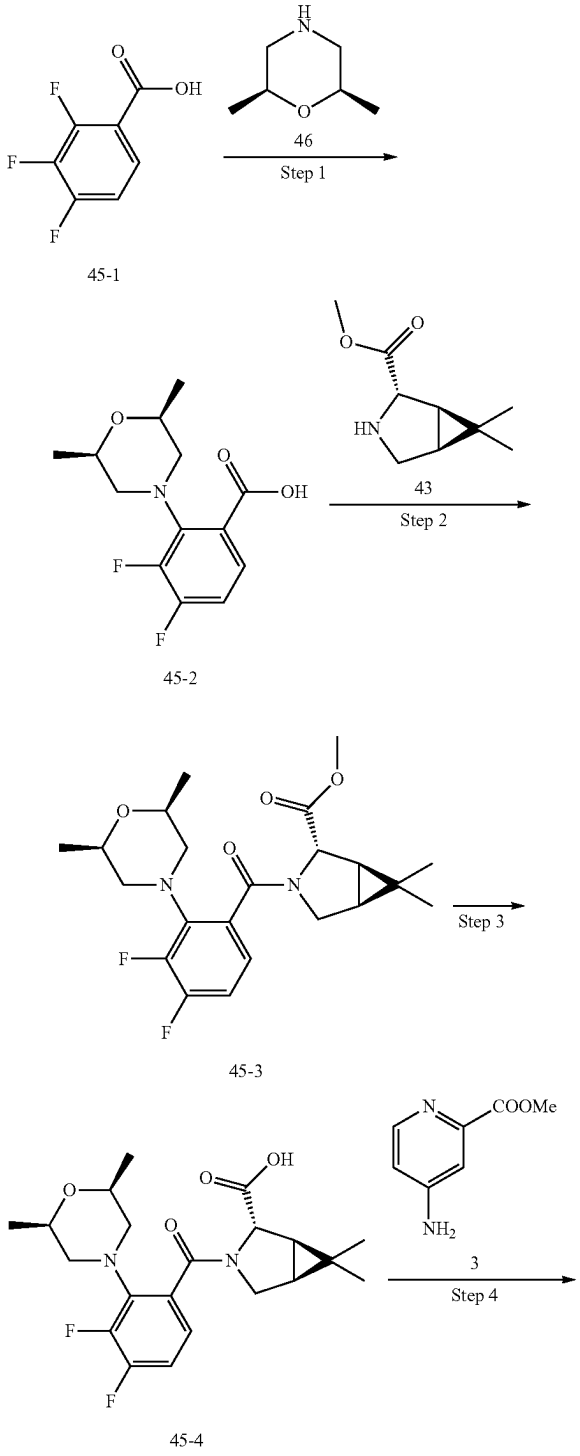
Step 5: General Procedure for Preparation of TM3-1



[0509] To a solution of compound 42-5 (50 mg, 0.11 mmol), NH_4Cl (17.5 mg, 0.33 mmol) in DMF (1 mL) was added HATU (63 mg, 0.16 mmol) and DIEA (71 mg, 0.55 mmol), then the whole mixture was stirred at 25° C. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with 0.1% $NH_3 \cdot H_2O$ in H_2O:ACN (5%~95%) to give the product TM3-1 (2.13 mg, 4.2% yield, 99.25% purity at 214 nm) as a white solid. LCMS: m/z=458.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.45 (q, J=5.4 Hz, 3H), 7.86 (s, 1H), 7.40 (dd, J=16.6, 8.4 Hz, 1H), 7.17-7.00 (m, 2H), 6.69 (s, 1H), 5.60 (s, 1H), 4.60 (s, 1H), 3.87 (dd, J=11.0, 5.4 Hz, 1H), 3.23 (d, J=11.2 Hz, 1H), 1.84 (d, J=7.4 Hz, 1H), 1.43-1.38 (m, 1H), 1.08 (d, J=5.7 Hz, 6H).

Example 3-2

(1R,2S,5S)—N-(2-carbamoylpyridin-4-yl)-3-(2-((2R,6S)-2,6-dimethylmorpholino)-3,4-difluorobenzoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (TM3-2)



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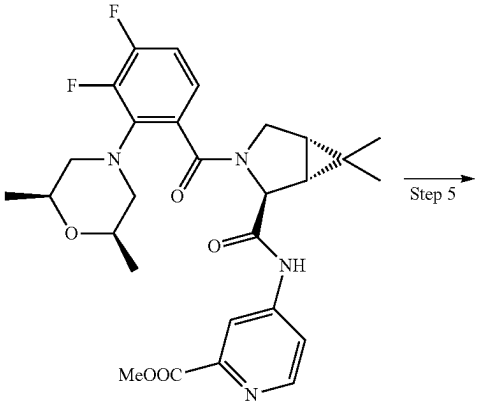
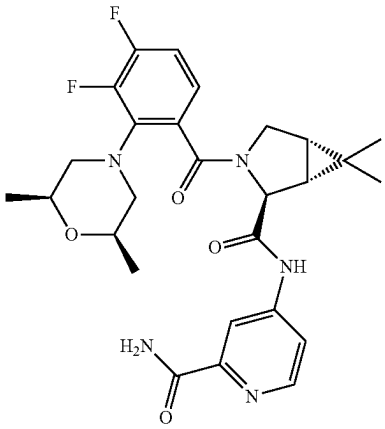
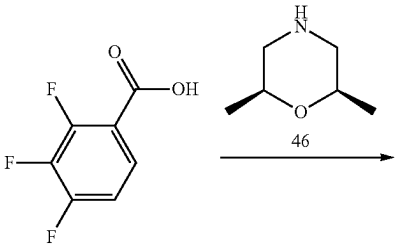


45-5



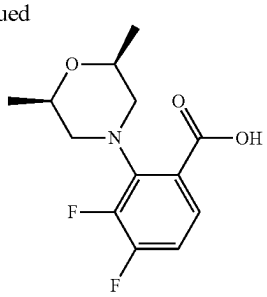
TM3-2

Step 1: General Procedure for Preparation of Intermediate 45-2



45-1

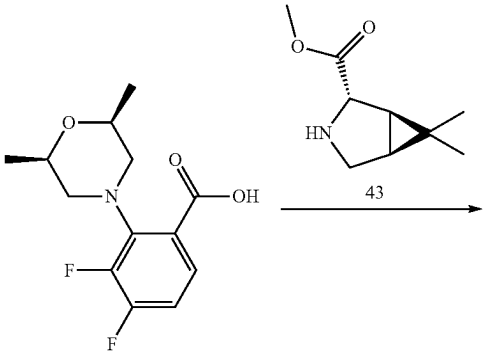
-continued



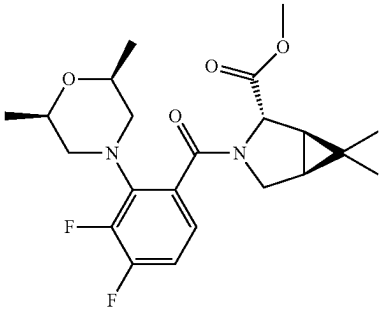
45-2

[0510] To a solution of compound 45-1 (4.5 g, 25.6 mmol) in THF (25 mL) was added LHMDS (1 M, 76.7 mL) at −78° C. for 30 min. To this reaction was added compound 46 (4.4 g, 4.26 mmol) in THF (25 mL) at −78° C. The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 12 h. LCMS detected the desired product. The reaction mixture was added EA (20 mL). The mixture was adjusted to pH=4 with 1 M HCl. The resulting mixture was extracted with EA (3×50 mL). The organic phases were combined, washed with NaCl (40 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (20%~40%) to give the desired product 45-2 (6 g, 78% yield) as a white solid. LCMS: m/z=272.1 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 45-3



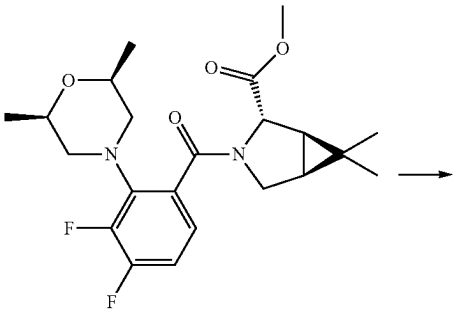
45-2



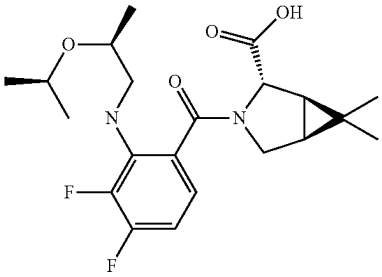
45-3

[0511] To a solution of compound 45-2 (500 mg, 1.85 mmol) in dry DCM (5 mL) and dry DMF (0.01 mL) was added $(CO)_2Cl_2$ (1.17 g, 9.25 mmol) at 0° C. for 20 min. To this reaction was added compound 43 (343 mg, 2.03 mmol), TEA (374 mg, 3.7 mmol) in at 0° C. The reaction mixture was degassed and purged with N2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product 45-3 (550 mg, 70.45% yield) as a yellow oil. LCMS: m/z=432.2 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 45-4



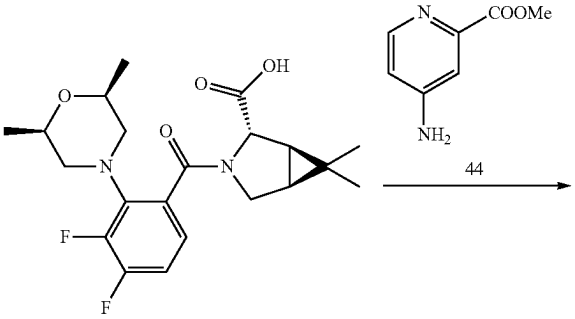
45-3



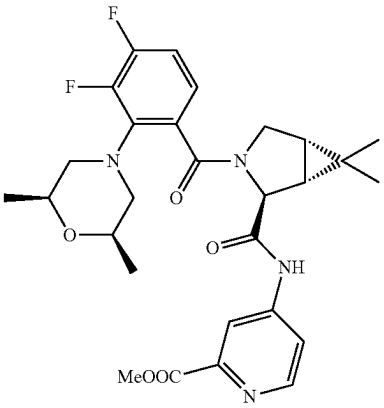
45-4

[0512] To a solution of compound 45-3 (500 mg, 1.3 mmol) in THF/MeOH=1:1 (5 mL) was added LiOH (1M, 3.9 mL, 3.9 mmol) at 0° C. The reaction mixture was degassed and purged with N2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The mixture was adjusted to pH=4 with 1 M HCl. The resulting mixture was extracted with EA (3×20 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get the crude product 45-4 (500 mg, 94.27% yield) as a yellow oil. LCMS: m/z=409.0 $[M+H]^+$.

Step 4: General Procedure for Preparation of Intermediate 45-5



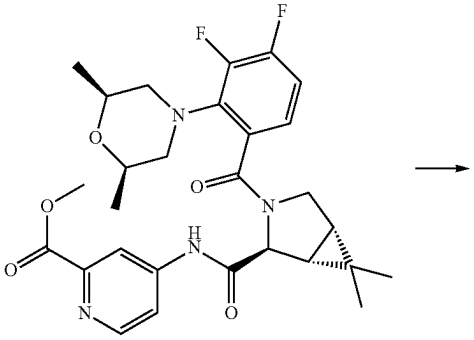
45-4



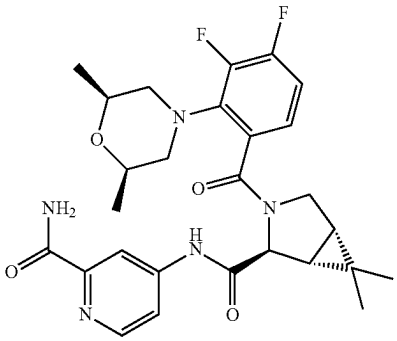
45-5

[0513] To a solution of compound 45-4 (500 mg, 1.22 mmol) in dry DMF (5 mL) was added compound 3 (186.3 mg, 1.22 mmol), NMI (400 mg, 4.88 mmol). To this reaction was added TCFH (683 mg, 2.44 mmol). The reaction mixture was degassed and purged with N2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA in H_2O (5%~95%) to give the product 45-5 (400 mg, 60.49% yield) as a yellow oil. LCMS: m/z=543.3 $[M+H]^+$.

Step 5: General Procedure for Preparation of TM3-2



45-5

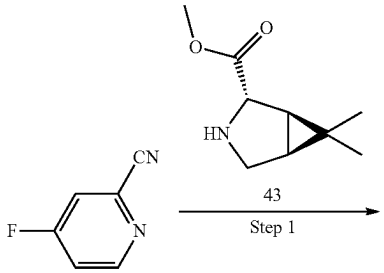


TM3-2

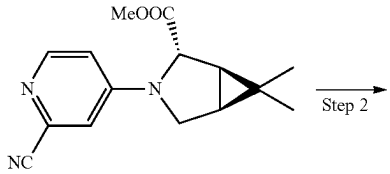
[0514] To a solution of compound 45-5 (200 mg, 0.37 mmol) in NH_3 in MeOH (7 M) (5 mL) The reaction mixture was degassed and purged with N2 and stirring was continued at r.t. for 2 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% $NH_3 \cdot H_2O$ in H_2O (5%~95%) to give the product TM3-2 (23.62 mg, 12.11% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=528.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.50 (t, J=7.0 Hz, 1H), 8.30-7.64 (m, 2H), 6.93 (dd, J=92.8, 48.1 Hz, 2H), 4.61 (d, J=26.1 Hz, 1H), 3.79 (t, J=47.1 Hz, 3H), 3.20 (d, J=11.0 Hz, 1H), 3.09-2.98 (m, 2H), 2.58 (d, J=10.3 Hz, 1H), 1.67-1.52 (m, 2H), 1.21-0.90 (m, 13H).

Example 3-3

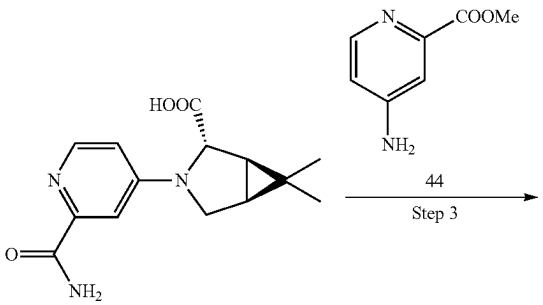
(1R,2S,5S)—N,3-bis(2-carbamoylpyridin-4-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (TM3-3)



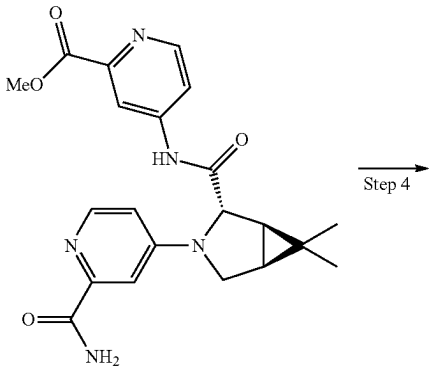
47-1



47-2



47-3



47-4

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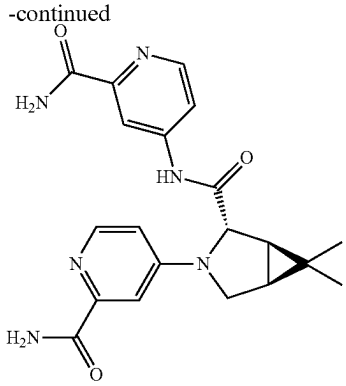
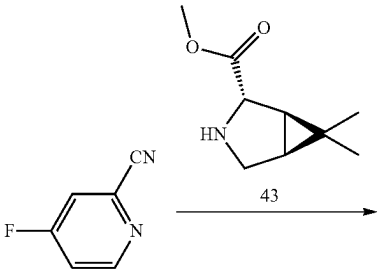
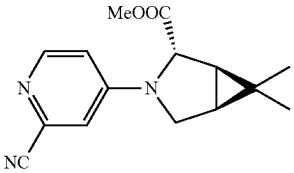


TM3-3

Step 1: General Procedure for Preparation of Intermediate 47-2



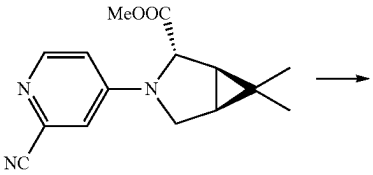
47-1



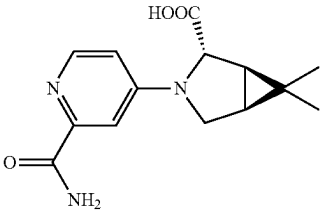
47-2

[0515] To a solution of compound 47-1 (3 g, 24.6 mmol) in DMA (15 mL) was compound 43 (5.54 g, 27.05 mmol), and DIEA (15.87 g, 123 mmol). The reaction mixture was degassed and purged with N2 and stirring was continued at 100° C. for 12 h. LCMS detected the desired product. The resulting mixture was extracted with EA (3×50 mL). The organic phases were combined, washed with NH_4Cl (50 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0%~10%) to give the product 47-2 (3.5 g, 50.85% yield) as a yellow oil. LCMS: m/z=272.3 $[M+H]^+$.

Step 2: General Procedure for Preparation of Intermediate 47-3



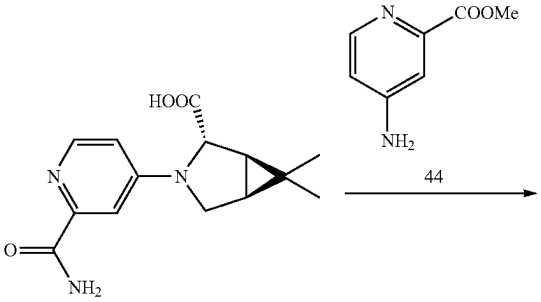
47-2



47-3

[0516] To a solution of compound 47-2 (2.2 g, 8.12 mmol) in THF (20 mL) was added TMSOK (3.12 g, 24.3 mmol) at 25° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at 25° C. for 2 h. LCMS detected the desired product. The mixture was adjusted to pH=4 with 1 M HCl. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% FA (5%~95%) to give the crude product 47-3 (1.6 g, 71.65% yield) as a yellow solid. LCMS: m/z=276.1 $[M+H]^+$.

Step 3: General Procedure for Preparation of Intermediate 47-4



47-3

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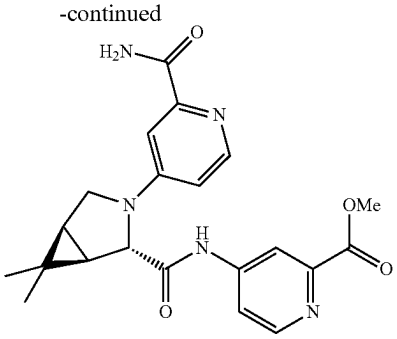
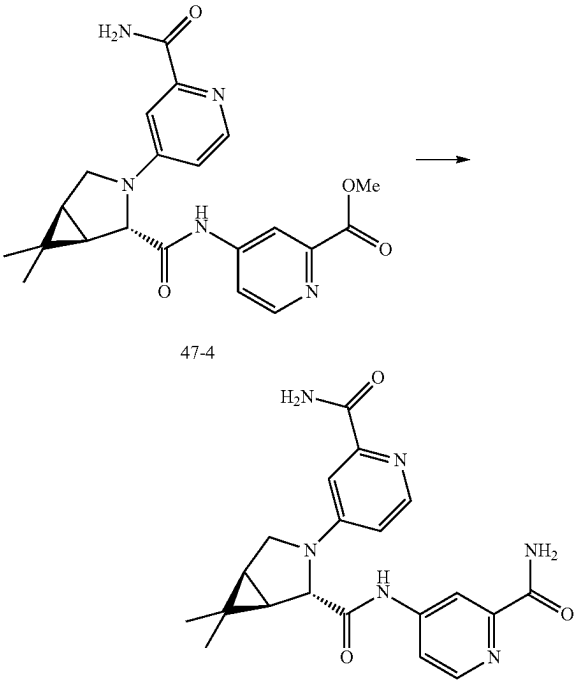


47-4

[0517] To a solution of compound 47-3 (1.5 g, 5.45 mmol) in dry DMF (15 mL) was added compound 44 (994.9 mg, 6.54 mmol), NMI (1.78 g, 21.8 mmol). To this reaction was added TCFH (3.05 g, 10.9 mmol). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 2 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by prep-HPLC (ACN/0.1% FA=5%~95%) to give the crude product 47-4 (600 mg, 26.92% yield) as a yellow oil. LCMS: m/z=410.0 $[M+H]^+$.

Step 4: General Procedure for Preparation of Compound TM3-3



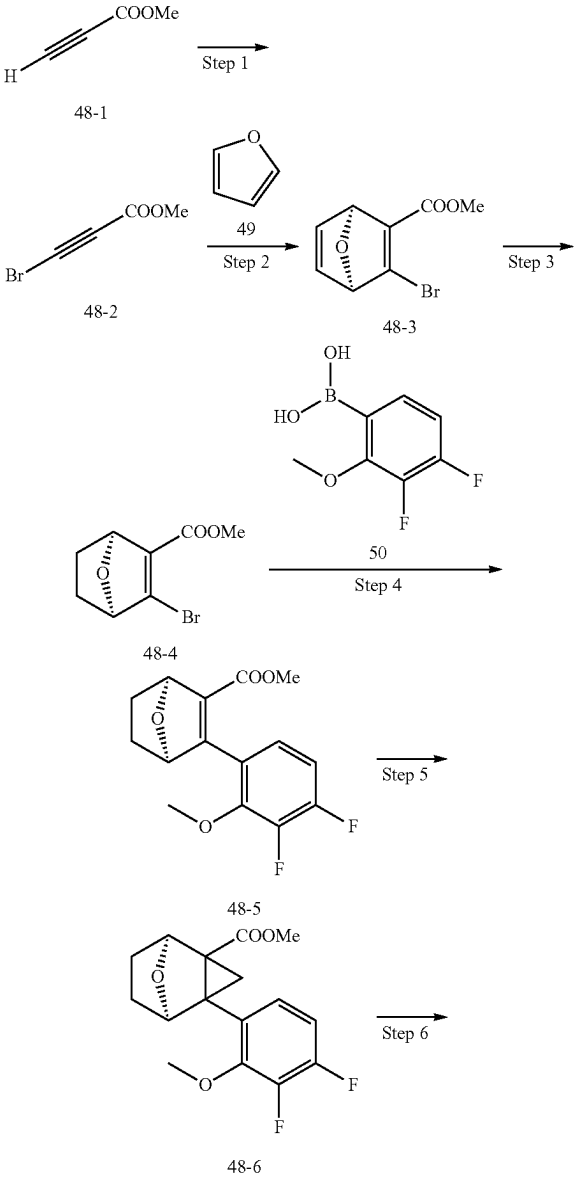
47-4

TM3-3

[0518] To a solution of compound 47-4 (500 mg, 1.22 mmol) in NH_3 in MeOH (7 M, 15 mL). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 48 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% NH_3—H_2O in H_2O (5%~95%) to give the product TM3-3 (69.65 mg, 14.49% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=395.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.49 (d, J=5.5 Hz, 1H), 8.25-8.04 (m, 3H), 7.96 (s, 1H), 7.82 (dd, J=5.5, 2.1 Hz, 1H), 7.61 (d, J=2.1 Hz, 1H), 7.49 (s, 1H), 7.11 (d, J=54.8 Hz, 1H), 6.57 (d, J=99.1 Hz, 1H), 4.32 (s, 1H), 3.77 (s, 1H), 3.43 (d, J=10.3 Hz, 1H), 1.74-1.63 (m, 2H), 1.09 (s, 3H), 0.85 (s, 3H).

Example 3-4

4-((1 S,5R)-4-(3,4-difluoro-2-methoxyphenyl)-8-oxatricyclo[3.2.1.02,4]octane-2-carboxamido)picolinamide (TM3-4)



48-1

48-2

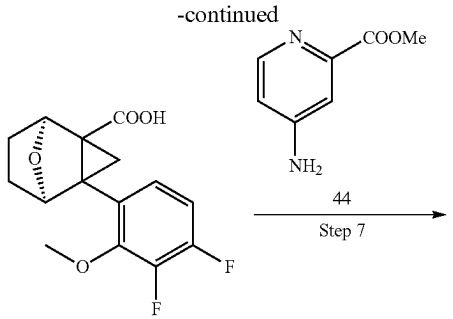
48-3

48-4

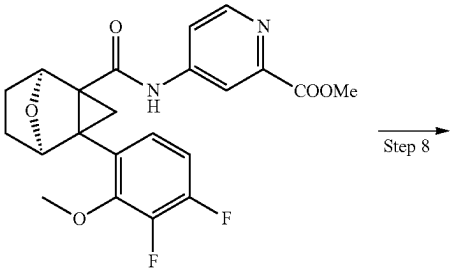
48-5

48-6

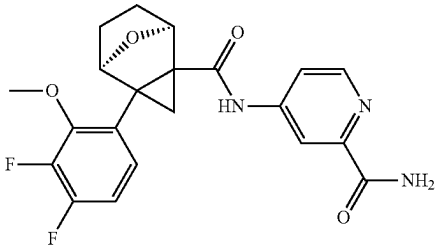
-continued



48-7

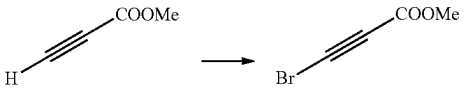


48-8



TM3-4

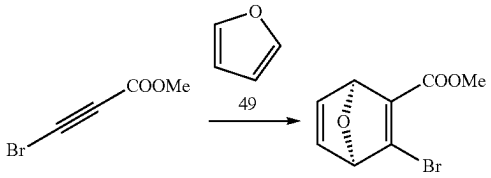
Step 1: General Procedure for Preparation of Intermediate 48-2



48-1 48-2

[0519] To a solution of compound 48-1 (12.0 g, 142.7 mmol) in acetone (250 mL) was added $AgNO_3$ (2.4 g, 14.3 mmol) and NBS (29.2 g, 164.1 mmol), then the reaction mixture was stirred at r.t. for 4 h. The acetone is removed under reduced pressure (25° C., bath temperature) to provide a gray slurry. The slurry is washed with hexane (2×200 mL), the gray solid is removed by filtration, and the filtrate is concentrated in vacuo to afford crude compound 48-2 (21.6 g, 93.94% yield) as a pale-yellow oil, which was used in next step without further purification.

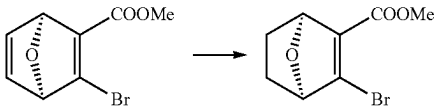
Step 2: General Procedure for Preparation of Intermediate 48-3



48-2 48-3

[0520] A solution of compound 48-2 (20.6 g, 0.13 mol) in furan (40.0 mL) was stirred at 80° C. in sealed tube for 16 h. The reaction was detected by LCMS. The mixture was concentrated, the residue was purified by silica gel column chromatography (EA/PE=0%~20%) to afford compound 48-3 (4.6 g, 15.75% yield) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=1.7 Hz, 1H), 7.20 (d, J=1.8 Hz, 1H), 5.70 (d, J=1.5 Hz, 1H), 5.33 (t, J=1.6 Hz, 1H), 3.80 (s, 3H).

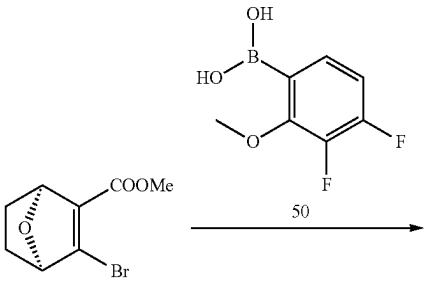
Step 3: General Procedure for Preparation of Intermediate 48-4



48-3 48-4

[0521] To a solution of compound 48-3 (3.6 g, 15.58 mmol) in EA (50 mL) was added Pd/C (1.8 g), then the reaction mixture was stirred at r.t. under H2 atmosphere for 3 h. The reaction was detected by LCMS. Reaction completely, the resulting mixture was filtered through celite, the filtrate was concentrated, the residue was purified by silica gel column chromatography (EA/PE=0%~15%) to afford compound 48-4 (3.2 g, 69.57% yield) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (d, J=3.1 Hz, 1H), 4.95 (d, J=3.6 Hz, 1H), 3.80 (s, 3H), 1.94-1.89 (m, 2H), 1.47-1.42 (m, 2H).

Step 4: General Procedure for Preparation of Intermediate 48-5



48-4

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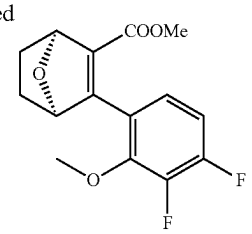
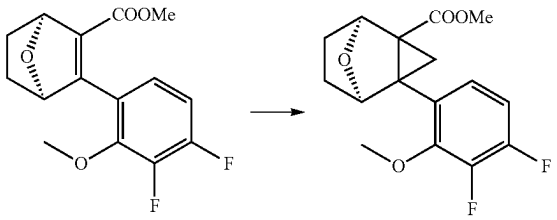


48-5

[0522] To a mixture of compound 48-4 (300 mg, 1.29 mmol), compound 0 (290 mg, 1.55 mmol), Na_2CO_3 (273 mg, 2.58 mmol) and PPh_3 (34 mg, 0.13 mmol) in toluene (6.0 mL) and ethanol (20 mL) was added $Pd(OAc)_2$ (15 mg, 0.06 mmol), then the whole mixture was stirred at 70° C. for 16 h under argon. The reaction was detected by LCMS. Reaction completely, the mixture was poured into water (20 mL), extracted with EA (20 mL*3), the combined organic layers were washed with brine, dried and concentrated, the residue was purified by silica gel column chromatography (EA/PE=0%~20%) to afford compound 48-5 (280 mg, 73.49% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.05 (m, 1H), 6.86 (td, J=9.1, 7.4 Hz, 1H), 5.31 (d, J=3.5 Hz, 1H), 5.21 (d, J=4.5 Hz, 1H), 3.96 (d, J=2.6 Hz, 3H), 3.69 (s, 3H), 2.02-1.91 (m, 2H), 1.55-1.45 (m, 2H).

Step 5: General Procedure for Preparation of Intermediate 48-6

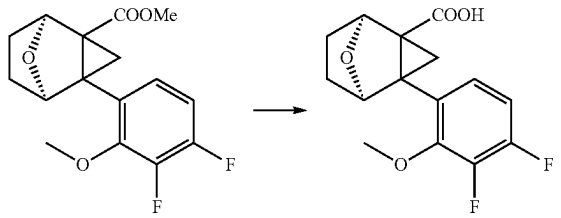


48-5 48-6

[0523] To a solution of trimethylsulfoxonium iodide (2.0 g, 9.09 mmol) in dry DMSO (30 mL) was added NaH (364 mg, 9.09 mmol), the mixture was stirred at r.t. for 0.5 h. Then a solution of compound 48-5 (0.9 g, 3.03 mmol) in dry DMSO (20 mL) was added. The whole mixture was stirred at 50° C. for 2 h. The reaction was detected by LCMS. Reaction completely, the mixture was poured into water (250 mL), extracted with EA (200 mL*2), the combined organic layers were washed with brine (2×100 mL), dried and concentrated, the residue was purified by silica gel column chromatography (EA/PE=0%~20%) to afford compound 48-6 (660 mg, 70.21% yield) as a colorless oil.

[0524] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81-6.73 (m, 1H), 6.67 (dd, J=10.3, 4.1 Hz, 1H), 4.61 (d, J=4.9 Hz, 1H), 4.37 (d, J=4.9 Hz, 1H), 4.01 (d, J=3.2 Hz, 3H), 3.63 (s, 3H), 2.26-2.19 (m, 1H), 1.88-1.70 (m, 3H), 1.57-1.47 (m, 1H), 1.10 (d, J=4.1 Hz, 1H).

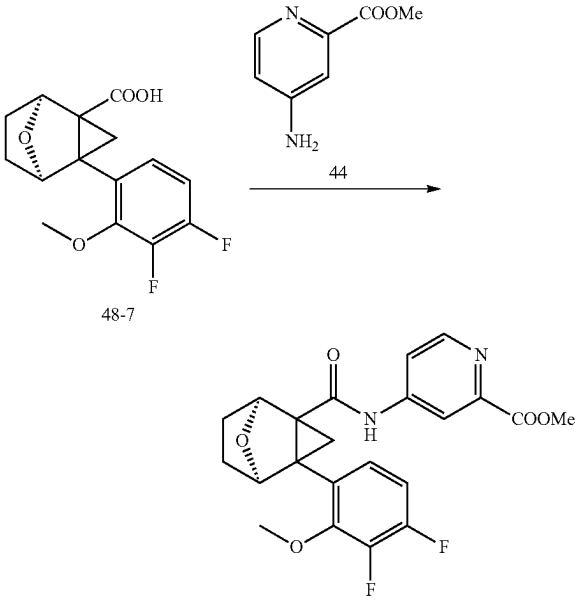
Step 6: General Procedure for Preparation of Intermediate 48-7



48-6 48-7

[0525] To a solution of compound 48-6 (600 mg, 1.94 mmol) in THF (10 mL) was added TMSOK (993 mg, 7.74 mmol), then the whole mixture was stirred at 40° C. for 24 h. The reaction was detected by LCMS. Reaction completely, the mixture was adjusted pH to 4 with 1N HCl, extracted with EA (30 mL*3), the combined organic layers were washed with brine, dried and concentrated to afford compound 48-7 (620 mg, 108.20% yield) as a white solid. LCMS: m/z=295.1 $[M-1]^-$.

Step 7: General Procedure for Preparation of Intermediate 48-8

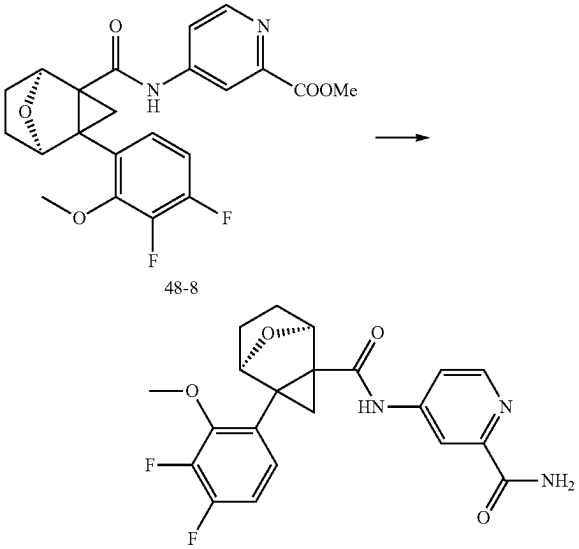


48-7 48-8

[0526] To a solution of compound 48-7 (560 mg, 1.89 mmol), compound 44 (287 mg, 1.89 mmol) in dry DMF (8 mL) was added NMI (620 mg, 7.56 mmol) and TCFH (1060 mg, 3.78 mmol), then the reaction mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. Reaction completely, the mixture was poured into water (25 mL), extracted with EA (2×30 mL), the combined organic layers were washed with brine (2×20 mL), dried and concentrated, the residue was purified by silica gel column chromatogra-

phy (MeOH/DCM=0%~8%) to afford compound 48-8 (210 mg, 25.83% yield) as a white solid. LCMS: m/z=431.1 $[M+H]^+$.

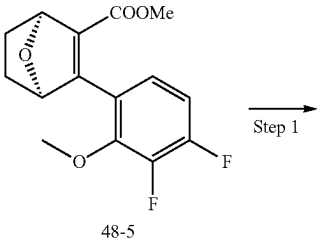
Step 8: General Procedure for Preparation of Compound TM3-4



[0527] A solution of compound 48-8 (180 mg, 0.16 mmol) in 7.0M NH_3/MeOH (5.0 mL) was stirred at r.t. for 24 h. The reaction was detected by LCMS. The resulting mixture was concentrated, the residue was purified by prep-HPLC (ACN/0.1% NH_3H_2O=5%~60%) to afford TM3-4 (48.66 mg, 27.97% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=416.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.45 (d, J=5.5 Hz, 1H), 8.19 (d, J=2.0 Hz, 1H), 8.05 (s, 1H), 7.88 (dd, J=5.5, 2.2 Hz, 1H), 7.60 (s, 1H), 7.05 (dd, J=17.3, 9.2 Hz, 1H), 6.91 (t, J=6.7 Hz, 1H), 4.81 (d, J=4.6 Hz, 1H), 4.39 (d, J=4.8 Hz, 1H), 3.93 (d, J=2.5 Hz, 3H), 2.35-2.25 (m, 1H), 1.83-1.65 (m, 3H), 1.50-1.39 (m, 1H), 1.31 (d, J=4.6 Hz, 1H).

Example 3-5

4-((1 S,4R)-3-(3,4-difluoro-2-methoxyphenyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxamido)picolinamide (TM3-5)



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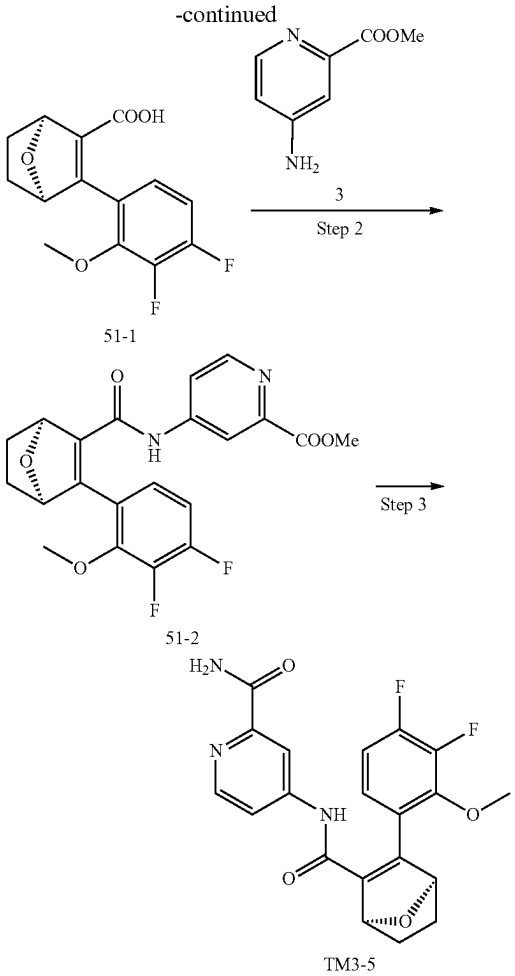
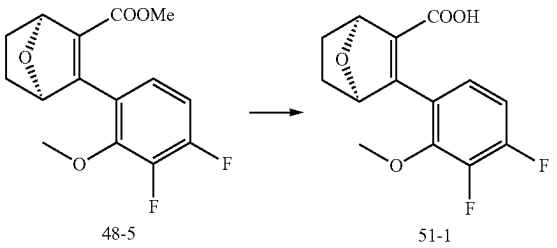
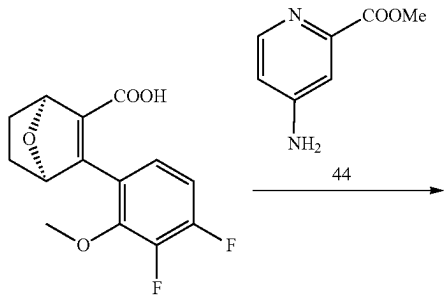


Step 1: General Procedure for Preparation of Intermediate 51-1

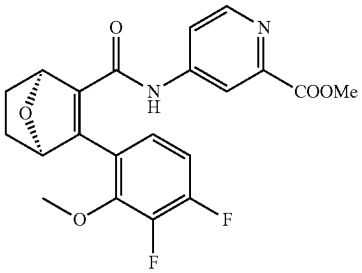


[0528] To a solution of previously synthesized compound 48-5 (shown in TM3-5; 140 mg, 0.47 mmol) in THF (3.0 mL) was added TMSOK (151 mg, 1.18 mmol), then the whole mixture was stirred at r.t. for 16 h. The reaction was detected by LCMS. Reaction completely, the mixture was adjusted pH to 4 with 1N HCl, extracted with EA (3×15 mL), the combined organic layers were washed with brine, dried and concentrated to afford compound 51-1 (330 mg, 123.60% yield) as a brown oil. LCMS: m/z=280.8 $[M-1]^-$.

Step 2: General Procedure for Preparation of Intermediate 51-2



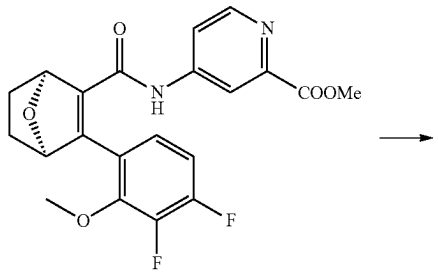
51-1



51-2

[0529] To a solution of compound 51-1 (300 mg, 1.06 mmol) and compound 44 (178 mg, 1.17 mmol) in dry DMF (4.5 mL) was added NMI (348 mg, 4.24 mmol) and TCFH (595 mg, 1.17 mmol), then the reaction mixture was stirred at r.t. for 16 h. Reaction completely, the mixture was poured into water (25 mL), extracted with EA (2×30 mL), then the combined organic layers were washed with brine (2×20 mL), dried and concentrated, the residue was purified by silica gel column chromatography (MeOH/DCM=0%~8%) to afford compound 51-2 (230 mg, 51.92% yield) as a brown oil. LCMS: m/z=417.1 $[M+H]^+$.

Step 3: General Procedure for Preparation of Compound TM3-5



51-2

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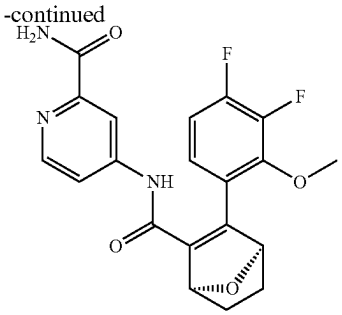
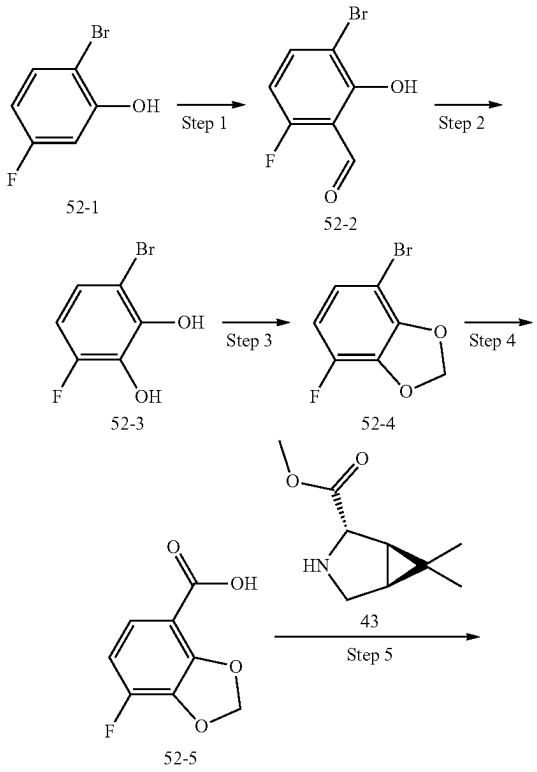


TM3-5

[0530] A solution of compound 51-2 (200 mg, 0.048 mmol) in NH_3/MeOH (5.0 mL) was stirred at r.t. for 24 h. The reaction was detected by LCMS. The mixture was filtered, the filter cake was purified by prep-HPLC to afford TM3-5 (60 mg, 31.09% yield, 100% purity at 214 nm) as a white solid. LCMS: m/z=402.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.45 (d, J=5.5 Hz, 1H), 8.18 (d, J=2.0 Hz, 1H), 8.05 (d, J=2.2 Hz, 1H), 7.81 (dd, J=5.5, 2.2 Hz, 1H), 7.60 (d, J=2.2 Hz, 1H), 7.17 (dd, J=8.9, 2.6 Hz, 2H), 5.36 (t, J=4.8 Hz, 2H), 3.83 (d, J=2.2 Hz, 3H), 1.97-1.80 (m, 2H), 1.64-1.51 (m, 1H), 1.42-1.27 (m, 1H).

Example 3-6

(1R,2S,5S)—N-(2-carbamoylpyridin-4-yl)-3-(7-fluorobenzo[d][1,3]dioxole-4-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (TM3-6)



52-1 52-2 52-3 52-4 52-5

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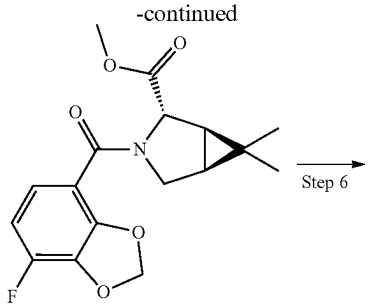
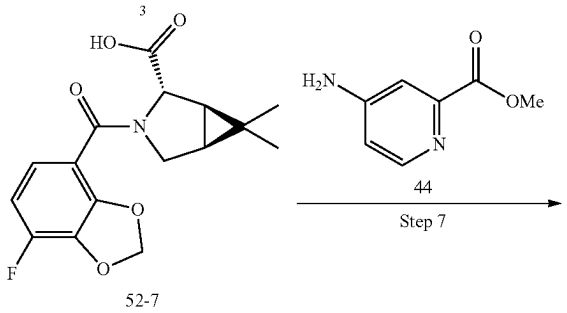
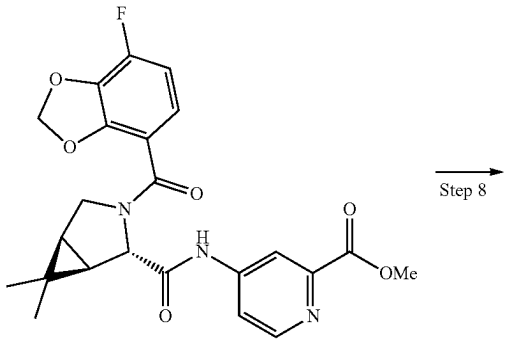
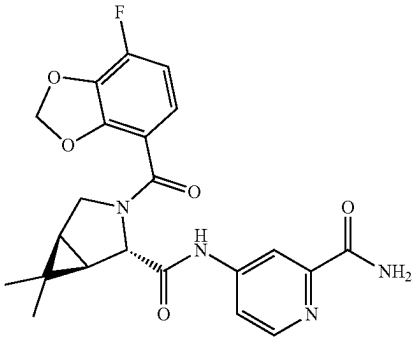
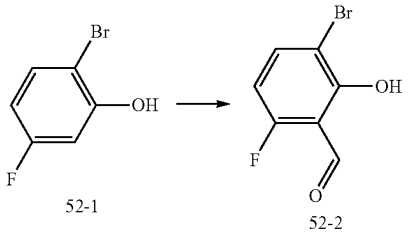






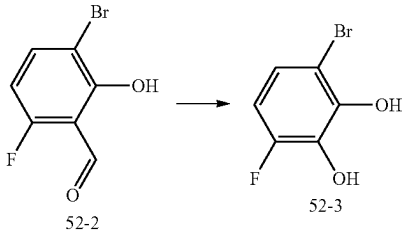


Step 1: General Procedure for Preparation of Intermediate 52-2



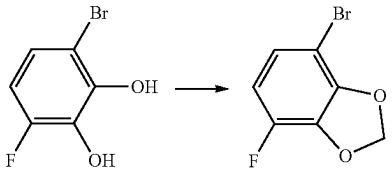
[0531] To a solution of Paraformaldehyde (11.78 g, 392.6 mmol) in dry THF (300 mL) was added $MgCl_2$ (24.8 g, 261.8 mmol) and Et_3N (26.4 g, 261.8 mmol) at r.t. for 10 min. To this reaction was added compound 52-1 (25 g, 130.8 mmol). The reaction mixture was degassed and purged with N_2 and stirring was continued at 70° C. for 12 h. LCMS detected the desired product. The reaction mixture was added EA (100 mL). The resulting mixture was extracted with EA (3×150 mL). The organic phases were combined, washed with NH_4Cl (50 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0%~10%) to give the desired product 52-2 (7 g, 24.5% yield) as a yellow solid. LCMS: m/z=216.9 $[M-H]^+$.

Step 2: General Procedure for Preparation of Intermediate 52-3



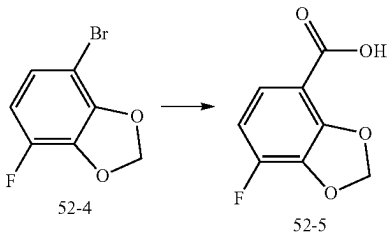
[0532] To a solution of compound 52-2 (4 g, 18.3 mmol) in THF (40 mL) was added NaOH (1.4 g, 36.7 mmol) in H_2O (24 mL). To this reaction was added 30% H_2O_2 (8 mL) at r.t. The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 2 h. LCMS detected the desired product. The reaction mixture was added EA (15 mL). The mixture was adjusted to pH=4 with 1M HCl. The resulting mixture was extracted with EA (3×50 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (20%~40%) to give the desired product 52-3 (4 g, 60% yield) as a yellow oil. LCMS: m/z=204.9 $[M-H]^+$.

Step 3: General Procedure for Preparation of Intermediate 52-4



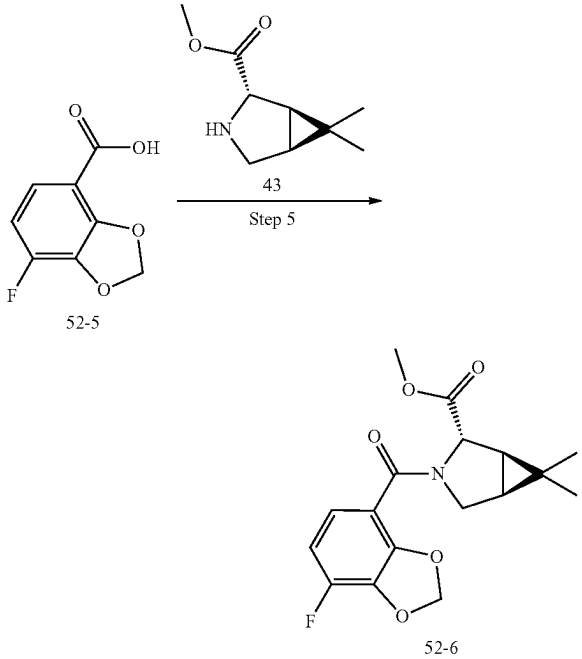
[0533] To a solution of compound 52-3 (2 g, 9.71 mmol) in DMF (30 mL) was added diiodomethane (3.9 g, 14.5 mmol) and Cs_2CO_3 (6.3 g, 19.4 mmol) at r.t. The reaction mixture was degassed and purged with N_2 and stirring was continued at 100° C. for 12 h. LCMS detected the desired product. The reaction mixture was added EA (10 mL). The resulting mixture was extracted with EA (3×20 mL). The organic phases were combined, washed with NaCl (30 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0%~10%) to give the desired product 52-4 (2.3 g, 54% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (dd, J=9.2, 4.4 Hz, 1H), 6.86 (dd, J=9.9, 9.2 Hz, 1H), 6.22 (s, 2H).

Step 4: General Procedure for Preparation of Intermediate 52-5



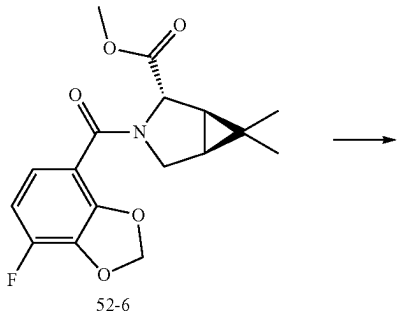
[0534] To a solution of compound 52-4 (1.8 g, 8.25 mmol) in dry THF (20 mL) was added n-BuLi (2.5 M, 5 mL) at −78° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at −78° C. for 2 h. After cooling again to −78° C., carbon dioxide from evaporation of dry ice was bubbled through the solution for 10 min. LCMS detected the desired product. The mixture was adjusted to pH 4 with 1 M HCl. The resulting mixture was extracted with EA (3×20 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (10%~30%) to give the crude product 52-5 (1.3 g, 85.6% yield) as a white solid. LCMS: m/z=183.1 $[M-H]^+$.

Step 5: General Procedure for Preparation of Intermediate 52-6



[0535] To a solution of compound 52-5 (700 mg, 3.8 mmol) in dry DCM (10 mL) and dry DMF (0.01 mL) was added $(CO)_2Cl_2$ (2.88 g, 22.8 mmol) at 0° C. for 20 min. To this reaction was added compound 2 (860 mg, 4.2 mmol), TEA (767.6 mg, 7.6 mmol) in at 0° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 48 h. LCMS detected the desired product. The resulting reaction was extracted with DCM (3×50 mL). The organic phases were combined, washed with NaCl (20 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by prep-HPLC (ACN/0.1% $NH_3 \cdot H_2O$=5%~95%) to give the product 52-6 (350 mg, 27.5% yield) as a yellow solid. LCMS: m/z=336.1 $[M+H]^+$.

Step 6: General Procedure for Preparation of Intermediate 52-7



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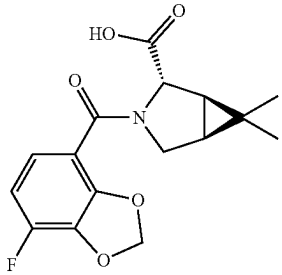
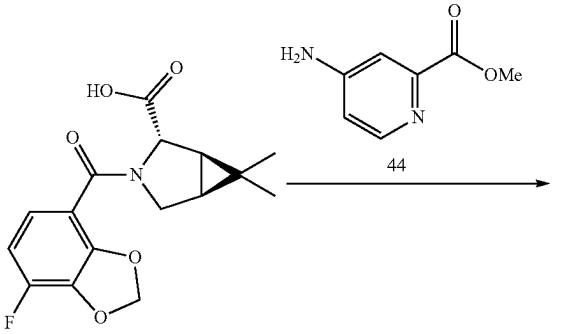


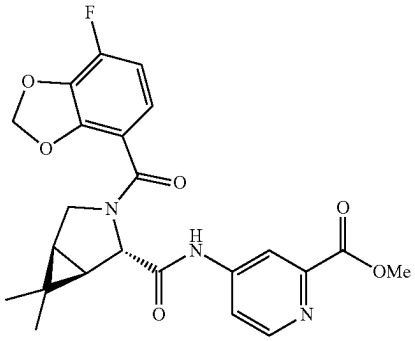
52-7

[0536] To a solution of compound 52-6 (330 mg, 0.98 mmol) in THF/MeOH=1:1 (3 mL) was added LiOH (1M, 3 mL, 2.95 mmol) at 0° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at 25° C. for 16 h. LCMS detected the desired product. The mixture was adjusted to pH=4 with 1 M HCl. The resulting reaction was extracted with EA (3×20 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get the crude product 52-7 (300 mg, 89% yield) as a yellow oil. LCMS: m/z=322.0 $[M+H]^+$.

Step 7: General Procedure for Preparation of Intermediate 52-8



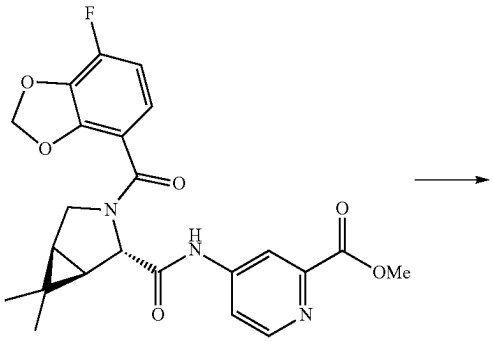
52-7



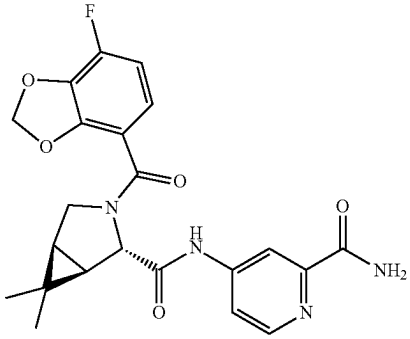
52-8

[0537] To a solution of compound 52-7 (300 mg, 0.93 mmol) in dry DMF (3 mL) was added compound 3 (156 mg, 1.03 mmol), NMI (305 mg, 3.72 mmol). To this reaction was added TCFH (521 mg, 1.86 mmol). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was later concentrated under reduced pressure to get residue. The residue was purified by prep-HPLC (ACN/0.1% FA=5%~95%) to give the product 52-8 (200 mg, 47.3% yield) as a white solid. LCMS: m/z=456.0 $[M+H]^+$.

Step 8: General Procedure for Preparation of TM3-6



52-8

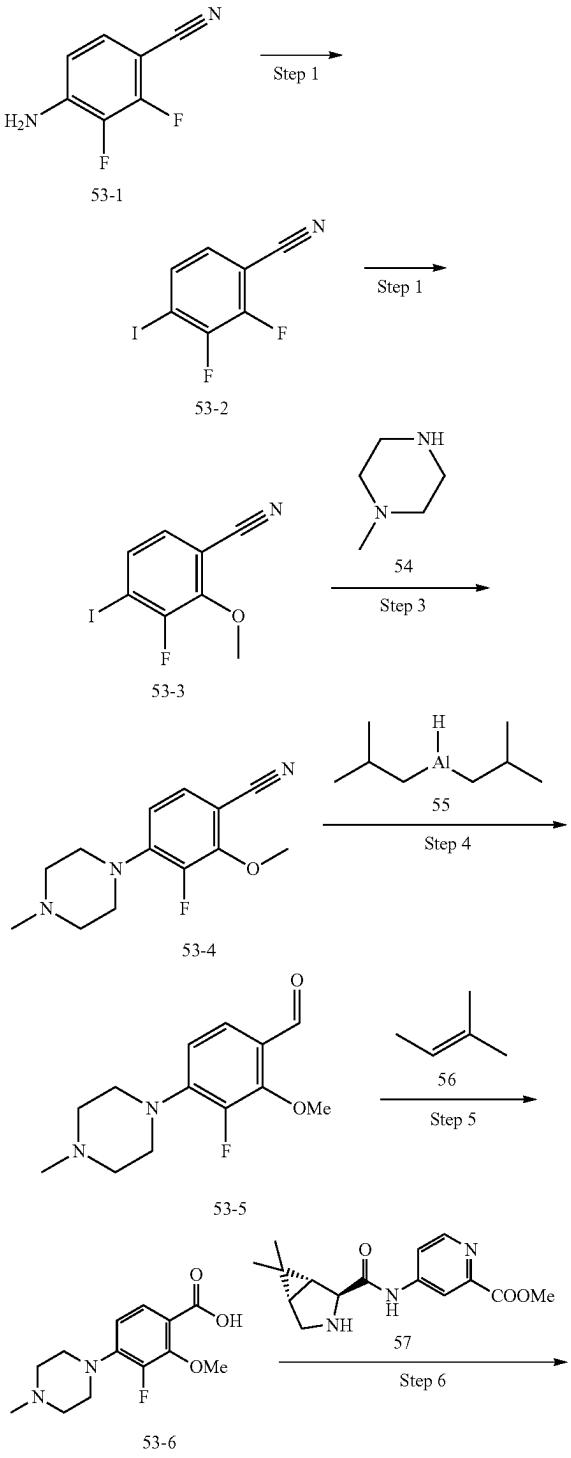


TM3-6

[0538] To a solution of compound 52-8 (200 mg, 0.44 mmol) in NH_3 in MeOH (7 M, 5 mL) The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with ACN/0.1% $NH_3 \cdot H_2O$ in H_2O (5%~95%) to give the product TM3-6 (30.31 mg, 15.6% yield, 99.84% purity at 214 nm) as a white solid. LCMS: m/z=441.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 10.48 (s, 1H), 8.50 (d, J=5.5 Hz, 1H), 8.44 (d, J=5.5 Hz, 1H), 8.31 (d, J=2.0 Hz, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 7.77 (dd, J=5.5, 2.2 Hz, 1H), 7.62 (s, 1H), 7.58 (dd, J=5.5, 2.1 Hz, 1H), 6.94-6.89 (m, 1H), 6.84 (dd, J=8.9, 5.0 Hz, 1H), 6.73-6.68 (m, 1H), 6.61 (dd, J=8.8, 4.9 Hz, 1H), 6.23 (d, J=5.2 Hz, 3H), 6.13 (s, 1H), 4.54 (s, 1H), 4.38 (s, 1H), 3.80 (dd, J=11.4, 6.0 Hz, 2H), 3.57 (d, J=12.3 Hz, 1H), 3.42 (d, J=10.8 Hz, 1H), 1.61-1.52 (m, 3H), 1.09 (s, 3H), 1.03 (d, J=9.9 Hz, 6H).

Example 3-7

(1R,2S,5S)—N-(2-carbamoylpyridin-4-yl)-3-(3-fluoro-2-methoxy-4-(4-methylpiperazin-1-yl)benzoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (TM3-7)



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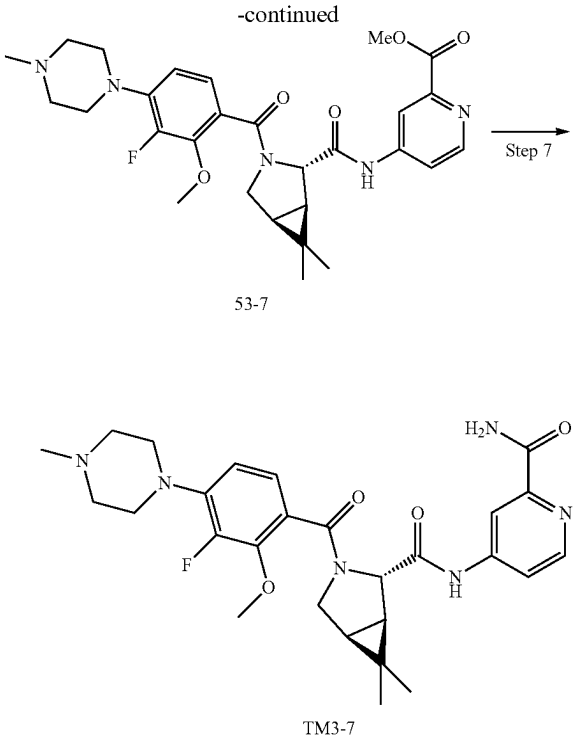
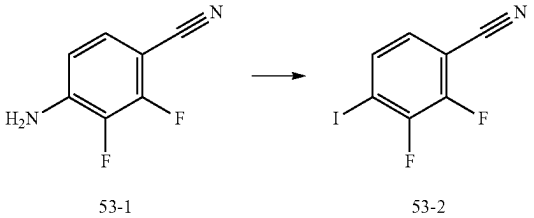
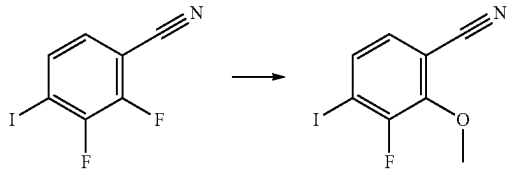


Step 1: General Procedure for Preparation of Intermediate 53-2



[0539] To a solution of tert-butylnitrite (16.1 g, 155.76 mmol) in ACN (120 mL) was added CuI (11.13 g, 58.2 mmol) at 65° C. for 10 min. To this reaction was added compound 53-1 (6 g, 38.94 mmol). The reaction mixture was degassed and purged with N_2 and stirring was continued at 65° C. for 12 h. LCMS detected the desired product. The reaction mixture was added $Na_2S_2O_3$ (50 mL). The resulting reaction was extracted with EA (2×120 mL). The organic phases were combined, washed with brine (50 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure. The crude product was purified using column chromatogram by eluting with EA/PE (0%~10%) to afford compound 53-2 (5.8 g, 56.2% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (ddd, J=8.3, 5.4, 1.8 Hz, 1H), 7.61-7.54 (m, 1H).

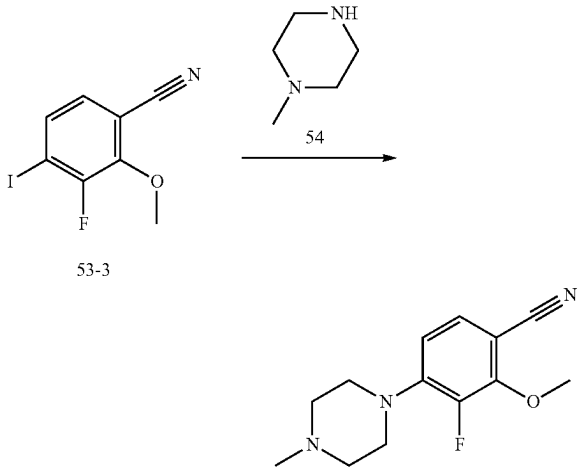
Step 2: General Procedure for Preparation of Intermediate 53-3



53-2 53-3

[0540] To a solution of compound 53-2 (5 g, 18.87 mmol) in dry THF (100 mL) was added 30% MeONa (4.07 g, 22.64 mmol) at 25° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at 25° C. for 12 h. LCMS detected the desired product. The reaction mixture was added EA (50 mL). The resulting mixture was extracted with EA (3×100 mL). The organic phases were combined, washed with NaCl (60 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0%~10%) to give the desired product 53-3 (5.4 g, 100% yield) as a yellow solid. GCMS: m/z=277 $[M+H]^+$

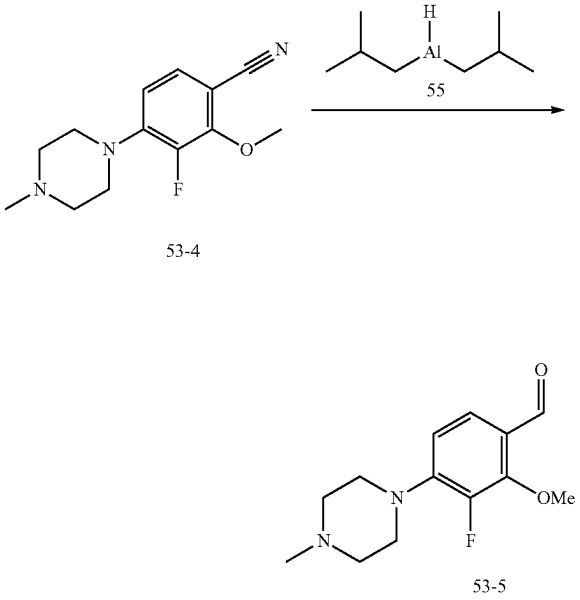
Step 3: General Procedure for Preparation of Intermediate 53-4



53-3 53-4

[0541] To a solution of compound 53-3 (5 g, 18.05 mmol) in dioxane (60 mL) was added 1-methylpiperazine (54; 1.8 g, 18.05 mmol), X-phos Pd G_3 (1.53 g, 1.8 mmol) and Cs_2CO_3 (11.76 g, 36.1 mmol) at 25° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at 110° C. for 12 h. LCMS detected the desired product. The reaction mixture was added EA (50 mL). The resulting mixture was extracted with EA (3×100 mL). The organic phases were combined, washed with NaCl (60 mL) and dried over Na_2SO_4. After filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0%~10%) to give the desired product 53-4 (2.8 g, 62.3% yield) as a yellow solid. LCMS: m/z=250.1 $[M+H]^+$

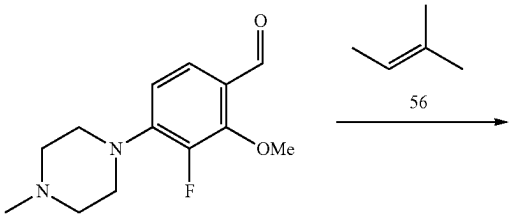
Step 4: General Procedure for Preparation of Intermediate 53-5



53-4 53-5

[0542] To a solution of compound 53-4 (2 g, 8.03 mmol) in dry DCM (20 mL) was added diisobutylaluminum hydride (55; 1.5 M, 10.7 mL) at 0° C. The reaction mixture was degassed and purged with N_2 and stirring was continued at 0° C. for 2 h. LCMS detected the desired product. The reaction mixture was added saturated aqueous Potassium sodium tartrate (15 mL). The resulting mixture was extracted with EA (3×10 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0%~10%) to give the desired product 53-5 (400 mg, 19.8% yield) as a yellow solid. LCMS: m/z=253.1 $[M+H]^+$

Step 5: General Procedure for Preparation of Intermediate 53-6



53-5

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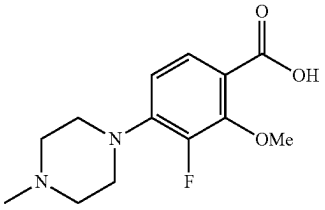
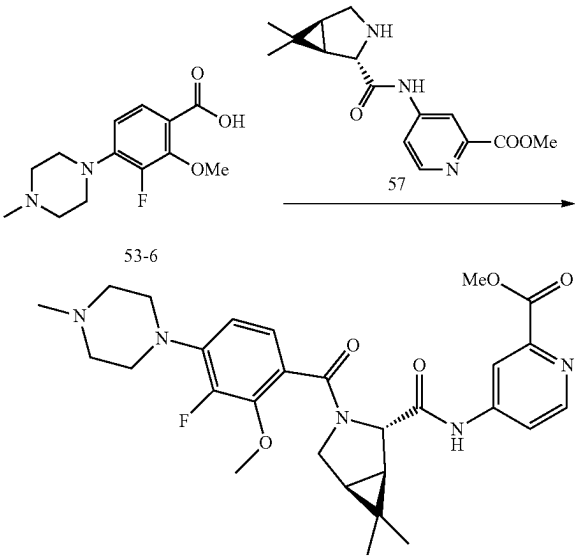


53-6

[0543] To a solution of compound 53-5 (200 mg, 0.79 mmol) in THF:t-BuOH:H_2O=7:2:1 (4 mL) was added 2-methylbut-2-ene (56; 555 mg, 7.9 mmol), NaH_2PO_4 (285.8 mg, 2.4 mmol). To this reaction was added $NaClO_2$ (142.9 mg, 1.58 mmol). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The mixture was adjusted to pH=4 with 1 M HCl. The resulting mixture was extracted with EA (3×10 mL). The organic phases were combined, washed with NaCl (10 mL) and dried over Na_2SO_4. And then filtrated, the filtrate was concentrated under reduced pressure to get residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0%~10%) to give the crude product 53-6 (200 mg, 46.6% yield) as a white solid. LCMS: m/z=269.1 $[M+H]^+$.

Step 6: General Procedure for Preparation of Intermediate 53-7



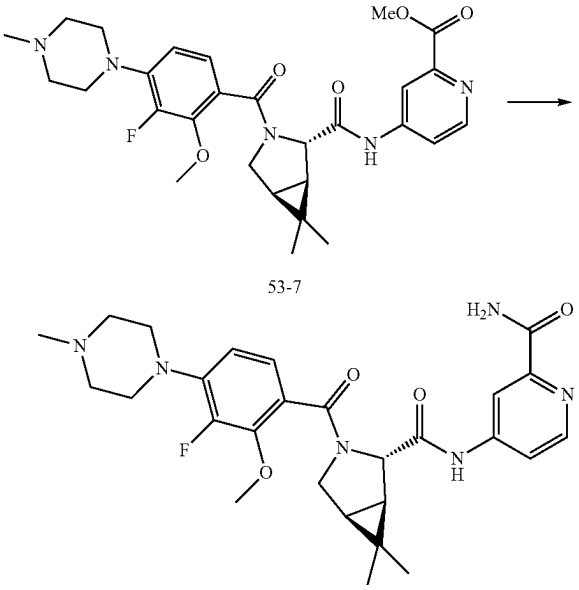
53-6

57

53-7

[0544] To a solution of compound 53-6 (60 mg, 0.21 mmol) in dry DMF (2 mL) was added compound 57 (60 mg, 0.21 mmol), NMI (51.7 mg, 0.63 mmol). To this reaction was added TCFH (117.8 mg, 0.42 mmol). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 2 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by prep-HPLC (ACN/0.1% FA=5%~95%) to give the crude product 53-7 (20 mg, 17.6% yield) as a white solid. LCMS: m/z=540.3 $[M+H]^+$.

Step 7: General Procedure for Preparation of TM3-7



53-7

TM3-7

[0545] To a solution of compound 53-7 (15 mg, 0.03 mmol) in NH_3 in MeOH (7M) (1 mL). The reaction mixture was degassed and purged with N_2 and stirring was continued at r.t. for 12 h. LCMS detected the desired product. The filtrate was concentrated under reduced pressure to get residue. The residue was purified by prep-HPLC (ACN/0.1% FA=5%~95%) to give the product TM3-7 (4.45 mg, 21.23% yield, 98.27% purity at 214 nm) as a white solid. LCMS: m/z=441.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.51 (d, J=4.9 Hz, 0.5H), 8.45 (d, J=5.5 Hz, 0.5H), 8.30 (s, 0.5H), 7.88 (d, J=21.5 Hz, 1H), 7.75 (d, J=4.0 Hz, 0.5H), 7.02 (d, J=7.2 Hz, 0.5H), 6.86 (t, J=8.0 Hz, 0.5H), 6.78 (d, J=7.1 Hz, 0.5H), 6.55 (s, 0.5H), 4.64 (s, 0.5H), 4.26 (s, 0.5H), 3.90 (dd, J=5.8, 1.3 Hz, 3H), 3.77 (s, 1H), 3.25 (s, 3H), 2.98 (d, J=13.5 Hz, 4H), 2.85 (d, J=4.6 Hz, 2H), 2.60 (s, 1.5H), 2.53 (s, 1.5H), 1.64-1.50 (m, 2H), 1.18 (s, 1.5H), 1.12 (s, 1.5H), 1.09 (d, J=2.4 Hz, 3H).

BIOACTIVITY STUDIES

Example-1. The Inhibitory Activity of the Compound Toward Nav1.8

Materials and Instrumentation

Materials	Vendor (Cat #)
6 cm cell culture dish	Nunc (150288)
3.5 cm cell culture dish	Nunc (153066)
Fetal Bovine Serum	BIOSUN (BS-0005-500)
DMSO	Solarbio (D8371-50)
DMEM medium	Gibco (10569)
HEPES	Gibco (15630080)

-continued

Materials	Vendor (Cat #)
TrypLE ™ Express	Gibco (12604)
1xPBS without Ca2+/Mg2+	Gibco (14190)
Penicillin-Streptomycin	Gibco (15140-122)
Puromycin	Sigma (P8833)
Hygromycin	Invivogen(ant-hg-5)
VX-548 (Suzetrigine phenol)	MCE (HY-148800)

Instrumentation	Vendor
Balance	METTLER TOLEDO(ME104E)
pH meter	METTLER TOLEDO(S220-USP)
Steri-Cycle CO2 Incubator	Thermo(Thermo371)
Micropipette Puller	NARISHIGE(PC-10 Puller)
Micro manipulator	Siskiyou(MC1000e)
Amplifier	HEKA(EPC10)
Microscope	Olympus(IX-71/IX-73)
Perfusion system	ALA(VM8)
no oil vacuum pump	Chemvak(V300)
Osmoeter	YASN(Osmo310)

Cell Lines and Cell Culture

[0546] HEK293 cell line stably expressing hNav1.8/P3 channel was constructed by IVB department and maintained at Pharmaron. hNav1.8/P3 cells are cultured in 90% DMEM, 10% FBS, 100 U/mL Penicillin-Streptomycin, 0.75 μg/mL Puromycin and 100 μg/mL of Hygromycin. The cells are split using TrypLE™ Express about three times a week, and maintained between ~40% to ~80% confluence. Before the assay, the cells are re-suspended and plated onto the coverslips at 5×105 cells/per 6 cm cell culture dish prior to use.

Solution Preparations

Extracellular Solution

Chemical	Vendor&Catalog No.	MW/stock concentration	Concentration(mM)
NaCl	Sigma S6191	58.44	132
KCl	Sigma P5405	74.55	4
$CaCl_2$	Sigma 21115	1M	3
$MgCl_2$	Sigma 63069	1M	0.5
D-(+) Glucose	sigma G7528	180.16	11.1
HEPES	Gibco 15630-080	1M	10

[0547] pH: adjusted to 7.35 with NaOH.

[0548] Osmolarity range: 285-295

[0549] Note: The solution is filtered by filter system and stored at 4° C. prior to use.

Intercellular Solution

Chemical	Vendor&Catalog No.	MW/stock concentration	Concentration(mM)
EGTA	Sigma E3889	0.1M	10
HEPES	Solarbio H8090	238.3	10

-continued

Chemical	Vendor&Catalog No.	MW/stock concentration	Concentration(mM)
CsCl	TCI C2203	74.55	10
NaCl	Sigma S5886	58.44	10
CsF	3A A11747	151.9	110

[0550] pH: adjusted to 7.2 with CsOH

[0551] Osmolarity range: 280-295

[0552] Use stock solution: 100 mM EGTA adjusted to pH 8.2 with CsOH

[0553] Note: The solution is filtered by filter system and stored at 4° C. prior to use

Experimental Procedure

[0554] Remove the coverslip from the cell culture dish and place it on the microscope stage in bath chamber.

[0555] Locate a desirable cell using the ×10 objective. Locate the tip of the electrode under the microscope using the ×10 objective by focusing above the plane of the cells. Once the tip is in focus, advance the electrode downwards towards the cell using the coarse controls of the manipulator, while simultaneously moving the objective to keep the tip in focus.

[0556] When directly over the cell, switch to the ×40 objective and use the fine controls of the manipulator to approach the surface of the cell in small steps.

[0557] Apply gentle suction through the side-port of the electrode holder to form a gigaohm seal.

[0558] Use the Cfast to remove the capacity current that is in coincidence with the voltage step. Obtain the whole cell configuration by applying repetitive, brief, strong suction until the membrane patch has ruptured.

[0559] Set membrane potential to −60 mV at this point to ensure that hNav1.8 channels are not open. The spikes of capacity current should then be cancelled using the Cslow compensation control on the amplifier.

[0560] Set holding potential to −80 mV for 200 ms; record current at 20 kHz and filter at 10 kHz. Leaking current is tested at −80 mV.

[0561] The Nav1.8 current is evoked by a 20 ms step voltage pulse to −10 mV from a holding potential of −80 mV at every 10 sec. The maximum amount of peak current size will be used to determine hNav1.8 current amplitude.

[0562] Record current for 120 sec to assess the current stability. Only stable cells with recording parameters passing acceptance criteria are applied for the perfusion of working solutions.

[0563] The cells under whole-cell patch clamp configuration are initially treated with blank vehicle to establish the baseline. Upon stabilization of baseline current, the assay buffer containing the test article at serial dose concentrations is subsequently perfused to cells by ALA VM8 liquid perfusion system. hNav1.8 current in the presence of each working solution is recorded for approximately 5 min to reach steady state and then 5 sweeps are captured. For dose response assay, test article is applied to the cells accumulatively from low to high concentrations. The positive control article, VX-548 at concentration of 5 nM was also applied to each cell post hNav1.8 current measurement at highest concentration of test compound as the internal low control for normalization of percentage inhibition. The positive

control article, VX-548, is also involved in same batch of experiments to ensure the good performance of the cells and operations as a necessary procedures of data quality verification. The hNav1.8 current inhibition in presence of test and control articles is examined in 2 independent experiments (n=2).

Data Analysis

[0564] Data that met the above criteria for hNav1.8 current quality were further analyzed as the following steps.

[0565] Percent hNav1.8 current inhibition was calculated using the following equation.

⑦

⑦ indicates text missing or illegible when filed

[0566] Note: PatchMaster or Clampfit software was used to extract the peak current from the original data.

[0567] The dose response curve of test compounds was plotted with percentage of hNav1.8 current inhibition against the concentration of test compounds using Graphpad Prism 8.0, and fit to a sigmoid dose-response curve with a variable slope.

Results

TABLE 1

The inhibiton rate toward hNav1.8

Cpd. No.	Inhibition (10 nM)
TM1-3	94.12%
TM1-4	71.21%
TM1-7	94.98%
TM1-9	84.09%
TM1-10	82.87%
TM1-11	96.28%
TM1-12	70.09%
TM1-14	88.23%
TM1-15	90.28%
TM1-20	91.62%
TM1-27	94.62%
TM2-6	82.83%
TM2-16	92.94%

TABLE 2

The IC_{50} value toward hNav1.8

Cpd. No.	IC_{50} (nM)
TM1-3	2.49
TM1-7	1.47
TM1-9	4.29
TM1-10	4.03
TM1-11	0.69
TM1-14	3.15
TM1-15	3.81
TM1-27	6.11
TM1-27	7.01
TM1-33	10.1
TM2-10	4.519
TM2-15	4.27
TM2-16	1.34

Example-2. Of Bioactivity Studies CYP Inhibition Studies of Compound TM2-10

Materials and Reagents

Substrates

[0568] Preparation of the substrate stock solution. The substrate stock solution is stored in a −20° C. freezer. Prior to use, remove the substrate stock solution from the freezer and allow it to rise to room temperature. Then mix the substrate stock solution on a whirly mixer for 30 seconds.

CYP Isoform	Substrate	MW(g/mol)	Stock solution Conc. (mM)	Final Conc. (μM)
2C9	diclofenac	318.13	10 (in MeOH)	10
2D6	dextromethorphan	370.3	10 (in MeOH)	10
3A4	midazolam	325.77	2 (in DMSO)	2

Human Liver Microsome (HLM)

[0569] HLMs are stored in a −80° C. freezer. Prior to use, remove the pooled HLM from the freezer and allow it to thaw in a 37° C. water bath and then stored on wet ice.

Inhibitors

Preparation of the Standard Inhibitors Solution

CYP Isofom	Inhibitor	MW (g/moL)	Stock solution Conc. (mM)	Final Conc. (μM)
2C9	Sulfa-phpenazole	314.4	10(in DMSO)	0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30
2D6	Quinidine	324.4	10(in DMSO)	0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
3A4	Ketoconazole	531.4	10(in DMSO)	0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1

Assay Procedure

Preparation of Human Liver Microsome Working Solution

Buffer	Stock Concentration	Final Concentration
Microsomes	20 mg/mL	0.2 mg/mL
Phosphate buffer	100 mM	100 mM
Substrate	—	—

Compound Dilution

[0570] The working solution of the test compound is configured to specified concentration, and the appropriate solvent is selected according to the solubility of the compound.

Stock Solution/mM	Final Conc. (μM)
20	200, 66.7, 22.2, 7.41, 2.47, 0.823, 0.274

Incubation

[0571] All samples were incubated in a 37° C. water bath, with two parallels for each concentration of the test compound and two parallels for each concentration of the positive control inhibitor. After pre-incubation, add NADPH regeneration solution to all samples to start the reaction. Then put it back in the water bath and incubate for a certain period of time. The experiments of each isozyme are summarized in the following table.

CYP Isoform	Substrate	Protein Conc.	Inhibitor	Metabolite
2C9	diclofenac	0.100	sulphaphenazole	4'-hydroxydiclofenac
2D6	dextromethorphan	mg/mL	quinidine	dextrorphan
3A4	midazolam		ketoconazole	1-hydroxymidazolam
	testosterone		ketoconazole	6β-hydroxytesterone

Reaction Quenching

[0572] Quench the reaction by 200 μL stop solution. Centrifuge the plate at 3,220 g for 10 minutes. Transfer appropriate volume of supernatant, add water and mix well to the analysis plate for LC-MS/MS analysis.

Data Processing

[0573] The automatic peak integration areas are checked for all of the samples. The Analyte Peak Area and Internal Standard Peak Area are exported into excel spreadsheet.

[0574] The inhibition of each P450 enzyme in human liver microsomes is measured as the percentage decrease in the activity of marker metabolite formation compared to non-inhibited DMSO controls (=100% activity). Calculate IC_{50} value (test compound concentration which produces 50% inhibition) by using GraphPad Prism 7. IC_{50} values were determined using 3- or 4-parameter logistic equation. IC_{50} values were reported as ">200 μM" when % inhibition at the highest concentration (200 μM) is less than 50%.

[0575] Calculate the percentage of remaining activity as follows:

$$\text{Area Ratio} = \text{Peak Area}_{Analyte}/\text{Peak Area}_{Internal\ Standard}$$

$$\text{Remaining Activity (\%)} = \text{Area Ratio}_{test\ compound}/\text{Area Ratio}_{vehicle} * 100\%$$

Equation for Three Parameters Logistic Sigmoidal Curve

$$y = \frac{\max}{1 + \left(\frac{x}{IC_{50}}\right)^{-hillslope}}$$

Equation for Four Parameters Logistic Sigmoidal Curve

$$y = \min + \frac{\max - \min}{1 + \left(\frac{x}{IC_{50}}\right)^{-hillslope}}$$

Example-3. Basic Information of PK Study

[0576] Administration route: IV

[0577] Recommended solvent: 5% DMSO+10% polyoxyethylene castor oil+85% saline

[0578] Dose (mg/kg): 1

[0579] Concentration (mg/mL): 0.5

[0580] Administration volume (mL/kg): 2

IV Preparation Process (Prepared and Used on the Day of Administration)

[0581] Species: SD rat, SPF level.

[0582] Source: Beijing Weitonglihua Experimental Animal Technology Co., Ltd.

[0583] Quantity: 8 pieces.

[0584] Experimental requirements: 6.

[0585] Animal selection: no random grouping

Example-4. Determination of Plasma Protein Binding Rate of Compounds in Rat Plasma

Study Design

Equipment, Materials and Reagents

Plasma

[0586] Plasma is stored in a −20° C. freezer. Prior to use, remove the plasma from the freezer and allow it to thaw in a 37° C. water bath and then stored on wet ice.

Test Compound Working Solution

[0587] Test compound working solutions are prepared in DMSO at the concentrations specified in Table 6.

Table 6: Preparation of the Test Compound Working Solution

Assay Procedure

Preparation of Plasma

[0588] Put the thawed plasma of various species in a centrifuge to remove the suspended matter and sediment, and adjust the plasma pH to 7.0-8.0.

Preparation of Operation Plate

[0589] Load the prepared membranes into the dialysis device and install the device following manufacturers guidelines.

Preparation of Control Sample at 0 Hour

[0590] Add blank plasma solution into each vial of a new plastic plate or separate plastic tube by addition working solution of test compound, vortex at 1000 rpm for 2 minutes.

The final concentration for test compound is 1 μM. Immediately transfer the spiked plasma solution suspension to a 96-well plate to act as T=0 control sample. The samples are treated the same as the samples after incubation. Place all remaining spiked plasma solution in the incubator for the duration of the study.

Stability Determination of Test Compounds in Plasma Solution

[0591] At the same time, the remaining spiked plasma solution sample in the plastic plate or separate plastic tube is incubated for 6 hours at 37° C. in a constant temperature shaking box.

[0592] At T=6 hours, transfer 50 μL of the original spiked plasma solution suspension to the 96-well plate for analysis.

Procedure for Equilibrium Dialysis

[0593] Assemble the dialysis set up following the manufacturer's instructions. Load cells with plasma sample and dialyzed against equal volume of dialysis buffer (PBS). The assay is performed in duplicate. Cover the unit with gas permeable lid and incubate for 6 hours at 37° C. at 100 rpm in a constant temperature shaking box At the end of incubation, remove lid and pipette post-dialysis samples from both buffer and plasma solution chambers into separated 96-well plate for analysis, respectively.

Procedure for Sample Preparation

[0594] Add plasma solution or PBS to the collected samples. Shake the plate at 1000 rpm for 2 minutes and add 500 μL of 80% ACN/MeOH containing an appropriate internal standard (IS) to precipitate protein and release compound. Vortex at 1000 rpm for 10 minutes. Centrifuge for 10 minutes at 4000 rpm. Then transfer 100 μL of the supernatant to new 96-well plates for analysis. Add 100 μL of distilled water to each sample and mix for analysis by LC-MS/MS.

Data Processing

[0595] The automatic peak integration areas are checked for all of the samples. The Analyte Peak Area and Internal Standard Peak Area are exported into excel spreadsheet.

[0596] The free rate (% Unbound), binding rate (% Bound), and recovery rate (% Recovery) of the compound are calculated as follows:

$$\%\,\text{Unbound} = \left(\text{Area ratio}_{buffer\ chamber}/\text{Area ratio}_{plasma\ solution\ chamber}\right)\times 100$$

$$\%\,\text{Bound} = 100 - \%\,\text{Unbound}$$

$$\%\,\text{Recovery} = (\text{Area ratio}_{buffer\ chamber} + \text{Area ratio}_{plasma\ solution\ chamber})/(\text{Area ratio Total sample})\times 100$$

$$\%\,\text{Remaining} = \text{Area ratio}_{6\,hr}/\text{Area ratio}_{0\,hr}\times 100$$

Example-5. Thermodynamic Solubility Determination of Compounds in FaSSIF, FaSSGF and PBS pH 7.4

Study Procedure

Procedure for Solubility Determination

[0597] Weigh out about 1 mg of test compound(s) or control compounds each into glass insert vials. Add buffer into each vial of the cap-less Solubility Sample plate with the volume of 1 mL per mg. Add one stir stick to each vial and seal with a molded PTDE/SIL 96-Well Plate Cover. Transfer the Solubility Sample plate to the Eppendorf Thermomixer Comfort plate shaker and shake the plate at 25° C. at 1,100 rpm for 24 hours. After completion of incubation, remove the stir sticks using a big magnet and transfer the samples from the Solubility Sample plate into a filter plate with pipettes. Using the Vacuum Manifold, all the compounds are filtered. Aliquot 5 μL filtrate and 5 μL DMSO followed by addition of 490 μL of a mixture of H2O and acetonitrile containing internal standard (1:1) as 100 fold diluted samples. Aliquot 50 μL of 100 fold diluted samples are further diluted by addition of 450 μL of a mixture of H2O and acetonitrile containing internal standard (1:1) as 1000 fold diluted samples. Aliquot 20 μL of 100 fold diluted samples are further diluted by addition of 180 μL of a mixture of H2O and acetonitrile containing internal standard (1:1) as 10000 fold diluted samples. A certain proportion of a mixture of H2O and acetonitrile containing internal standard (1:1) was used to dilute the diluent according to the peak shape. The dilution factor was changed according to the solubility values and the UPLC-MS/MS signal response.

Preparation of Standards (STD)

[0598] Accurately weigh about 1 mg of the powder of each compound into a glass insert vial. Add DMSO into each vial of the Standard Plate with the volume of 1 mg per mL. Add one stir stick to each vial and seal with a molded PTDE/SIL 96-Well Plate Cover. Transfer the Solubility Sample plate to the Eppendorf Thermomixer Comfort plate shaker and shake the plate at 25° C. at 1,100 rpm for 2 hours to dissolve the powder. Observe to see if there is any stock solution undissolved, take a record if the compound is insoluble in DMSO solution.

[0599] Aliquot 5 μL 1000 μg/mL STD and 5 μL buffer followed by addition of 490 μL of a mixture of H2O and acetonitrile containing internal standard (1:1) as 100 fold diluted STD concentration of 10 μg/mL. Aliquot 50 μL of 100 fold diluted STD samples are further diluted by addition of 450 μL of a mixture of H2O and acetonitrile containing internal standard (1:1) as 1000 fold diluted STD to have a STD concentration of 1 μg/mL. Aliquot 20 μL of 100 fold diluted STD samples are further diluted by addition of 180 μL of a mixture of H2O and acetonitrile containing internal standard (1:1) as 10000 fold diluted STD to have a final STD concentration of 0.1 μg/mL. A certain proportion of a mixture of H_2O and acetonitrile containing internal standard (1:1) was used to dilute the diluent according to the peak shape. The concentrations of the standard samples were changed according to the UPLC-MS/MS signal response.

Procedure for Sample Analysis

[0600] The plate was placed into the well plate autosampler. The samples were evaluated by LC-MS/MS analysis.

Data Analysis

[0601] All calculations were carried out using Microsoft Excel.

[0602] The filtrate was analyzed and quantified against a standard of known concentration using LC coupled with

mass spectral peak identification and quantitation. Solubility values of the test compound and control compound were calculated as follows:

$$[Sample] = \frac{\text{Area ratio Sample} \times DF \text{ Sample} \times [STD]}{\text{Area ratio } STD}$$

[0603] Any value of the compounds that was not within the specified limits was rejected and the experiment was repeated.

Example-6. The Assessment of Induction Potentials of CYP3A4 by 2 YCRF Compounds Using Plateable Cryopreserved Human Hepatocytes Study Design

Preparation and Plating of Human Hepatocytes

[0604] Prepare the following media in a biosafety hood and store at 4° C. before use:

[0605] Hepatocyte thawing medium (prepared by mixing the following ingredients: Williams E Medium, isotonic percoll, DPBS, glutaMAX, HEPES, FBS, human recombinant insulin and dexamethasone)

[0606] Plating medium (prepared by mixing the following ingredients: Williams E Medium, FBS, dexamethasone, penicillin/streptomycin, human recombinant insulin, glutaMAX and HEPES)

[0607] Incubation medium (prepared by mixing the following ingredients: Williams E Medium, dexamethasone, ITS, penicillin/streptomycin, glutaMAX and HEPES, serum-free)

[0608] Thaw one vial of cryopreserved human hepatocytes in 37° C. water bath for 2 minutes. Wipe the vial with 70% alcohol in hood. Use wide-bore pipette tip to transfer hepatocytes into 50 mL pre-warmed Hepatocyte thawing medium. Rinse the vial thoroughly by adding approximately 500 μL of Hepatocyte thawing medium, recap, and invert several times.

[0609] Centrifuge at 100 g for 10 minutes at room temperature. Aspirate carefully and dilute with plating medium to a seeding density of 0.55×106 cells/mL. Transfer 100 μL to each well of collagen I coated 96-well plate. Place plate in incubator and incubate at 37° C. with 5%/95% CO2/Ambient atmosphere and 95% relative humidity for 4-6 hours.

[0610] After incubation, observe cell morphology under microscope. Agitate plate(s) to loosen debris and replace medium with 125 μL of 0.25 mg/mL Matrigel diluted with incubation medium. Place plate in incubator and incubate for 18 hours. Then the cultures are ready for induction studies.

Incubation with Test Compound

[0611] Dissolve test compound in DMSO at 1000× highest working concentration and incubation medium at highest working concentration, and check if the compounds are soluble in both solutions by visual inspection. Then prepare stock solutions of test compounds, negative control and positive control inducers at 1000× final concentration in DMSO and dilute with 37° C. prepared incubation medium to respective working concentrations. Final concentration of DMSO in the treatment group will be 0.1%. Prepare 25 mM chlorpromazine in DMSO and dilute 1000-fold with incubation medium as a cytotoxicity control. Prepare a negative control by adding 5 μL DMSO into 5 mL warm incubation medium. On occasion test compounds may be prepared with a higher concentration of DMSO or at final concentration directly in media with 0.1% DMSO.

Test Compound(s), Toxicity Control and Positive Control Induce Concentrations

Enzyme	Treatment	Concentration (μM)
CYP3A4 (toxicity)	Chlorpromazine	25
CYP3A4	Rifampicin	10
CYP3A4	Test compound(s)	10

[0612] After 24 hours and 48 hours, remove the Hepatocyte plate from the incubator and observe cell morphology under microscope. Renew the medium with test articles that are freshly diluted from DMSO stocks. Return the plate to the incubator. The total incubation time is 72 hours.

Enzyme Activity Assay

[0613] Prepare stock solutions of marker substrates phenacetin and midazolam in DMSO at 1000× working concentration in the same tube. Prepare stock solutions of marker substrates bupropion in H2O at 100× working concentration in the same tube. Dilute the substrates with 37° C. prepared incubation medium to respective working concentrations:

Enzyme	Substrate	Concentration	Marker Metabolite
CYP3A4	Midazolam	10 mM	1-HydroxyMidazolam

[0614] Remove the medium from the plate(s) and replace with 125 μL of the probe substrate solutions prepared in the previous step. Incubate at 37° C. in the incubator for 60 minutes. At the end of the incubation period, remove 100 μL directly from the wells and transfer to a new 96-well plate. Mix samples with 4 volumes of methanol containing IS

[0615] Dilute the marker metabolite with Williams E Medium to respective concentrations as calibration curve and QC samples:

Marker Metabolite	Standard Concentration (nM)	QC Sample (nM)
1-HydroxyMidazolam	1, 2, 5, 10, 50, 100, 500 and 1000	3, 80, 800 and 1000

[0616] Samples for calibration curve and QC are mixed with 4 volumes of methanol containing IS. Vortex for 10 minutes. Centrifuge samples in plate at 3220 g for 30 minutes to precipitate protein. Transfer 100 μL of the supernatant to a new plate. The supernatant may be diluted with 100 μL pure water. Mix well and analyze samples using LC/MS/MS.

[0617] Induction of CYP3A4 by inducers and test compounds are investigated using cells from one individual human donors. All incubations are conducted in triplicate.

Cell Viability Assessment

[0618] Aspirate the dosing medium from each well.

[0619] Completely thaw the CellTiter-Fluor™ Cell Viability Assay components in a 37° C. water bath. Transfer the GF-AFC Substrate (10 μL) into the Assay Buffer container (10 mL) to form 2× reagent, then dilute to 1× reagent by adding 10 mL PBS. Remove the 96-well plates from the incubator and aspirate the medium from all the wells. Then add 100 μL of 1× CellTiter Reagent to each well of the cell plates and to 3 wells of a new collagen I coated plate as background. Incubate the plates for 30 minutes at 37° C.

[0620] Remove the 96-well plates from the incubator; briefly allow cooling to ambient temperature. Transfer 80 μL 1× CellTiter Reagent from the cell plate to 96-well black plates. Measure the fluorescence of individual wells with Infinite 200 PRO microplate reader in fluorescence mode at 400 nm excitation and 505 nm emission.

mRNA Preparation and RT-PCR

[0621] mRNA is prepared and measured using the Cells-to-Ct kit purchased from Life Technologies. Remove the remaining CellTiter Cell Viability Reagent, wash cell monolayers twice with 125 μL phosphate buffer solution and then place the plates on ice.

[0622] Add DNAse to Lysis solution as per instructions. Add 50 μL Lysis Solution to each well of Hepatocytes cell plates and mix the Lysis reaction by pipetting up and down 5 times. Incubate the lysis reactions for 8 minutes at room temperature, then pipette 5 μL Stop Solution to each lysis reaction and mix by pipetting up and down for 5 times. Incubate for another 2 minutes at room temperature. The lysate can be stored at −20° C. or −80° C. for up to 5 months before the RT reaction.

Program the QPCR System for Reverse Transcription:

QPCR Conditions for Reverse Transcription

	Stage	Reps	Temp (° C.)	Time
Reverse transcription (hold)	1	1	37	60 min
RT inactivation (hold)	2	1	95	5 min
Hold	3	1	4	Indefinite

[0623] Prepare the mixture of 106 reactions in a 15 mL tube and then distribute to 96-well PCR plates in appropriate wells. One tube of the mixture is prepared for each plate.

Reverse Transcriptase Master Mix

Component	Each rxn
2x RT Buffer	25 μL
20x RT Enzyme Mix	2.5 μL
Nuclease-free Water	7.5 μL
Final volume RT master mix	35 μL

[0624] Add 15 μL sample lysate to each aliquote of RT Master Mix for a final 50 μL reaction volume. Negative controls (NC) were prepared by adding 15 μL mixture from previous step without incubation with cells. Once assembled, mix reactions gently, then centrifuge briefly to collect the contents at the bottom of the reaction vessel.

[0625] Using QPCR system to incubate samples at 37° C. for 60 minutes, then at 95° C. for 5 minutes to inactivate the RT enzyme. Store the prepared RT samples at −20° C. until QPCR reaction.

Program the QPCR System for Real-Time PCR Cycling:

	Stage	Reps	Temp (° C.)	Time
Enzyme Activation (hold)	1	1	95	5 min
PCR (cycle)	2	45	95	15 sec
			60	1 min

[0626] Separate PCR cocktails are prepared for CYP3A4; each containing the CYP specific probe set and that of ACTB as the endogenous control gene.

Component	Each rxn
Taqman Gene Expression Master Mix (2x)	10 μL
Taqman Gene Expression Assay probe (20x, CYP3A4, FAM labeled)	1 μL
Taqman Gene Expression Assay probe (20x, ACTB, VIC labeled)	1 μL
Nuclease-free Water	4 μL
Final volume RT master mix	16 μL

[0627] Distribute the PCR Cocktail into wells of a real-time PCR plate at room temperature.

[0628] Dilute the cDNA samples 3 folds with Nuclease-free Water. Add 4 μL diluted cDNA samples to each aliquot of PCR Cocktail to make the final volume of 20 μL, cover the plate, and mix gently. Then centrifuge briefly to collect the contents at the bottom of wells. 4 μL of RT mix without cell lysate is added to PCR cocktail as negative control in 2 wells of every PCR plate. Templates for standard curve are prepared from a 3-fold serial dilution of the cDNA sample mixture of respective Rifampicin induced samples at highest concentration.

[0629] Place the reactions in QPCR system and start the run using the Real-Time PCR cycling program.

Data Analysis

[0630] All calculations are carried out using Microsoft Excel.

Enzyme Activity

[0631] CYP activity is expressed as pmol/min/million cells where pmol is defined as the amount of metabolite formed during the reaction. The number of hepatocytes per well (N) is related to the seeding density. The fold-induction enzyme activity is determined by the ratio:

[0632] The percent adjusted positive control is determined by:

$$\%\text{ positive control} = \left(\left[CYP\text{ activity}_{(induced)} - CYP\text{ activity}_{(vehicle)}\right]/\left[CYP\text{ activity}_{(positive\ control)} - CYP\text{ activity}_{(vehicle)}\right]\right)\times 100$$

Cell Viability

[0633] Percent cell viability will be calculated by the equation:

$$\text{Percent cell viability (\%)} = (I_{(sample)} - I_{(background)})/(I_{(vehicle)} - I_{(background)})\times 100$$

[0634] Where I(sample) is the fluorescence intensity of sample wells, I(vehicle) means fluorescence intensity of the 0.1% DMSO treated cells, and I(background) is mean fluorescence intensity of culture medium without cells.

[0635] Cell viability will be reported for every compound as the Mean percent cell viability at each concentration.

mRNA Level Assay

[0636] For mRNA level determination, the mRNA content in each vial was expressed as $2^{Ct(ACTB)-Ct(CYP)}$. The fold-induction mRNA level was determined by the equation:

$$\text{Fold of induction} = mRNA_{(induce)}/mRNA_{(vehicle)}$$

$$\text{Percentage of positive control (\%)} = \frac{\text{Fold induction}_{test\ article} - 1}{\text{Fold induction}_{positive\ control} - 1}\times 100$$

Example-7. Permeability of Compounds in Caco-2 Assay

Materials

[0637] Caco-2 cell was obtained from the CO—BIOR and the CO—BIOR Number is CBP60025. The cell generation used in the experiment was RM15. Trypsin/EDTA and DMSO are purchased from Corning. HEPES, Hank's balanced salt solution (HBSS) and Non-essential amino acids (NEAA), Penicillin, Streptomycin, Fetal bovine serum, Dulbecco's Modified Eagle's Medium (DMEM) are all purchased from Gibco PET Transwell-96 Well Permeable Supports and other sterile plastic ware are purchased from Millipore.

[0638] Millicell Epithelial Volt-Ohm measuring system is purchased from Millipore. Cellometer® Vision is purchased from CNOPTEC. SpectraMax Paradigm microplate reader is purchased from Molecular Decices.

Study Design

Preparation of Monolayer

[0639] Add cell culture medium to each well of the transwell reservoir. And then the PET transwell plates were incubated at 37° C., 5% CO_2 for 1 hour before cell seeding.

[0640] Caco-2 cells were diluted to 3.43×10^5 cells/mL with culture medium and 100 μL of cell suspension were dispensed into the filter well of the 96-well PET Transwell plate. Cells were cultivated for 14-18 days in a cell culture incubator at 37° C., 5% CO_2, 95% relative humidity. Cell culture medium was replaced every other day, beginning no later than 24 hours after initial plating.

[0641] Measure the electrical resistance across the monolayer by using Millicell Epithelial Volt-Ohm measuring system. Record the electrical resistance for each well. Once all wells have been measured, return the plate(s) to the incubator.

[0642] TEER of each well is calculated by the equation below. The TEER value of each well should be greater than 230 ohms·cm^2.

$$TEER\text{ value}\left(\text{ohm}\bullet\text{cm}^2\right) = TEER\text{ measurement (ohms)}\times\text{Area of membrane}\left(\text{cm}^2\right).$$

Procedures of Transport Assay

[0643] Remove the Caco-2 plate (s) from the incubator. Wash the monolayer twice with pre-warmed HBSS (10 mM HEPES, pH 7.4). Then incubate the plate(s) at 37° C. for 30 minutes.

[0644] Prepare stock solutions of control compounds in DMSO at 5 mM and dilute with HBSS (10 mM HEPES, pH 7.4) to get 5 μM working solutions. Prepare stock solutions of test compounds in DMSO at 10 mM and dilute with HBSS (10 mM HEPES, pH 7.4) to get 10 μM working solutions. Digoxin is used as the reference substrate of Pgp. Atenolol is used as the low permeability marker, minoxidil is used as the high permeability marker.

[0645] To determine the rate of drug transport in the apical to basolateral direction, add 100 μL of the working donor solutions (without inhibitor) to the transwell insert (apical compartment). To determine the rate of drug transport in the basolateral to apical direction, add 300 μL of the working donor solutions (without inhibitor) to the receiver plate wells (basolateral compartment).

[0646] Transfer 50 μL samples from the working solutions to 300 μL of cold MeOH:acetonitrile=1:1 with IS (50 ng/mL Labetalol, 50 ng/mL Tolbutamide) to prepare the time 0 samples. Incubate the transwell plate at 37° C., 5% CO_2 with shaking at 60 rpm on a rotary shaker for 2 hours.

[0647] At the end of the transport period, transfer 50 μL of samples from apical and basolateral wells to a new 96-well plate. Add 300 μL of quenching solution (MeOH:acetonitrile=1:1 with IS (50 ng/mL Labetalol, 50 ng/mL Tolbutamide)) into each well of the plate(s). Vortex for 10 minutes. Samples are centrifuged at 4000 rpm g for 10 minutes. An aliquot of 100 μL of the supernatant is mixed with an appropriate volume of ultra-pure water before LC-MS/MS analysis.

[0648] To determine the Lucifer Yellow leakage after 2-hour transport period, prepare stock solutions of Lucifer yellow in DMSO and dilute with HBSS to reach the final concentration of 100 μM. Add 100 μL of the Lucifer yellow solution to the apical compartment. Fill the basolateral compartment with 300 μL of HBSS. Incubate the plate(s) at 37° C. for 30 minutes and remove 80 μL directly from the apical and basolateral wells and transfer to new 96 wells plates. Measure Lucifer Yellow fluorescence (to monitor

monolayer integrity) in a fluorescence plate reader at 485 nM excitation and 530 nM emission.

[0649] Discard the remaining solution in the cell plate, add quenching solution into each well of the plate(s), blow up and down and mix well for 5 times. Transfer 50 μL of lysate to a new 96-well plate. Add quenching solution into each well of the plate(s). Vortex for 10 minutes. Samples are centrifuged at 4000 rpm g for 10 minutes. An aliquot of 100 μL of the supernatant is mixed with an appropriate volume of ultra-pure water before LC-MS/MS analysis.

Data Analysis

[0650] All calculations are carried out using Microsoft Excel. Percent parent compounds remaining at each time point are estimated by determining the peak area ratios from extracted ion chromatograms.

[0651] The apparent permeability coefficient (Papp), in units of centimeter per second, can be calculated for Caco-2 drug transport assays using the following equation:

$$\text{Papp}=(\text{VA}\times[\text{drug}]\text{acceptor})/(\text{Area}\times\text{Timex}[\text{drug}]\text{initial, donor})$$

[0652] Where VA is the volume (in mL) in the acceptor well, Area is the surface area of the membrane (0.143 cm2 for Transwell-96 Well Permeable Supports), and time is the total transport time in seconds.

[0653] The efflux ratio will be determined using the following equation:

$$\text{Efflux Ratio} = Papp\,(B-A)/Papp\,(A-B)$$

[0654] Where Papp (B−A) indicates the apparent permeability coefficient in basolateral to apical direction, and Papp (A−B) indicates the apparent permeability coefficient in apical to basolateral direction.

[0655] The recovery can be determined using the following equation:

$$\text{Recovery \%} = \left(VA\times[\text{drug}]_{acceptor} + VD\times[\text{drug}]_{donor}\right)/\left(VD\times[\text{drug}]_{initial,donor}\right)$$

[0656] Where VA is the volume (in mL) in the acceptor well (0.3 mL for Ap→BI flux, and 0.1 mL for BI→Ap), VD is the volume (in mL) in the donor well (0.1 mL for Ap→BI flux, and 0.3 mL for BI→Ap).

[0657] The leakage of Lucifer Yellow, in unit of percentage (%), can be calculated using the following equation:

$$\%\,LY\ \text{leakage} = 100\times VA\times[LY]_{acceptor}/\left([LY]_{donor}\times VD + [LY]_{acceptor}\times VA\right)$$

[0658] LY leakage of <1.5% is acceptable to indicate the well-qualified Caco-2 monolayer.

Results

TABLE 3

CYP inhibition, Plasma protein binding and solubility of compounds

Test	CYP inhibition (2C9/2D6/3A4T/3A4M) [IC_{50}, μM]	PPB(% Fu)	CYP induction 3A4 mRNA (fold)	Thermodynamic solubility FaSSIF/FeSSIF/PBS pH 1.6/6.5/7.4 [μg/mL]
VX-548	11.7/21.2/39.0/35.1	0.7	26.7	66/4.5/1.7
TM2-10	40.1/69.9/48.5/35.7	3.3	1.15	235.02/25.7/10
TM1-33	43.8/43.5/52.3/>200	2.8	10.1	56.61/80.88/67.86
TM1-10	13.3/20/9.2/9.8	1.2	8.11	777.78/277.67/5.02
TM1-3	24.3/30.2/23.1/13.5	4.1	9.31	778.43/4.22/1.79

TABLE 4

Mean pharmacokinetic parameters of compounds after IV dose of 1 mg/kg in male SD rats

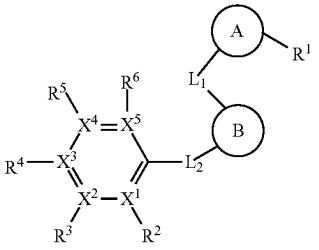
PK parameters	Unit	VX-548	TM1-10	TM1-11	TM2-10	TM1-33	TM1-3	TM2-16	TM1-18	TM1-20	TM1-15
CL	L/hr/kg	37	25.7	42.6	13	22.6	13.2	44.7	33.9	15.5	14.72
V_{ss}	L/kg	2.33	2.43	4.13	2.64	0.790	1.35	1.73	2.24	2.57	1.05
AUC_{last}	hr*ng/mL	442	667	379	1231	754	1273	374	484	1081	1137
AUC_{INF}	hr*ng/mL	460	676	393	1285	757	1284	377	493	1096	1140
$T_{1/2}$	hr	0.9	1.3	2	8.51	0.503	1.85	0.607	1.09	4.31	0.9
MRT_{INF}	hr	1.05	1.61	1.61	3.38	0.591	1.74	0.655	1.10	2.74	1.2

CONCLUSION

[0659] Based on the results presented above, the compounds synthesized in this patent demonstrate significant potential as Nav1.8 inhibitors. These findings suggest that compounds exhibit promising pharmacological activity and pK profile which could be leveraged for the development of novel therapeutic agents targeting Nav1.8 channels. Further preclinical and clinical studies are warranted to fully evaluate their safety, efficacy, and therapeutic potential in treating disorders associated with Nav1.8 dysfunction.

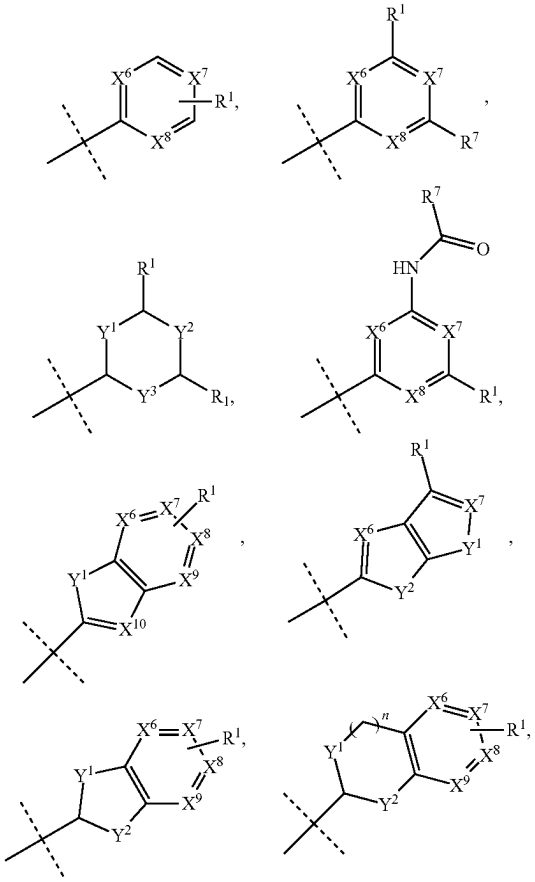
1. A compound of the formula (I), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated derivatives, metabolites, or prodrugs;

I



wherein,

ring A is selected from



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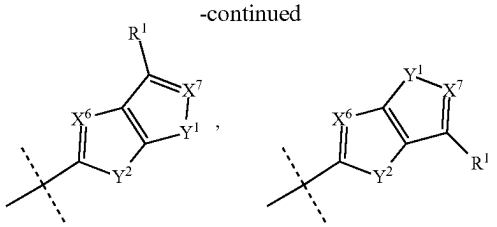
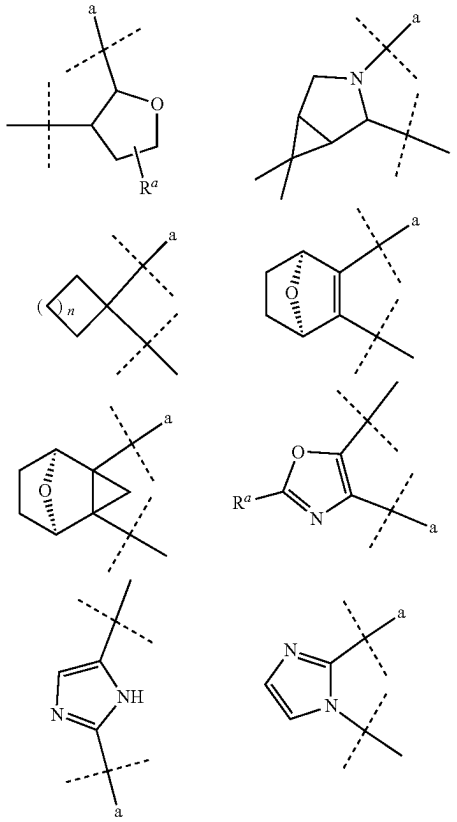


the A ring is optionally substituted with 0 to 5 independent R^1 groups,

the B ring is selected from 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl, where the heteroatoms or heteroatom groups in the 3-8 membered heterocycles and 5 or 8 membered heteroaryls are selected from N, O, and S, with the number of heteroatoms or heteroatom groups being 1-4;

the 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 Ra groups: hydrogen, deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogenated C1-C6 alkyl, 3-6 membered heterocyclic alkyl;

the 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl include, but are not limited to, the following (where the a-end is connected to L_1);



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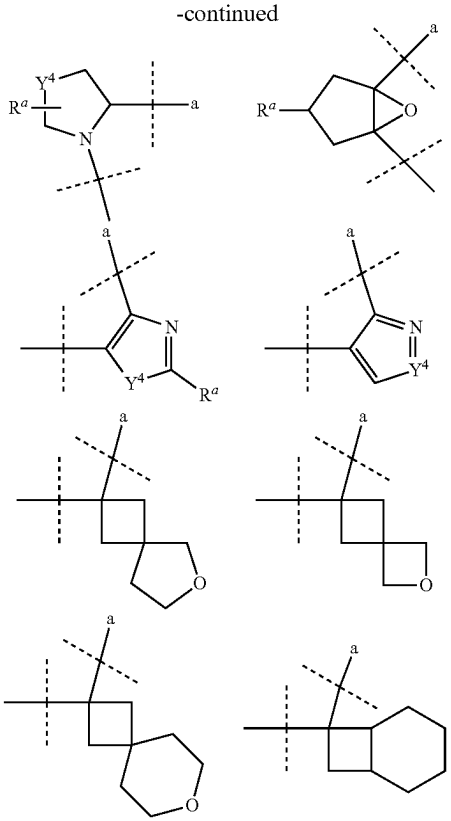
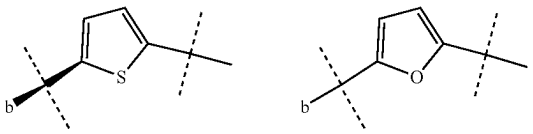


L_1 and L_2 are selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl, where the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl-3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, and —S(O)2C3-C6 cycloalkyl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocyclic alkyl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

the above 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl include, but are not limited to, the following: (where the b-end is connected to the B ring);



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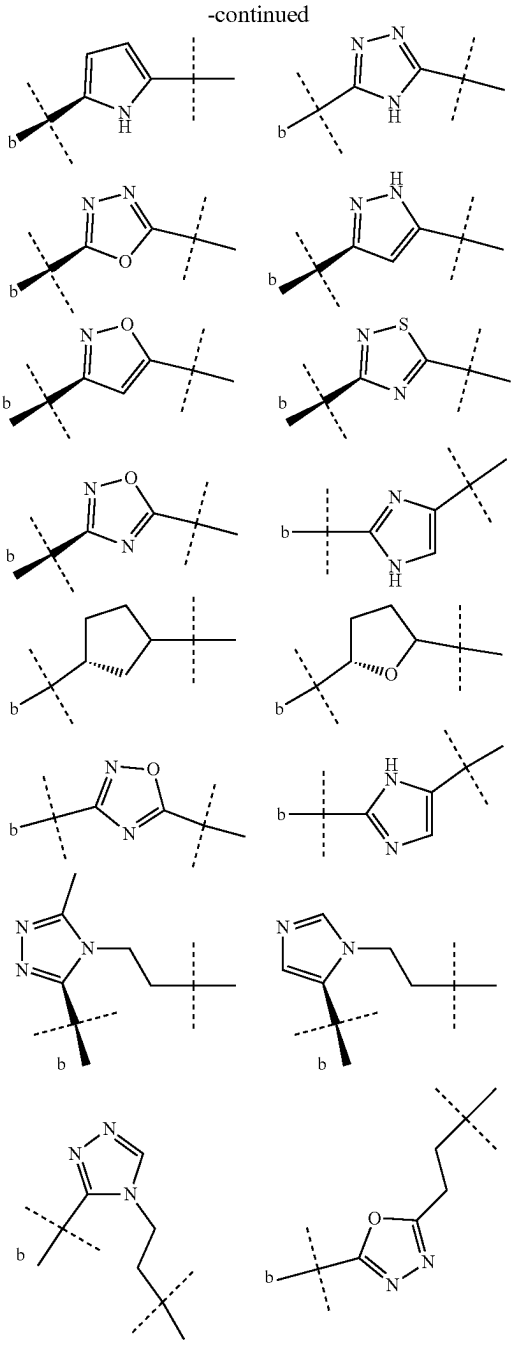


R^1 and R^7 are each independently selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CON R^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8 membered heterocyclic alkyl, 5 or 6 membered heteroaryl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

alternatively, any two adjacent R^1 (or R^7) and the atoms to which they are connected may form a five-membered ring, and any two ortho-positioned R^1 (or R^7) and the atoms to which they are connected may form a heterocyclic alkenyl;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —$OCOR^e$, C1-C6 alkyl, C1-C6 thioalkyl, and C1-C6 alkoxy, C(O)O(C1-C6 alkyl)OC(O)(C1-C6) alkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, where the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, and halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl, where the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 substituents: deuterium, halogen, C1-C3 alkyl;

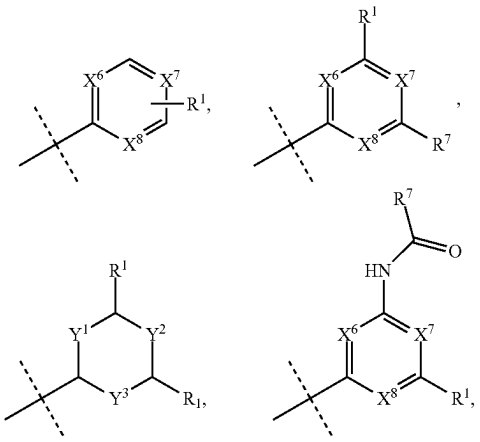
X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives;

Y^1, Y^2, Y^3, and Y^4 are each independently selected from CH_2, NH, O, S; and

n=0, 1, 2, 3.

2. The compound of formula (I) as claimed in claim **1**, or its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs:

A ring selected from



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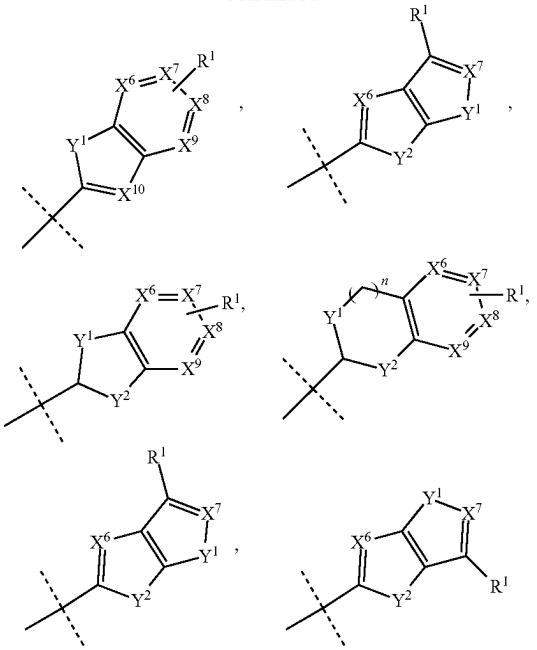
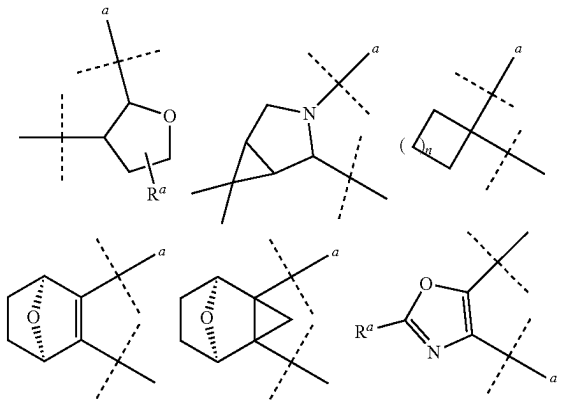


the A ring is optionally substituted with 0 to 5 independently selected R^1 groups;

the B ring is selected from 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl, where the 3-8 membered heterocyclic and 5 or 8 membered heteroaryl contain heteroatoms or heteroatom groups selected from N, O, and S, with the number of heteroatoms or heteroatom groups being 1-4;

the 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0 to 3 Ra groups: hydrogen, deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogenated C1-C6 alkyl, or 3-6 membered heterocyclic alkyl;

the 3-8 membered cycloalkyl, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl include but are not limited to the following: (where the a-end is connected to L_1);



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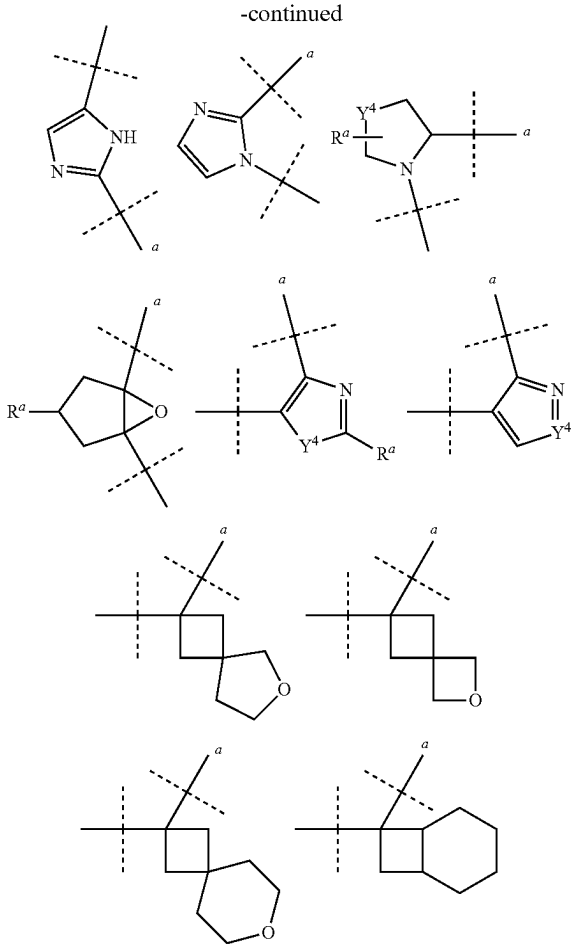
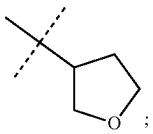


R^a is selected from hydrogen, methyl, trifluoromethyl, or cyclopropyl;

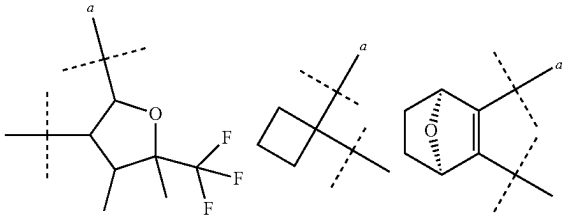
This specifies the preferred substituent options for the group R^a



;

Y^4 is selected from NH, O, S;

More preferably, the B ring is selected from the following (where the a-end is connected to L_1);



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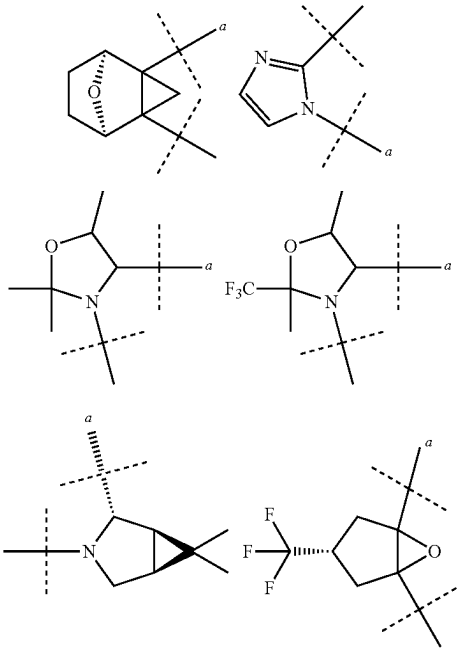

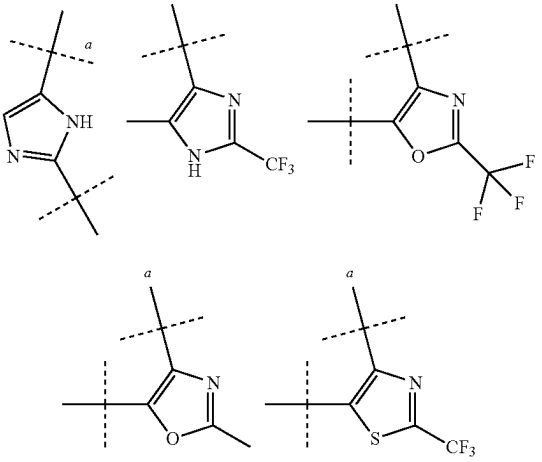

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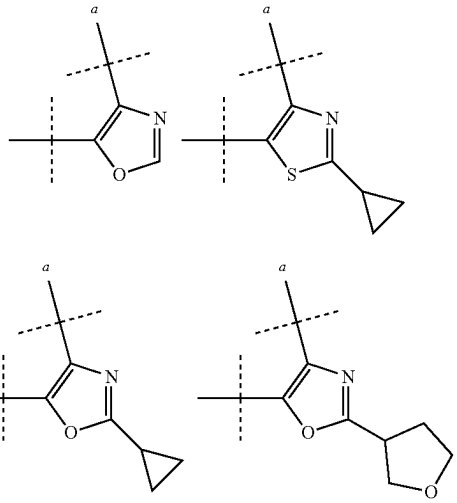
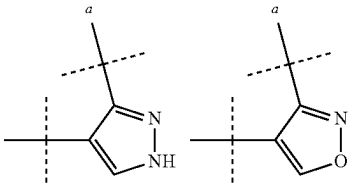
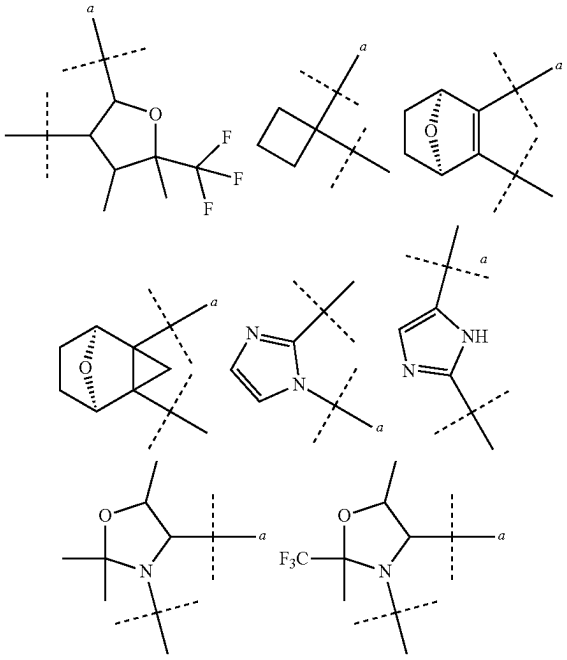




the B ring is selected from the following (where the a-end is connected to L_1):



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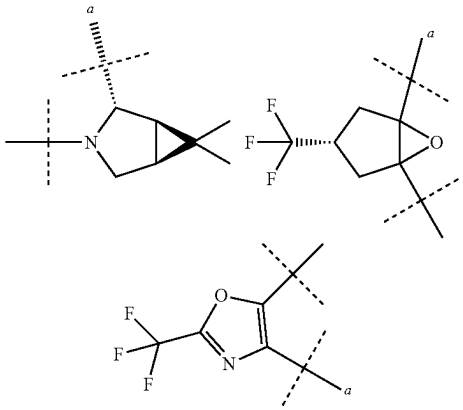
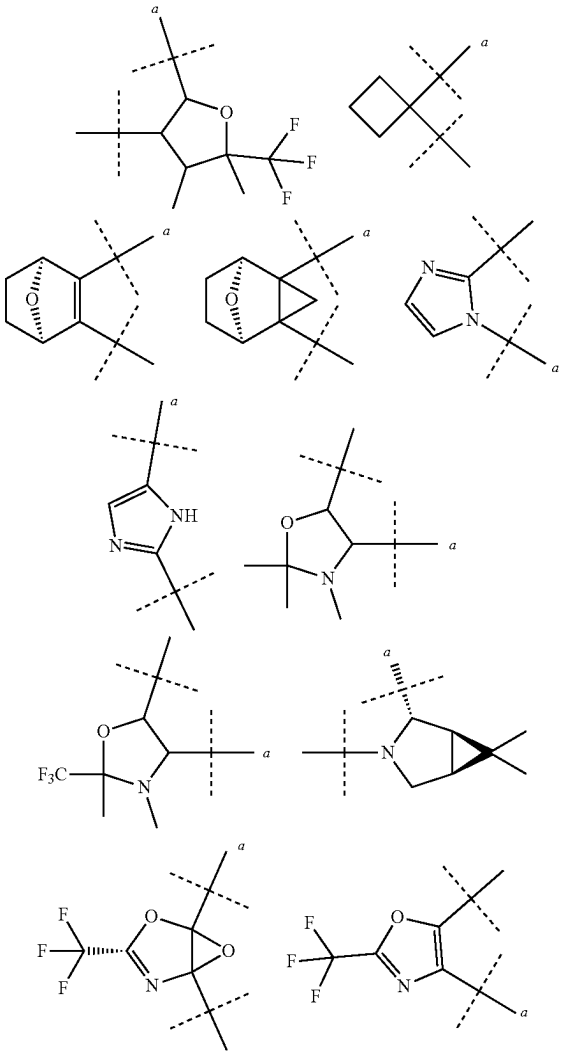


further preferably, the B ring is selected from the following (where the a-end is connected to L_1):



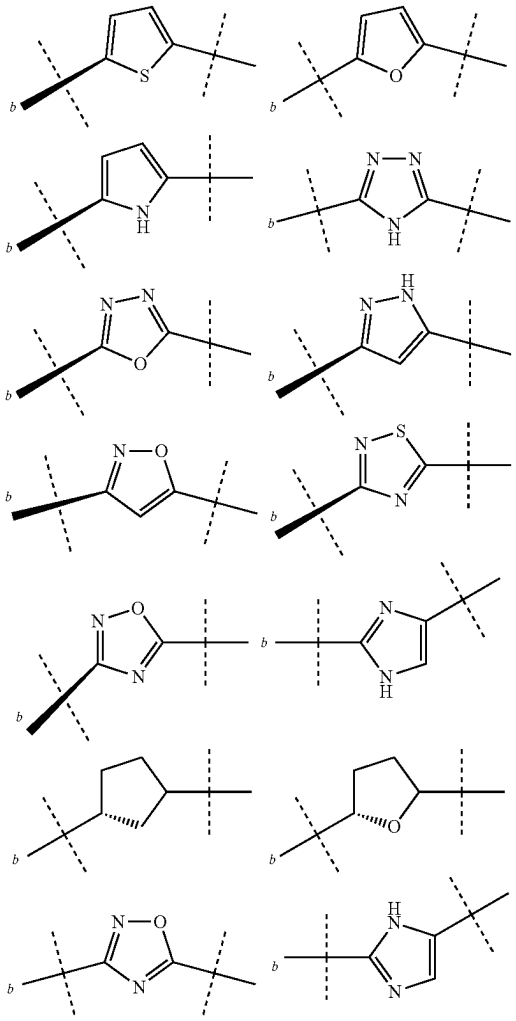
L_1 is selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl;

the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl 3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, —S(O)2C3-C6 cycloalkyl;

the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

the 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl include but are not limited to the following (where the b-end is connected to the B ring):



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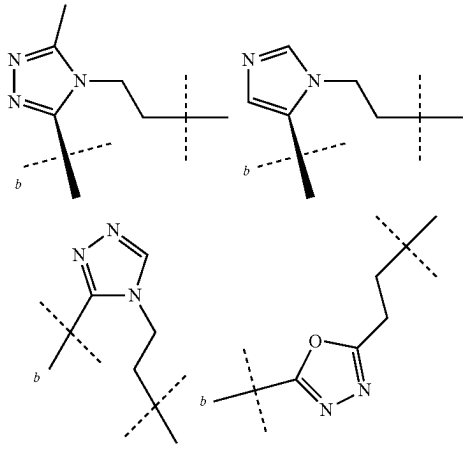


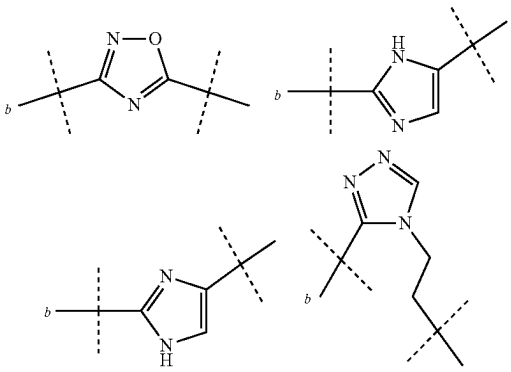
preferably, L_1 is selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaryl;

the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaryl may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl 3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, —S(O)2C3-C6 cycloalkyl;

the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocyclic alkyl may optionally be substituted with 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

the above 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaryl include but are not limited to the following: (where the b-end is connected to the B ring):



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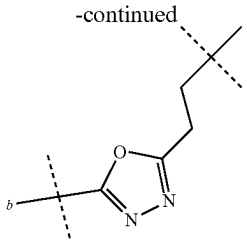


preferably, L_2 is selected from a single bond, —CO—;

R^1 and R^7 are each independently selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —NHCOR^c, —$NHSO_2R^c$, —P(O) R^cR^d, —NHR^c, —NHCOR^cNHR^d, —C(O)OR^c, 3-8 membered heterocyclic alkyl, 5 or 6 membered heteroaromatic, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents, selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl); alternatively, any two adjacent R^1 (or R^7) form a five-membered ring with the atoms to which they are bonded, or any two meta-positioned R^1 (or R^7) form a heterocyclic alkenyl with the atoms to which they are bonded;

Rc and Rd are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic, where the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents, selected from deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0-3 substituents, selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic, where the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents, selected from deuterium, halogen, and C1-C3 alkyl;

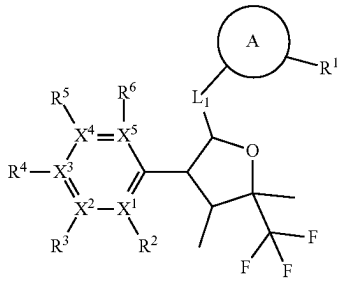
X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives;

Y^1, Y^2, Y^3, and Y^4 are each independently selected from CH_2, NH, O, and S; and

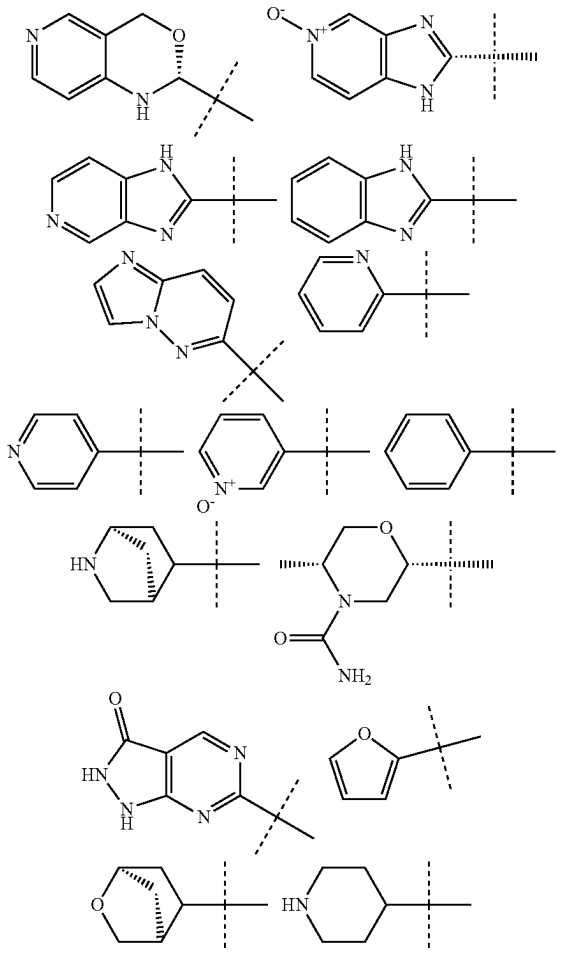
n=0, 1, 2, 3.

3. The compound of formula (I) as claimed in claim **1**, or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs, is the compound of formula (II), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs

II



wherein, the A ring is selected from but not limited to the following:



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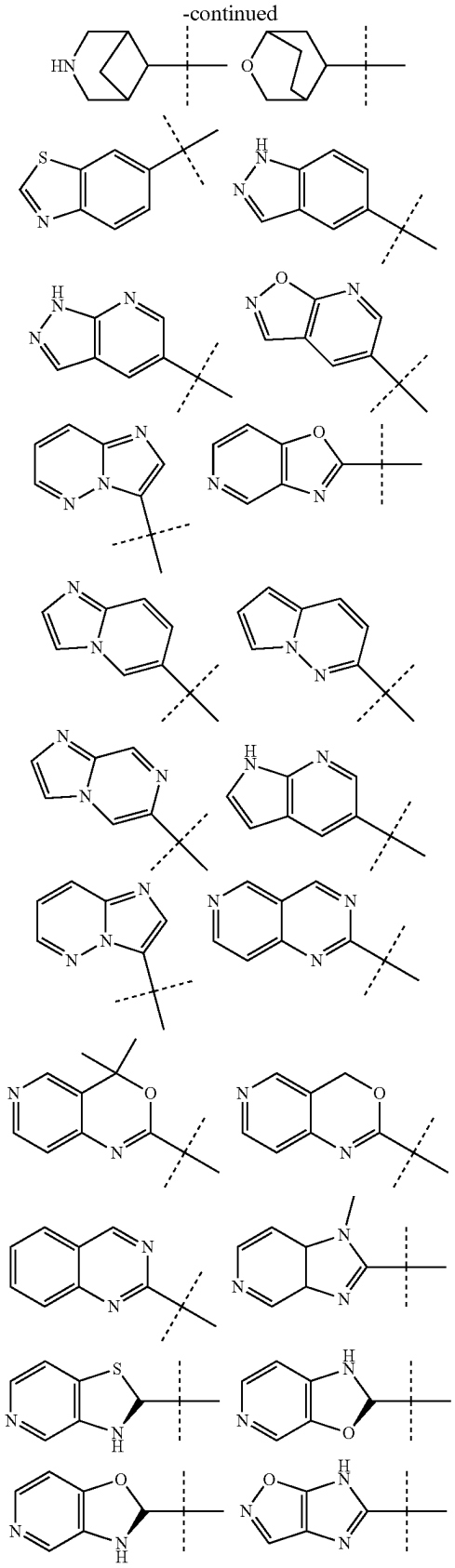

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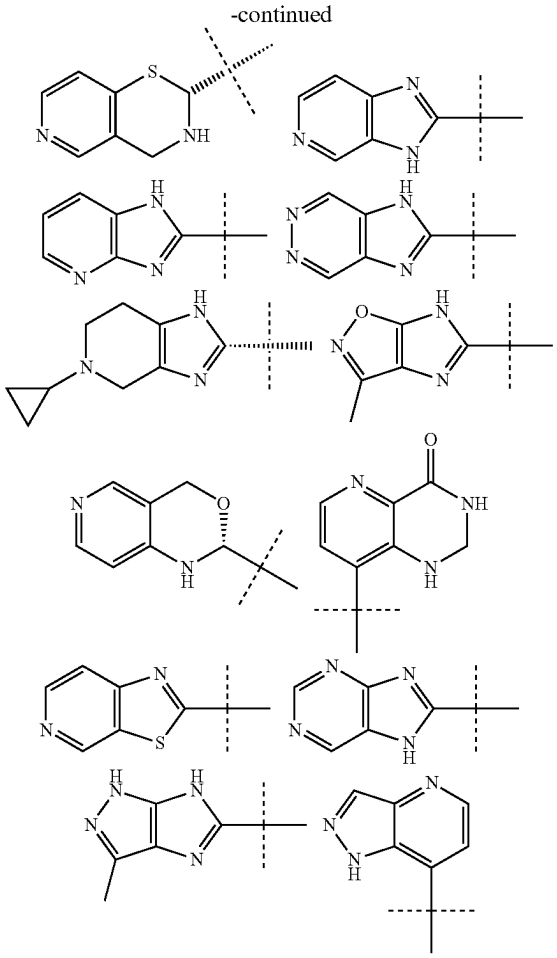
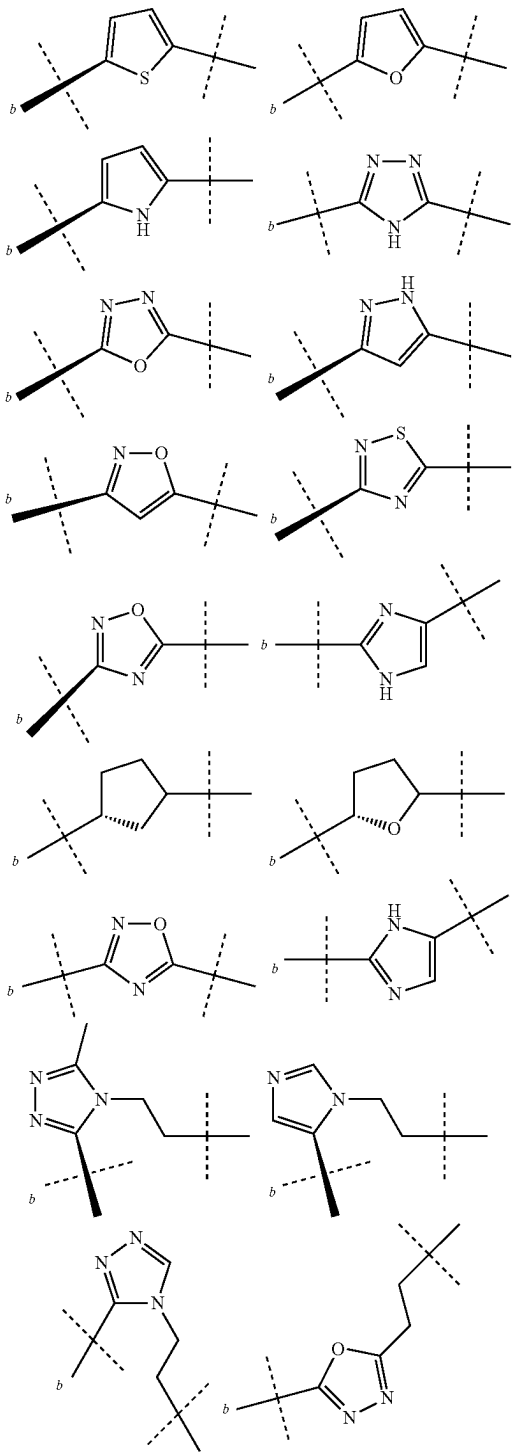


wherein, the A ring is optionally substituted with 0-5 independent R1 groups;

L_1 is selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8 membered heterocyclic alkyl, and 5 or 8 membered heteroaromatic, where the 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, C1-C6 alkyl 3-8 membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)$_2$C1-C6 alkyl, —S(O)$_2$C3-C6 cycloalkyl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8 membered heterocyclic alkyl may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

the above 3-8 membered heterocyclic alkyl and 5 or 8 membered heteroaromatic include, but are not limited to, the following (where the b-end is connected to the B ring):



R^1 is selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —NHCOR^c, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —NHCOR^cNHR^d, —C(O)OR^c, 3-8 membered heterocyclic alkyl, 5 or 6 membered heteroaromatic, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

alternatively, any two adjacent R^1 form a five-membered ring with the atoms to which they are connected, or any two meta-positioned R^1 form a heterocyclic alkenyl with the atoms to which they are connected;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic, where the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, and halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

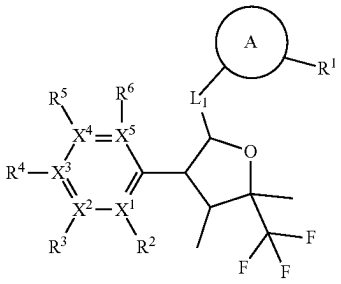
R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic, where the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocyclic alkyl, 3-8 membered heterocyclic alkenyl, and 5 or 8 membered heteroaromatic may optionally be substituted with 0-3 substituents selected from deuterium, halogen, and C1-C3 alkyl;

X^1, X^2, X^3, X^4, and X^5 are each independently selected from O, S, N, CH, or N-oxide derivatives; and

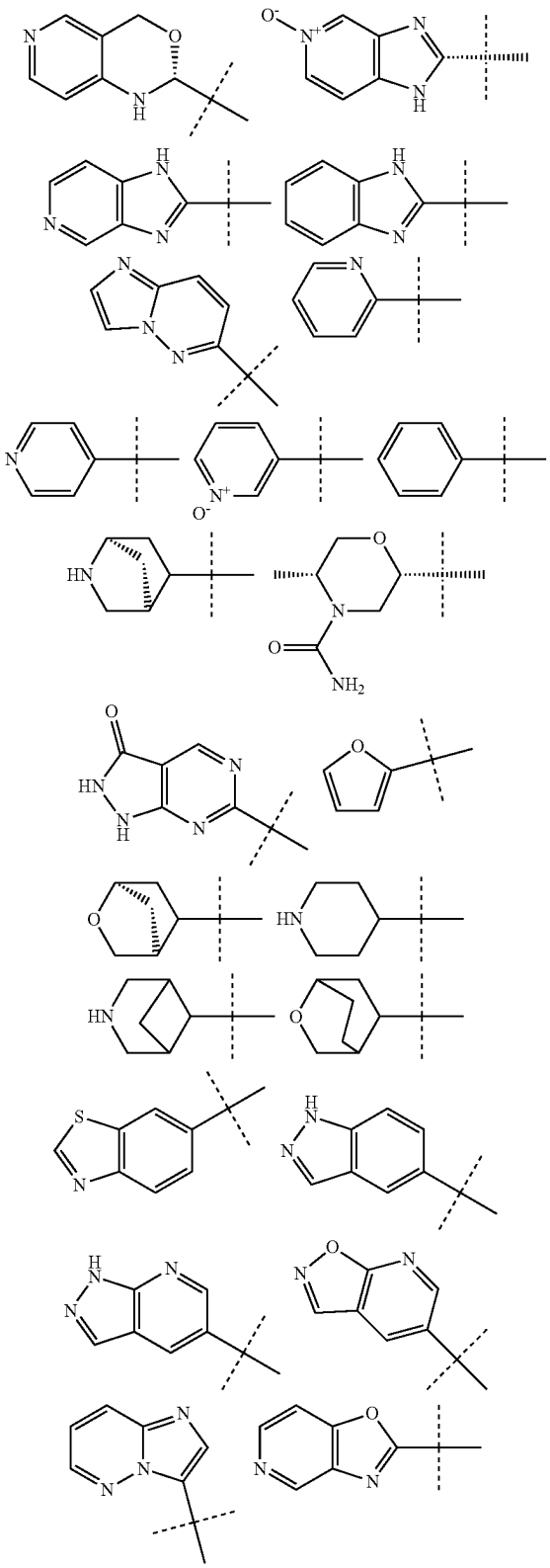
Y^4 is selected from CH_2, NH, O, and S.

4. The compound of formula (I) as claimed in claim **1**, or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs is the compound of formula (II), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs

II



the A-ring is selected from but not limited to the following:



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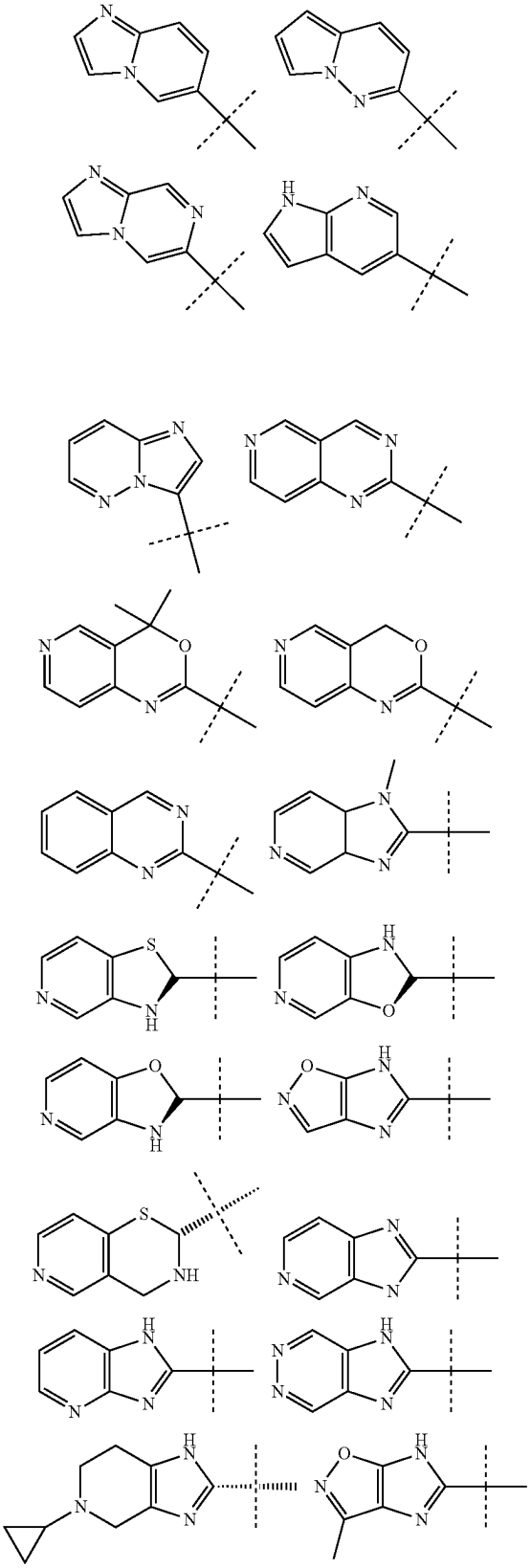

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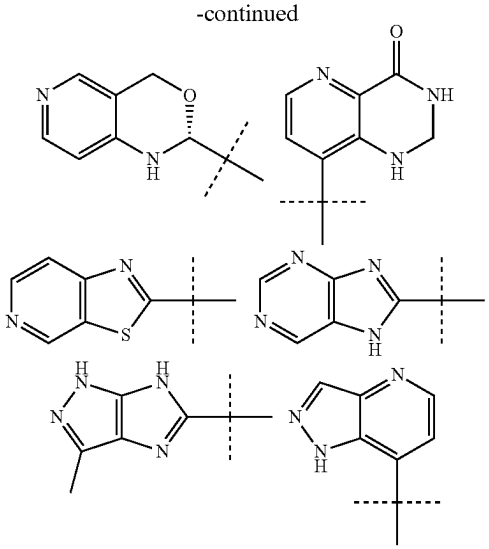
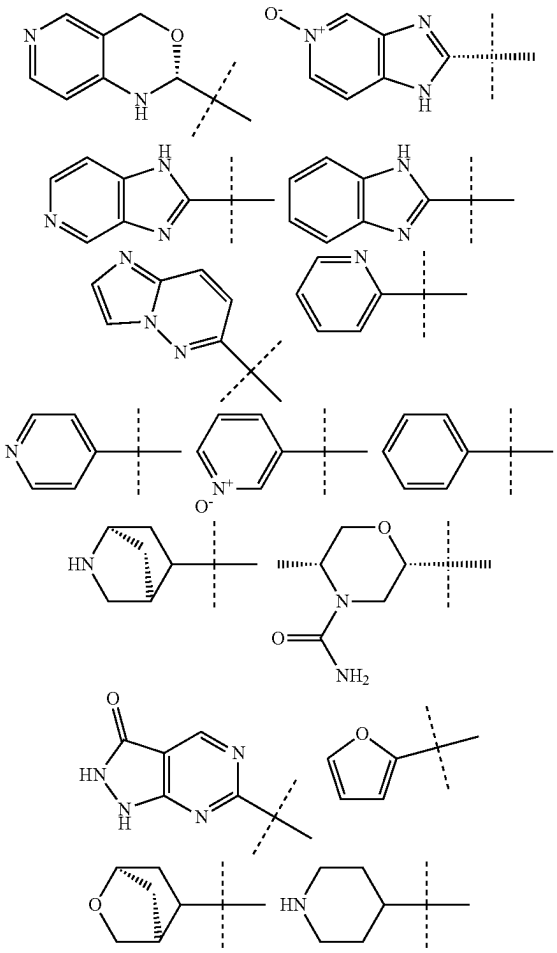


among them, the A-ring is optionally replaced by 0-5 independent R^1 groups;

preferably, the A-ring is selected from the following:



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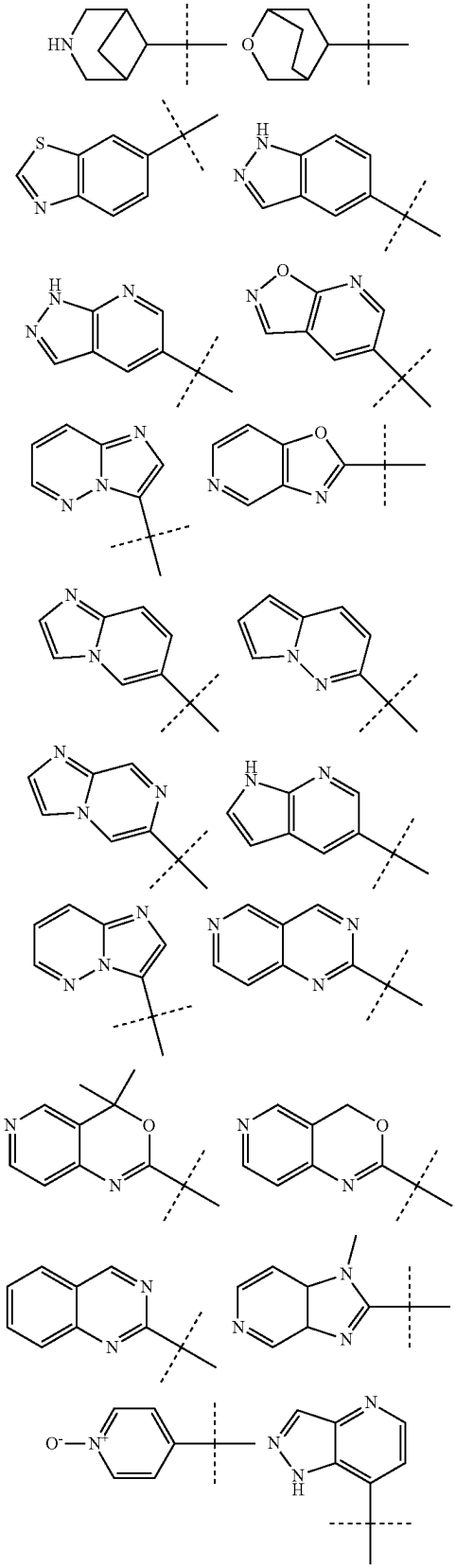

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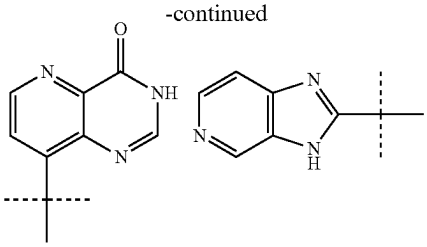
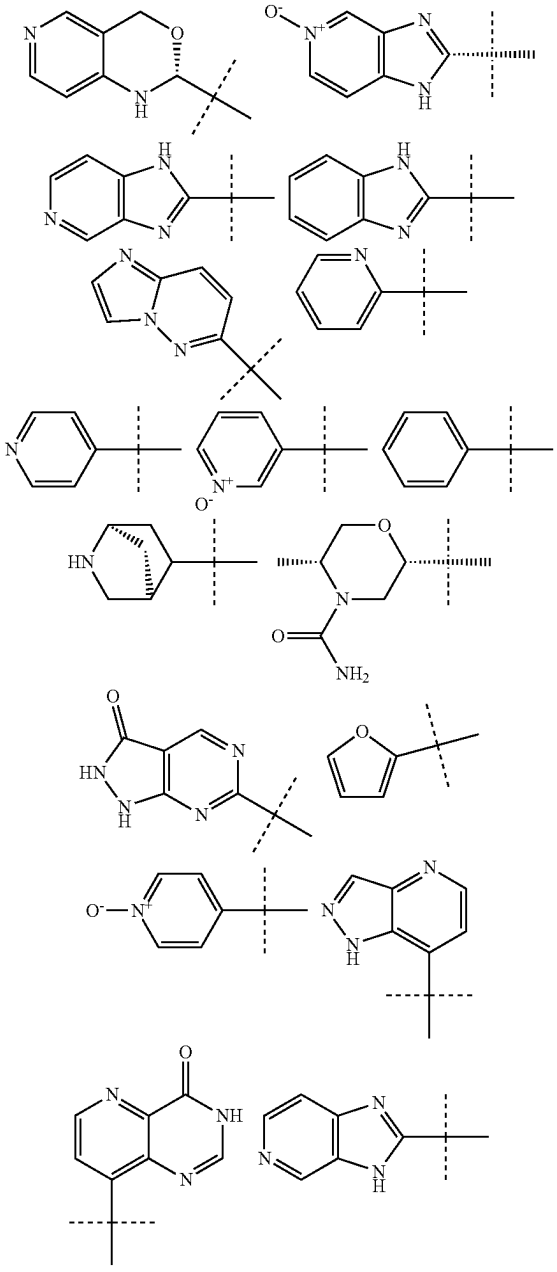
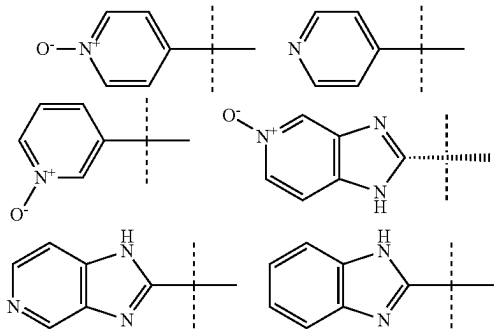


preferably, the A-ring is selected from the following:



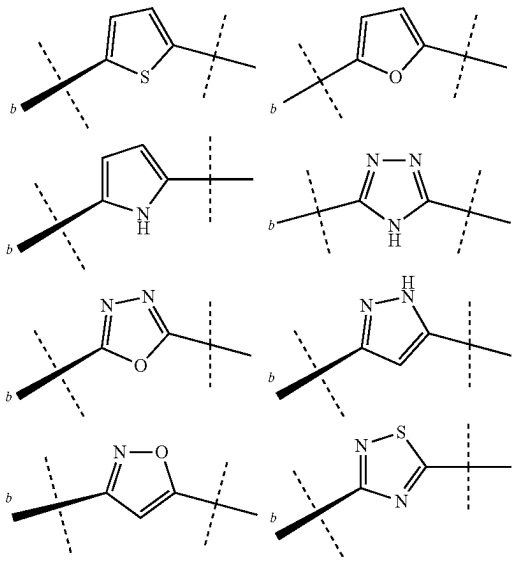
optimally, the A-ring is selected from the following:



L_1 is selected from a single bond, —CONR^b—, —CO—, —NHCONH—, 3-8-membered heterocyclic alkyl, and 5- or 8-membered heteroaryl, where the 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaryl may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, C1-C6 alkyl 3-8-membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)$_2$C1-C6 alkyl, —S(O)$_2$C3-C6 cycloalkyl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

the 3-8-membered heterocyclic alkyl and 5- or 8-membered heteroaryl described above include but are not limited to the following (where the b-end is connected to the B-ring):



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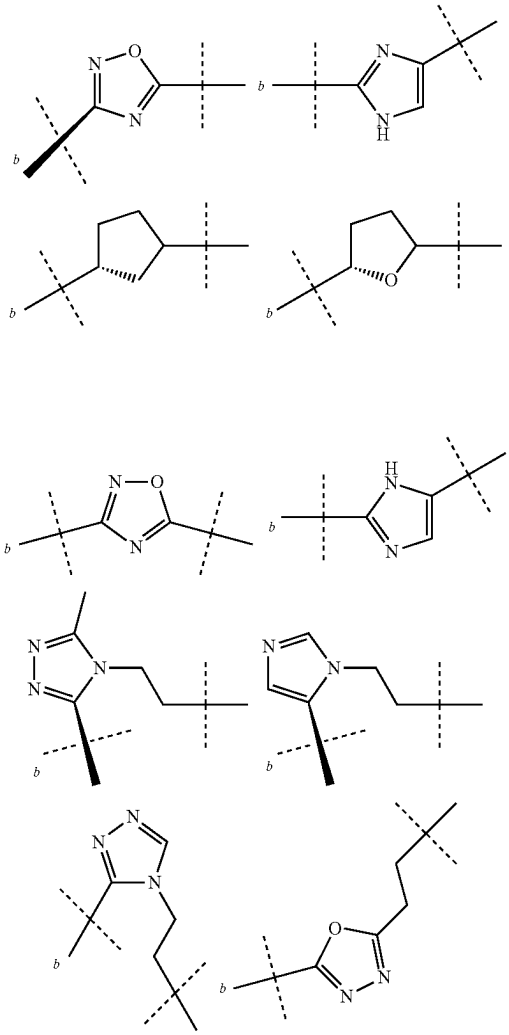
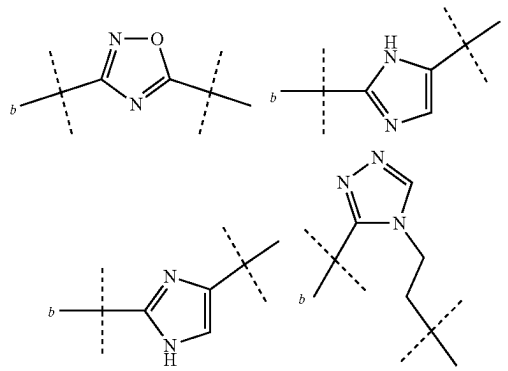


preferably, the 3-8-membered heterocyclic alkyl and 5- or 8-membered heteroaryl described above include but are not limited to the following: (where the b-end is connected to the B-ring):



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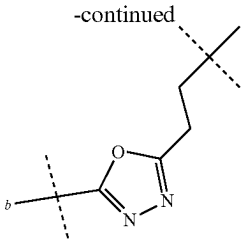


R^1 is selected from hydrogen, halogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8-membered heterocyclic alkyl, 5- or 6-membered heteroaryl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaryl may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

alternatively, any two adjacent R^1 groups and the atoms they are connected to form a five-membered ring, and any two meta-positioned R^1 groups and the atoms they are connected to form a heterocyclic alkenyl;

R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaryl, where the amino group, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaryl may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, where the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

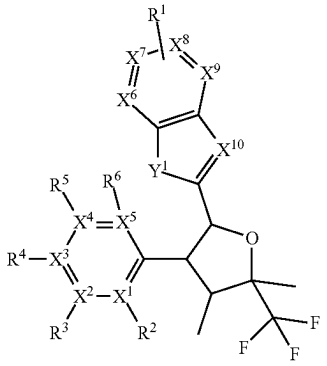
R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen, deuterium, halogen, —CONH$_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaryl, where the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaryl may optionally be substituted by 0-3 substituents: deuterium, halogen, C1-C3 alkyl; and

X^1, X^2, X^3, X^4, and X^5 are independently selected from O, S, N, CH, or N-oxide derivatives.

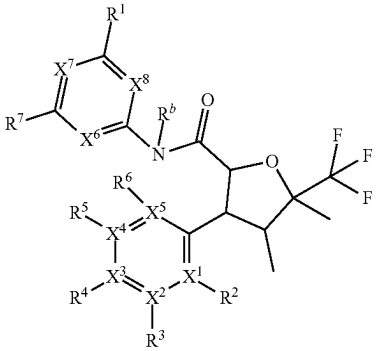
5. The compound of formula (I) as claimed in claim **1**, or its stereoisomers, tautomeric isomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs, is a compound of formula (II-1), (II-2), or

its stereoisomers, tautomeric isomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs:

II-1

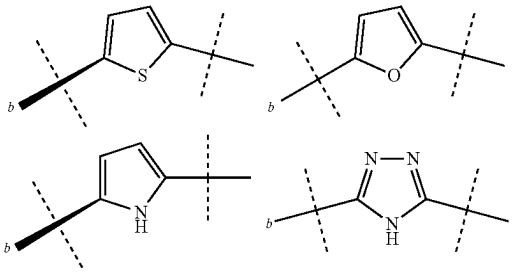


II-2



R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, C1-C6 alkyl 3-8-membered heterocyclic alkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —$S(O)_2$C1-C6 alkyl, —$S(O)_2$C3-C6 cycloalkyl, where the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, and 3-8-membered heterocyclic alkyl may optionally be substituted by 0-3 substituents: deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

the 3-8-membered heterocyclic alkyl and 5- or 8-membered heteroaryl described above include but are not limited to the following: (where the b-end is connected to the B-ring)



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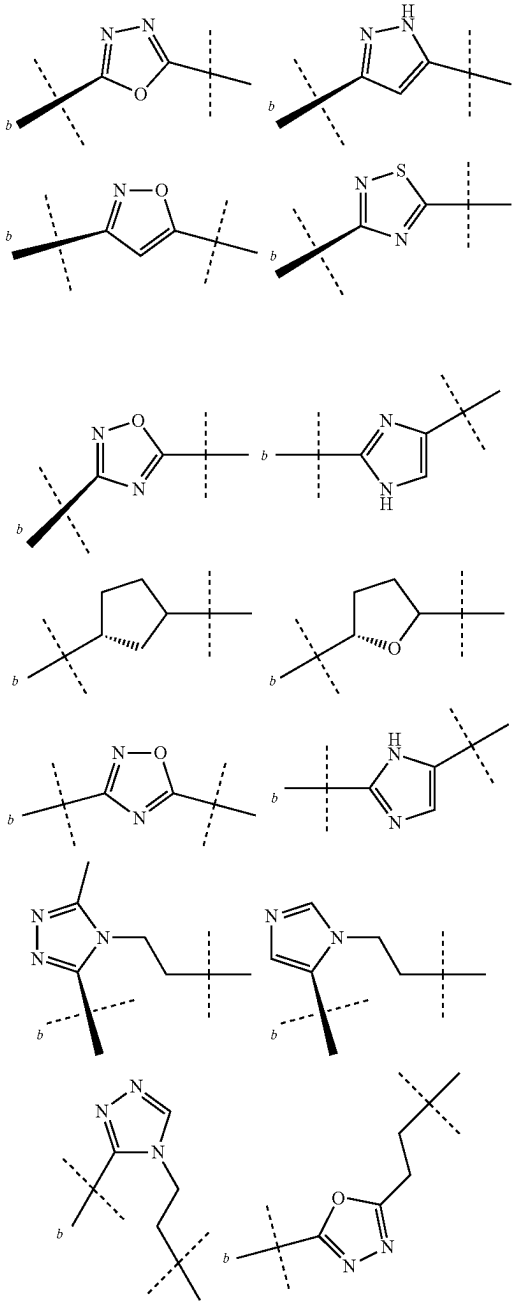
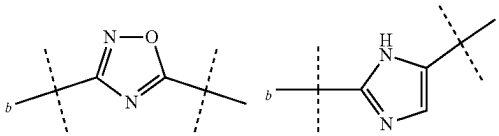


preferably, the 3-8-membered heterocyclic alkyl and 5- or 8-membered heteroaryl described above include but are not limited to the following: (where the b-end is connected to the B-ring)



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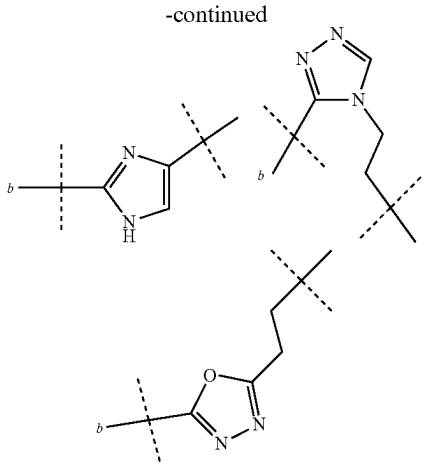


R^1 is selected from hydrogen, halogens, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8-membered heterocyclic alkyl, 5 or 6-membered heteroaryl;

the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

alternatively, any two adjacent R1 groups, together with the atoms they are connected to, form a five-membered ring, and any two meta-positioned R^1 groups, together with the atoms they are connected to, form a heterocyclic alkenyl group;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl, wherein the amino group, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, wherein the C1-C6 alkyl and C3-C6 cycloalkyl may optionally be substituted with 0-3 substituents selected from deuterium, halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogen, —CONH2, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl, wherein the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5 or 8-membered heteroaryl may optionally be substituted with 0-3 substituents selected from deuterium, halogen, C1-C3 alkyl;

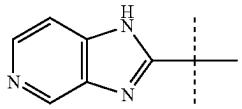
X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from O, S, N, CH, or N-oxide derivatives;

Y^1, Y^2, Y^3, and Y^4 are each independently selected from CH_2, NH, O, S;

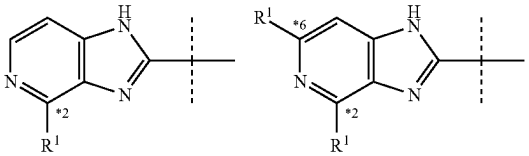
Preferably, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from N, CH, or N-oxide derivatives;

Preferably, Y^1 is selected from NH;

among them, when the A ring is



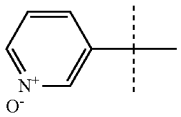
When R^1 is substituted at the 6-position and is —CONH$_2$, the R^1 at the 2-position is not H;



among them, when the A ring is a pyridine ring with X^7 being N or N—O, both R^1 and R^7 can be hydrogen;

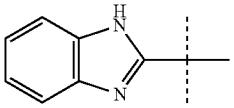
Among them, when R^1 (R^7) is CONH$_2$, the other substituent is not hydrogen;

When the A ring is selected from

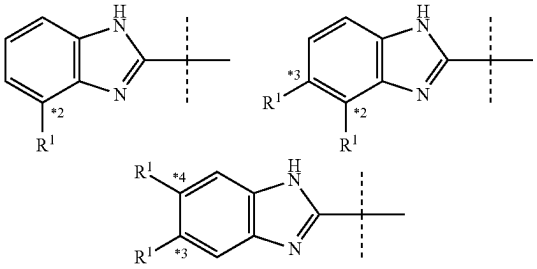


When, preferably, R^1 is H; L_1 is —CONH$_2$; L_2 is a single bond; R^2 and R^6 are each independently selected from H, methoxy; R^3, R^4, and R^5 are each independently selected from H, F; X^1, X^2, X^3, X^4, and X^5 are selected from CH;

when the A ring is selected from



At this time, R^1 is preferably located at the following positions

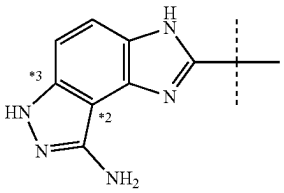


Preferably, when the A ring is substituted with only one R^1 and the substitution site is *2, R^1 is selected from —S(O)(NH_2)CH_3;

Preferably, when the A ring is substituted with two R^1 groups and the substitution sites are *2 and *3, the R^1 at *2 is selected from $CONH_2$, C(NH)NH_2, C(NH)NHOH, C(NH)NHOC(O)CH_3, and the R^1 at *3 is F;

Preferably, when the A ring is substituted with two R^1 groups and the substitution sites are *3 and *4, the R^1 at *3 is independently selected from F, $CONH_2$, and the R^1 at *4 is selected from $CONH_2$, C(NH)NHOH;

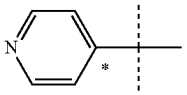
Preferably, when the A ring is substituted with two R^1 groups and the substitution sites are *3 and *4, the R^1 at *3 is independently selected from F, and the R^1 at *4 is selected from $CONH_2$, C(NH)NHOH, or when the A ring is substituted with two R^1 groups and R^1 is at *2 and *3, the atoms connected to them can form the following structure:



Preferably, L_1 and L_2 are single bonds;

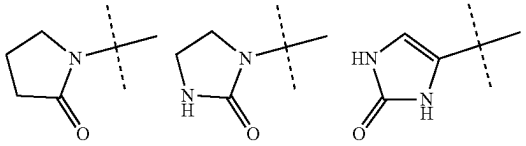
Preferably, R^2 and R^6 are each independently selected from H, methoxy; R^3, R^4, and R^5 are each independently selected from H, F;

Preferably, X^1, X^2, X^3, X^4, and X^5 are selected from CH; when the A ring is selected from



when L_1 is —$CONH_2$;

preferably, the A ring is optionally substituted with one R^1, and R^1 is located at the * meta position:



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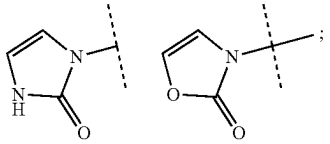
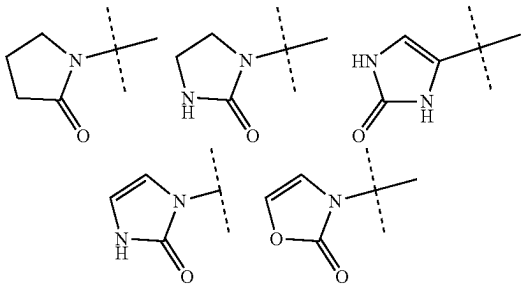
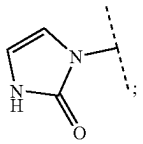


alternatively, the A ring is substituted with two R^1 groups, and both R^1 groups are located at the * meta position, where one R^1 is selected from —$CONH_2$, and the other R^1 is selected from the following:



Preferably, the A ring is optionally substituted with one R^1, and R^1 is located at the * meta position, where R^1 is



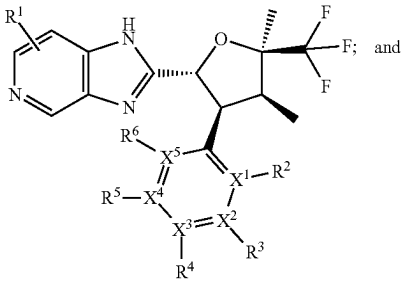
Preferably, L_2 is a single bond;

Preferably, R^2 and R^6 are each independently selected from H, methoxy; R^3, R^4, and R^5 are each independently selected from H, F; and

Preferably, X^1, X^2, X^3, X^4, and X^5 are selected from CH.

6. The compound of formula (I) according to claim **1**, or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, deuterated compound, metabolite or prodrug thereof, which is a compound of formula (II-1A), or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, deuterated compound, metabolite or prodrug thereof:

(II-1A)



F; and

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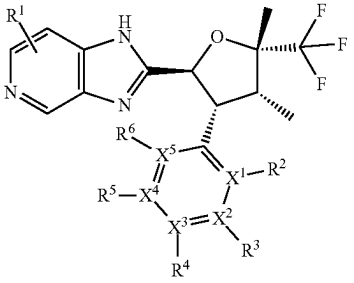
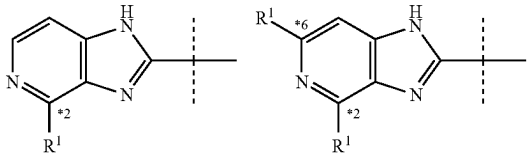


among them, the A ring is optionally substituted with 0 to 3 R^1 groups, with R^1 preferably located at the positions shown below;

when R^1 is substituted at the 6-position and is —$CONH_2$, the R^1 at the 2-position is not H;



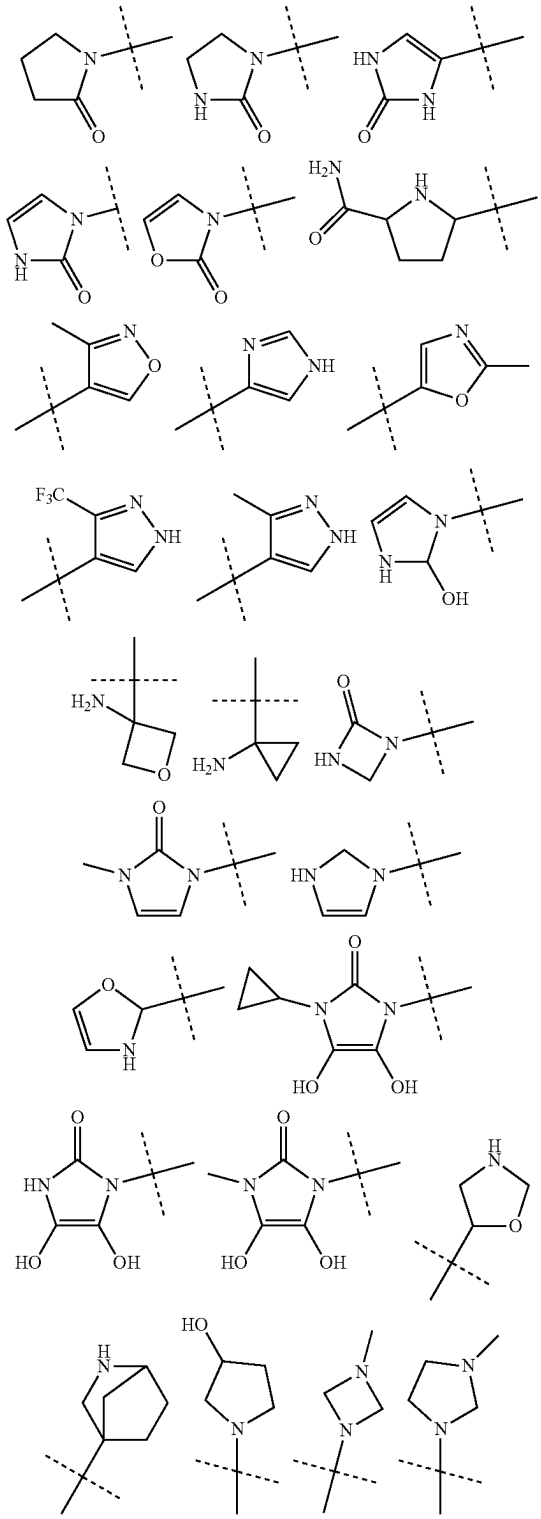
R^1 is independently selected from hydrogen, halogens, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —$NHCOR^c$, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —$NHCOR^cNHR^d$, —C(O)OR^c, 3-8 membered heterocycloalkyl, 5 or 8 membered heteroaryl, wherein the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, CO(C1-C6 alkyl);

alternatively, any two ortho-positioned R^1 (or R^7) with the atoms they are connected to form a five-membered ring, and any two meta-positioned R^1 (or R^7) with the atoms they are connected to form a heteroalkenyl ring;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —$OCOR^e$, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, wherein the amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl and C3-C6 cycloalkyl, wherein the C1-C6 alkyl and C3-C6 cycloalkyl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

the 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 6 membered heteroaryl include, but are not limited to, the following:



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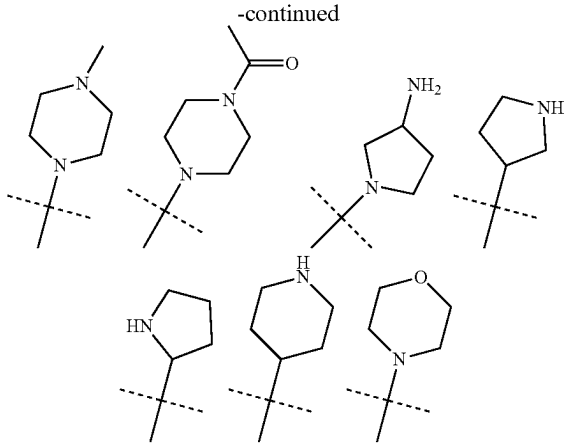
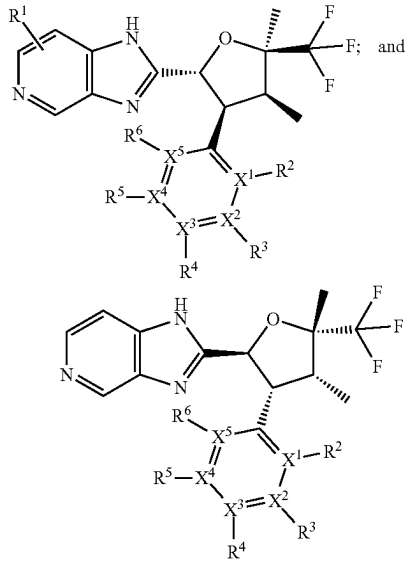


R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogens, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, wherein the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, C1-C3 alkyl; and

X^1, X^2, X^3, X^4, and X^5 are each independently selected from O, S, N, CH, or N-oxide derivatives.

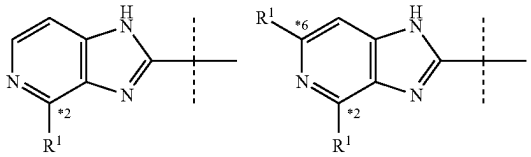
7. The compound of formula (I) as described in claim **1**, or its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs, wherein it is a compound of formula (II-1A), or its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs:

(II-1A)



Among them, the A ring is optionally substituted with 0 to 3 R^1 groups, with R^1 preferably located at the positions shown below;

when R^1 is substituted at the 6-position and is —$CONH_2$, the R^1 at the 2-position is not H;



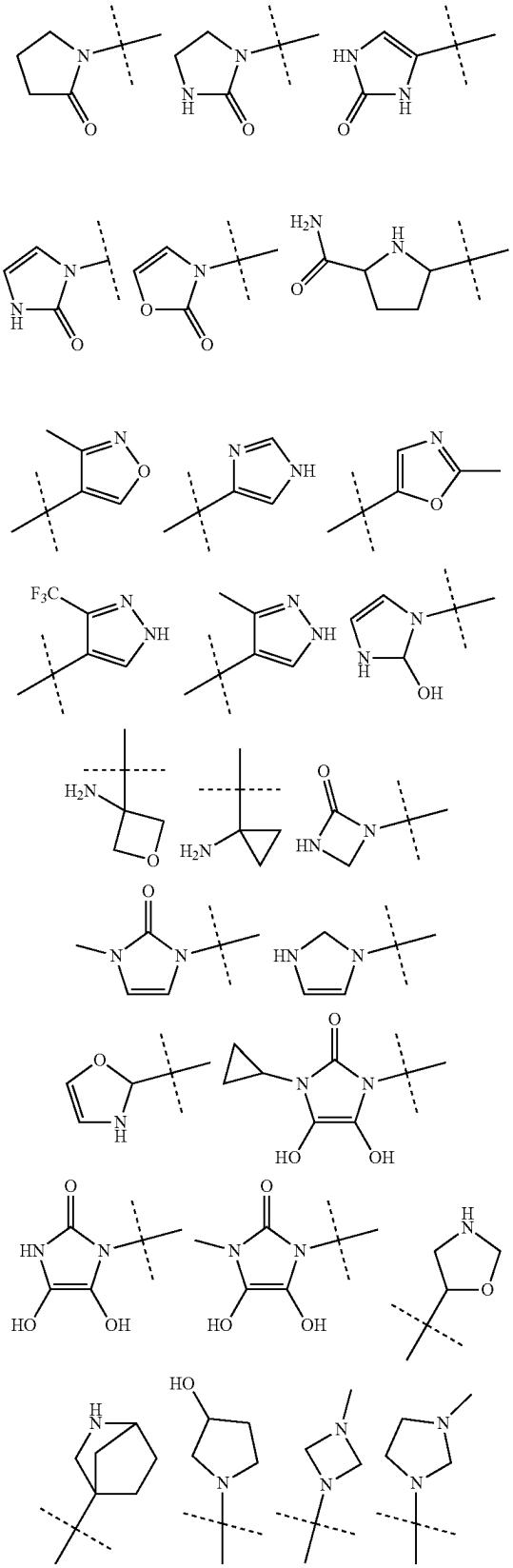
R^1 is independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —S(O)(NH)R^c, —CON R^cR^d, C(NR^c)NHR^d, —NHCOR^c, —$NHSO_2R^c$, —P(O)R^cR^d, —NHR^c, —NHCOR^c-NHR^d, —C(O)OR^c, 3-8 membered heterocycloalkyl, 5 or 8 membered heteroaryl, wherein the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, F, Cl, Br, I, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)(methyl), C(O)(ethyl), C(O)(propyl);

Alternatively, any two ortho-positioned R^1 (or R^7) with the atoms they are connected to form a five-membered ring, and any two meta-positioned R^1 (or R^7) with the atoms they are connected to form a heteroalkenyl ring;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, wherein the amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, C(O)(methyl), C(O)(ethyl), C(O)(propyl), methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoromethyl, difluoromethyl, trifluoromethyl;

R^e is selected from methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, wherein the methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl;

the 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 6 membered heteroaryl include, but are not limited to, the following:



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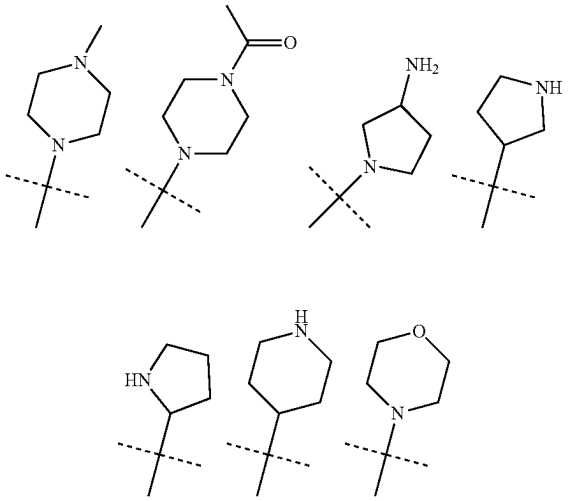
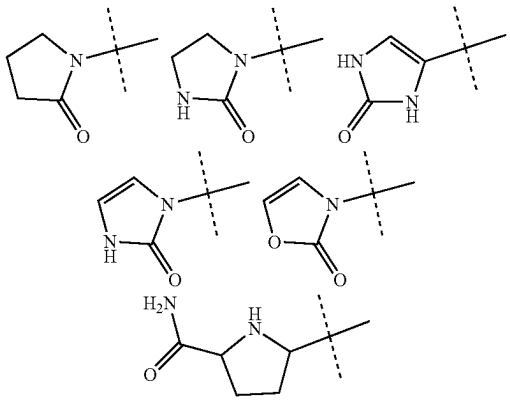


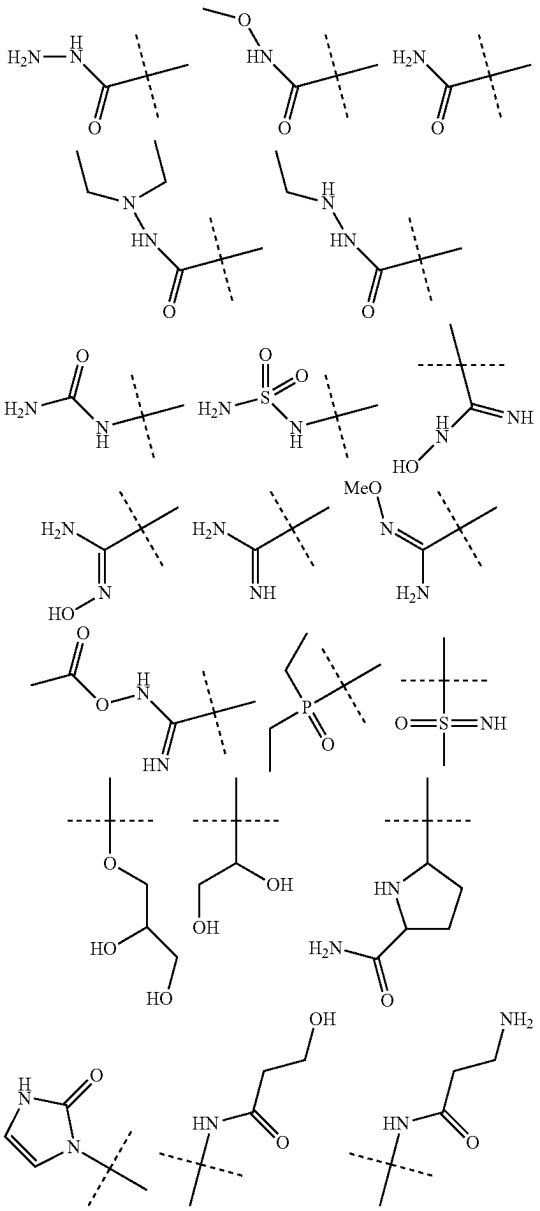
R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, F, Cl, Br, I, —$CONH_2$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, wherein the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, F, Cl, Br, I, methyl, ethyl, propyl, isopropyl;

X^1, X^2, X^3, X^4, and X^5 are each independently selected from N, CH, or N-oxide derivatives;

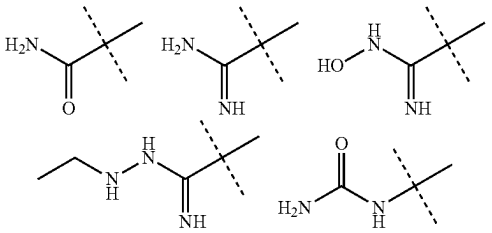
when R^1 is selected from 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, it includes, but is not limited to, the following structures:



R^1 is selected from hydrogen, amino, or the following groups:



further preferably, R^1 is selected from hydrogen, amino, or the following groups:



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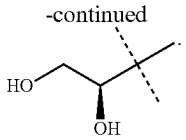
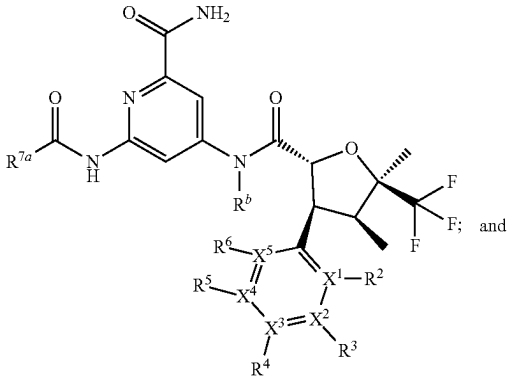
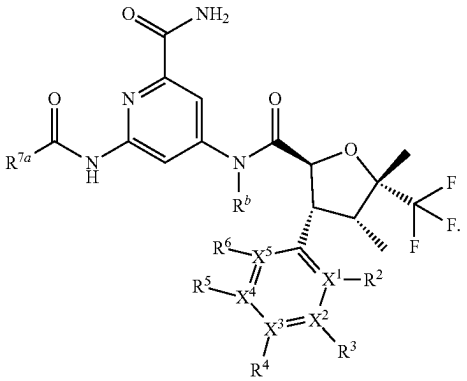


8. The compound of formula (I) as described in claim **1**, or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs, wherein it is a compound of formula (II-2A), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs:

(II-2A)





Wherein,

R^b is selected from hydrogen, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, C1-C6 alkyl 3-8 membered heterocycloalkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —$S(O)_2$C1-C6 alkyl, —$S(O)_2$C3-C6 cycloalkyl, wherein the C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogen, hydroxyl, cyano,

amino, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C(O)C1-C6 alkyl, and C3-C6 cycloalkyl;

R^{7a} is selected from, —R^cNHR^d;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, wherein the amino group, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, halogen-substituted C1-C6 alkyl;

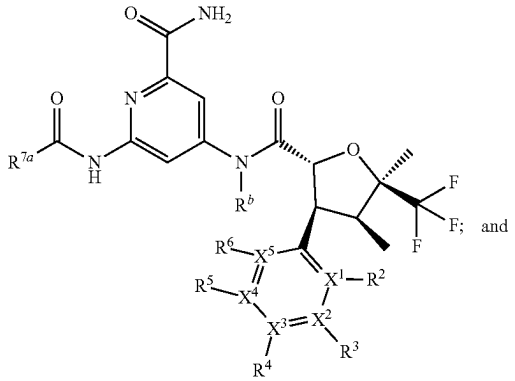
R^e is selected from C1-C6 alkyl, C3-C6 cycloalkyl, wherein the C1-C6 alkyl and C3-C6 cycloalkyl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, and C3-C6 cycloalkyl;

R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, halogens, —$CONH_2$, C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl, wherein the C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heteroalkenyl, and 5 or 8 membered heteroaryl are optionally substituted with 0 to 3 of the following substituents: deuterium, halogens, C1-C3 alkyl; and

X^1, X^2, X^3, X^4, and X^5 are each independently selected from O, S, N, CH, or N-oxide derivatives.

9. The compound of formula (I) as described in claim **1**, or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs, wherein it is a compound of formula (II-2A), or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated compounds, metabolites, or prodrugs:

(II-2A)



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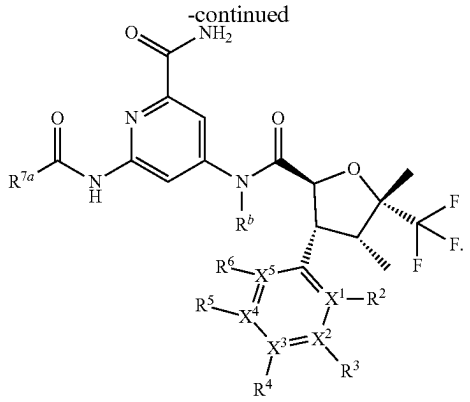


wherein,

R^b is selected from hydrogen, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, cyclopropyl, cyclobutyl, 3-8 membered heterocycloalkyl, methyl 3-8 membered heterocycloalkyl, ethyl 3-8 membered heterocycloalkyl, propyl 3-8 membered heterocycloalkyl, —C(O)C1-C6 alkyl, —C(O)C3-C6 cycloalkyl, —S(O)2C1-C6 alkyl, —$S(O)_2$C3-C6 cycloalkyl, wherein the methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, cyclopropyl, cyclobutyl, 3-8 membered heterocycloalkyl, methyl 3-8 membered heterocycloalkyl, ethyl 3-8 membered heterocycloalkyl, propyl 3-8 membered heterocycloalkyl are optionally substituted with 0 to 3 of the following substituents: deuterium, F, Cl, Br, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, C(O)(methyl), C(O)(ethyl), C(O)(propyl), cyclopropyl, cyclobutyl; R^{7a} is selected from R^c, —R^cNHR^d;

R^c and R^d are each independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, and 5 or 8 membered heteroaryl, where the amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, and 5 or 8 membered heteroaryl can optionally be substituted with 0-3 of the following substituents: deuterium, F, Cl, Br, hydroxyl, cyano, amino, C(O)(methyl), C(O)(ethyl), C(O)(propyl), methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoromethyl, difluoromethyl, trifluoromethyl;

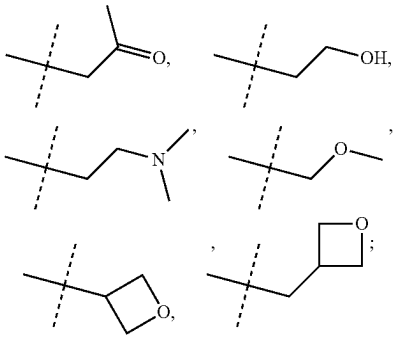
R^e is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, where the C1-C6 alkyl and C3-C6 cycloalkyl can optionally be substituted with 0-3 additional substituents, selected from deuterium, F, Cl, Br, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

R^2, R^3, R^4, R^5, and R^6 are each independently selected from hydrogen, deuterium, F, Cl, Br, I, —$CONH_2$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocy-

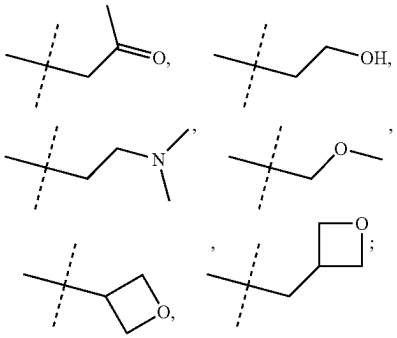
cloalkenyl, and 5 or 8 membered heteroaryl, where these groups (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C3-C6 cycloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, and 5 or 8 membered heteroaryl) can optionally be substituted with 0-3 additional substituents, selected from deuterium, F, Cl, Br, I, methyl, ethyl, propyl, or isopropyl;

X^1, X^2, X^3, X^4, and X^5 are each independently selected from N, CH, or N-oxide derivatives;

R^b is selected from H, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, C(O)cyclopropyl, C(O)cyclobutyl, C(O)cyclopentyl, $S(O)_2$cyclopropyl, $S(O)_2$cyclobutyl, $S(O)_2$cyclopentyl;



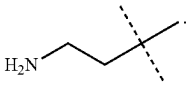
further preferably, R^b is selected from H, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $C(O)CH_3$, C(O)cyclopropyl, $S(O)_2$cyclopropyl,



optimally, in an optional embodiment of the present invention, Rb is selected from H, methyl;

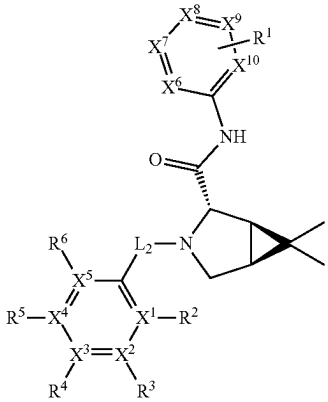
R^{7a} is selected from methylamino, ethylamino, propylamino, butylamino; and

Preferably, R^{7a} is selected from

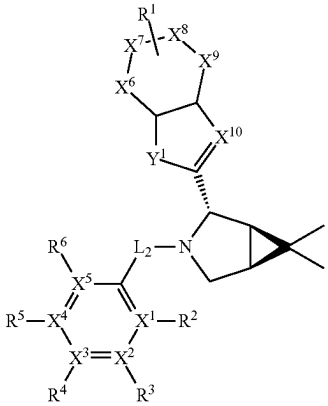


10. The compound of formula (I) as described in claim **1**, or its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated forms, metabolites, or prodrugs, which is the compound of formula (III) or (IV), or its stereoisomers, tautomeric forms, pharmaceutically acceptable salts, solvates, deuterated forms, metabolites, or prodrugs:

(III)



(IV)



L_2 is selected from a single bond, —CO—;

R^1 is selected from hydrogen, halogens, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8-membered heterocyclic alkyl, and 5- or 6-membered heteroaromatic groups;

the aforementioned C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups may optionally be substituted with 0-3 substituents selected from deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or CO(C1-C6 alkyl);

Alternatively, any two adjacent R^1 (or R^7) groups and the atoms to which they are connected may form a five-membered ring, and any two meta-positioned R^1 (or R^7) groups and the atoms to which they are connected may form a heteroaromatic alkenyl group;

R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, C1-C6 alkyl,

C1-C6 thioalkyl, C1-C6 alkoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups;

the amino group, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, —C(O)O(C1-C6 alkyl)OC(O)(C1-C6 alkyl), 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups may optionally be substituted with 0-3 substituents selected from deuterium, halogens, hydroxyl, cyano, amino, CO(C1-C6 alkyl), C1-C6 alkyl, C1-C6 thioalkyl, C3-C6 cycloalkyl, or halogen-substituted C1-C6 alkyl;

R^e is selected from C1-C6 alkyl or C3-C6 cycloalkyl, where these C1-C6 alkyl and C3-C6 cycloalkyl groups may optionally be substituted with 0-3 substituents selected from deuterium, halogens, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 thioalkyl, or C3-C6 cycloalkyl;

R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen, deuterium, halogens, —$CONH_2$ (amide group), C1-C6 alkyl, C1-C6 thioalkyl, C2-C6 alkenyl, C1-C6 halogenated alkyl, C1-C6 alkoxy, C1-C6 deuterated alkoxy, C1-C6 halogenated alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups;

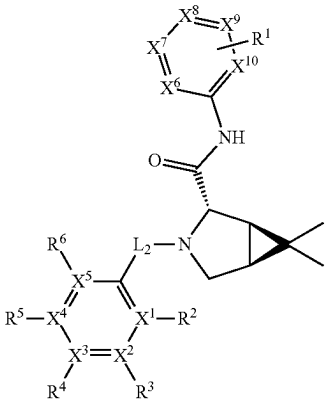
the aforementioned C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkoxy, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups may optionally be substituted with 0-3 substituents selected from deuterium, halogens, or C1-C3 alkyl groups;

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are each independently selected from oxygen (O), sulfur (S), nitrogen (N), methylene (CH), or N-oxide derivatives; and

Y^1 is selected from CH_2, NH, O, or S.

11. The compound of formula (I) as described in claim **1**, or its stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, deuterated derivatives, metabolites, or prodrugs, which is a compound of formula (III) or (IV), or its stereoisomers, pharmaceutically acceptable salts, solvates, deuterated derivatives, metabolites, or prodrugs

(III)



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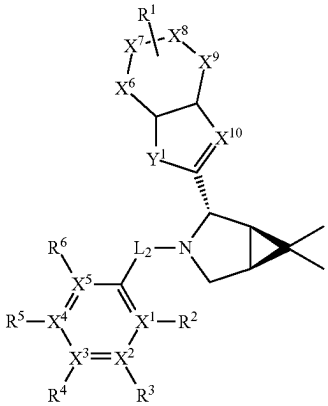
(IV)



L_2 is selected from a single bond, —CO—;

R^1 is selected from hydrogen, F (fluorine), Cl (chlorine), Br (bromine), I (iodine), methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —S(O)(NH)R^c, —CONR^{c}R^d, C(NR^c)NHR^d, —NHCOR^c, —NHSO$_2$R^c, —P(O)R^{c}R^d, —NHR^c, —NHCOR^{c}NHR^d, —C(O)OR^c, 3-8-membered heterocyclic alkyl, 5- or 6-membered heteroaromatic groups;

the aforementioned methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups may optionally be substituted with 0-3 substituents selected from deuterium, F, Cl, Br, I, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C(O)(methyl), C(O)(ethyl), and C(O)(propyl);

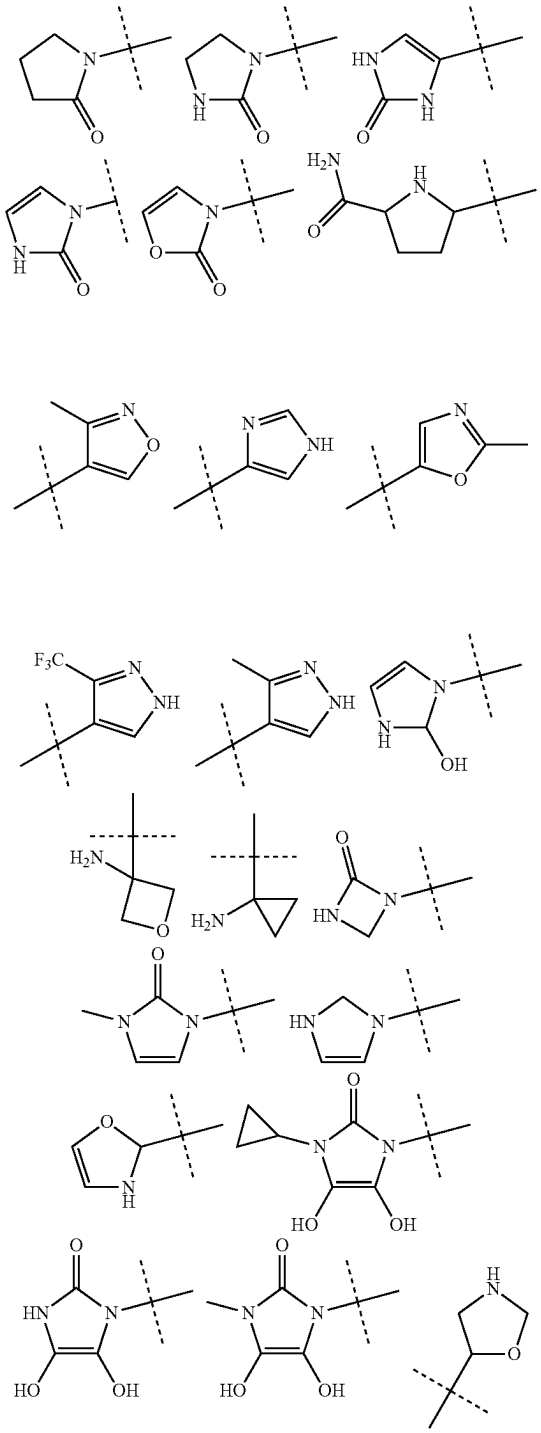
Alternatively, any two adjacent R^1 (or R^7) groups and the atoms they are connected to may form a five-membered ring, and any two meta-positioned R^1 (or R^7) groups and the atoms they are connected to may form a heteroaromatic alkenyl ring;

R^c and R^d are independently selected from hydrogen, amino, hydroxyl, —COR^e, —OCOR^e, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, and butoxy, —C(O)O(C1-C3 alkyl)OC(O)(C1-C3 alkyl), 3-8-membered heterocyclic alkyl groups, 3-8-membered heterocyclic alkenyl groups, and 5- or 8-membered heteroaromatic groups, wherein the amino group, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups may optionally be substituted with 0-3 substituents selected from: deuterium, halogens, hydroxyl, cyano, amino, C(O)(methyl), C(O)(ethyl), C(O)(propyl), methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoromethyl, difluoromethyl, trifluoromethyl;

R^e is selected from methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, wherein these groups may optionally be substituted with 0-3 substituents selected from deuterium, halo-

gens, hydroxyl, cyano, amino, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

the 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 6-membered heteroaromatic groups include, but are not limited to the following:



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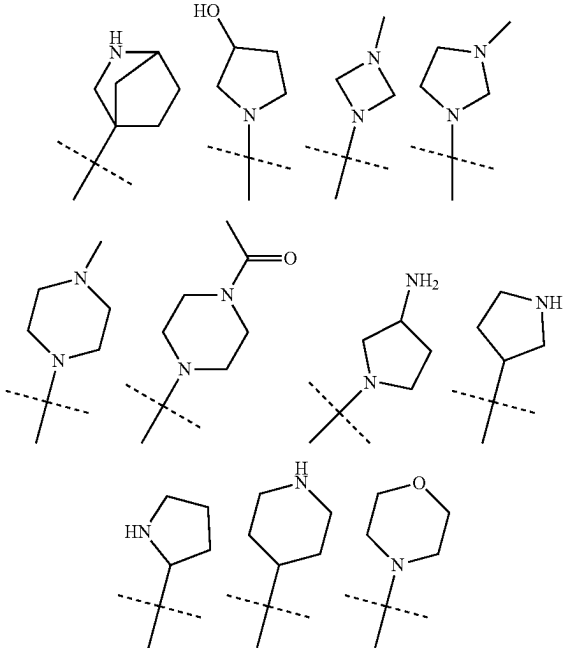
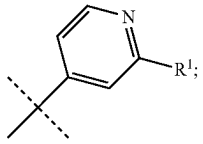


R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen, deuterium, F (fluorine), Cl (chlorine), Br (bromine), I (iodine), —$CONH_2$ (amide group), methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic groups;

the aforementioned groups (ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, C3-C6 cycloalkyl, 3-8-membered heterocyclic alkyl, 3-8-membered heterocyclic alkenyl, and 5- or 8-membered heteroaromatic) may optionally be substituted by 0-3 substituents selected from deuterium, F, Cl, Br, I, methyl, ethyl, propyl, or isopropyl;

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, and X^{10} are independently selected from O (oxygen), S (sulfur), N (nitrogen), CH (methylene), or N-oxide derivatives;

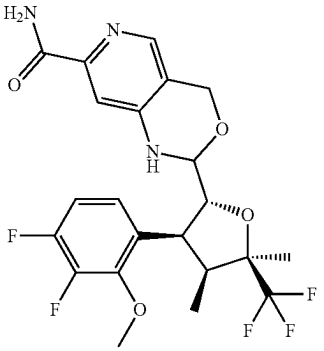
Y^1 is selected from CH_2, NH, O, S; Optimally, the A ring is selected from

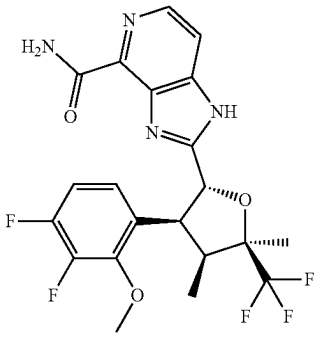


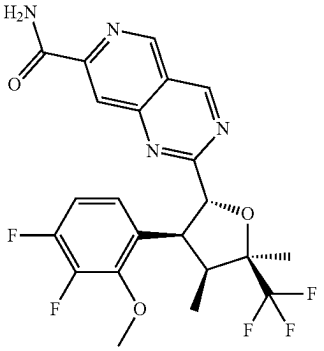
and

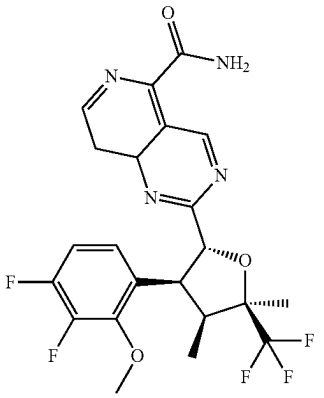
R^1 is selected from —$CONH_2$.

12. The compound of claim **1**, wherein the compound is any one of the following:









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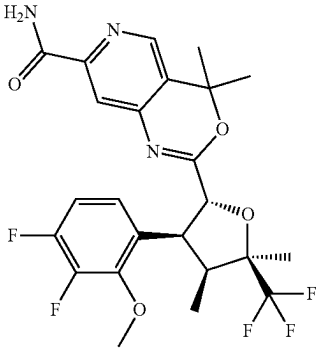

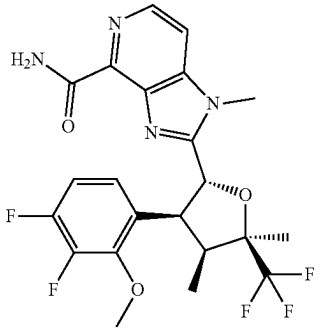

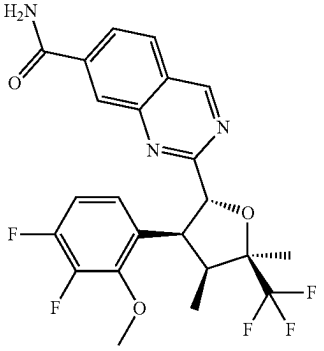

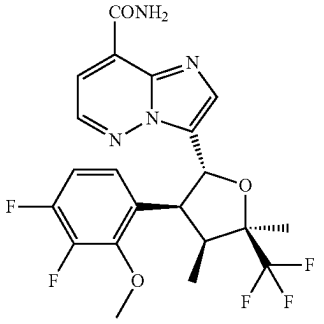

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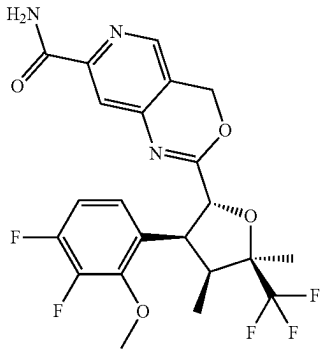

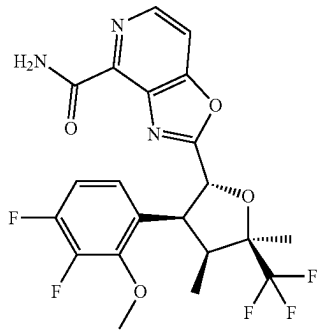

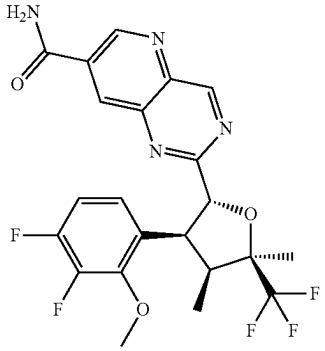

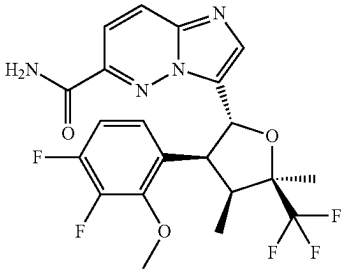

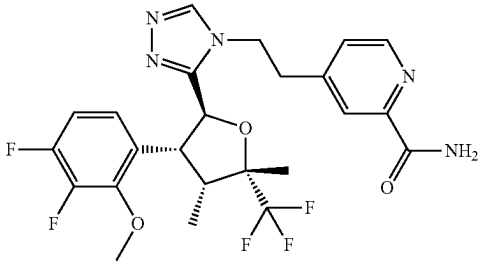

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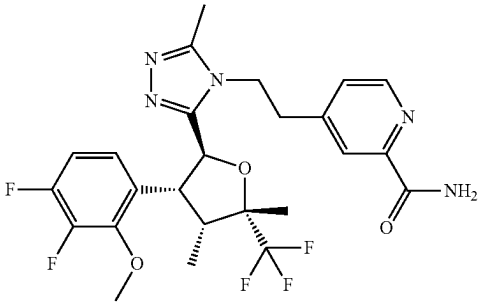

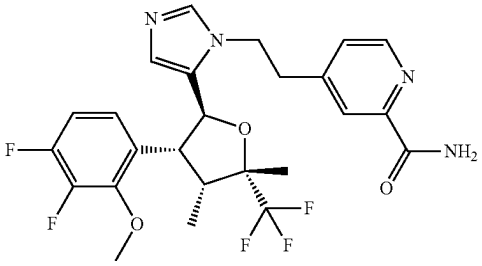

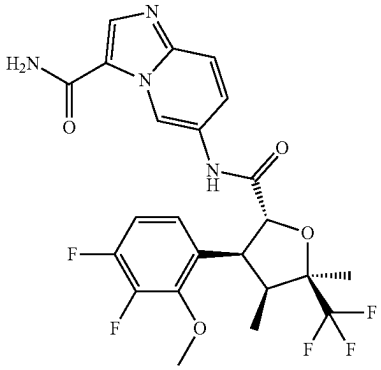

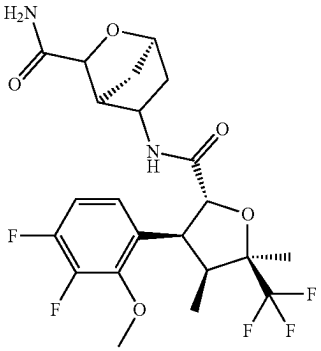

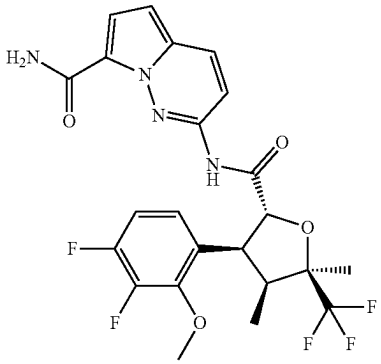

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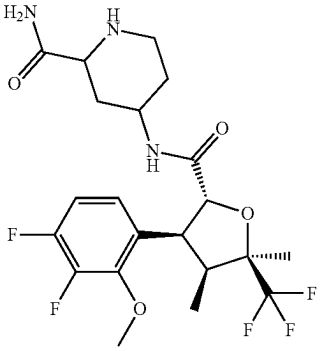

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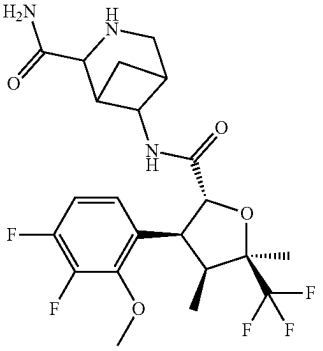

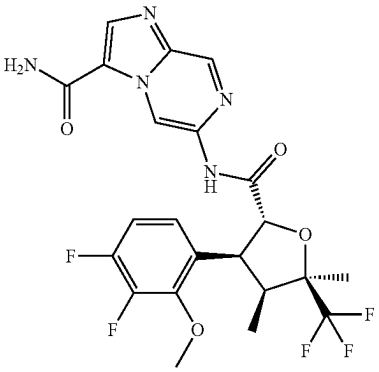

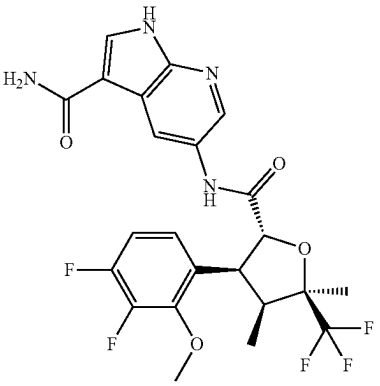

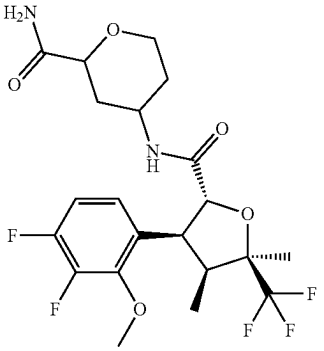

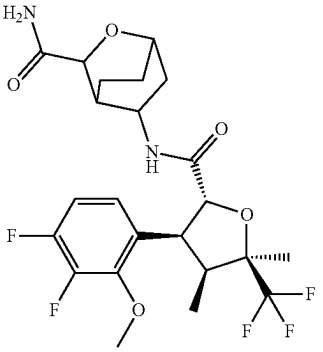

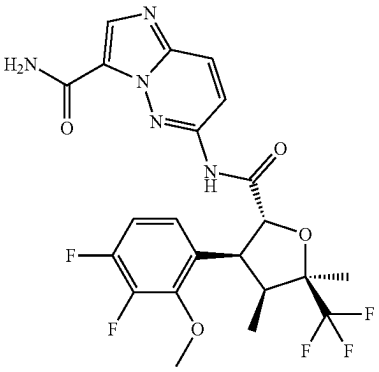

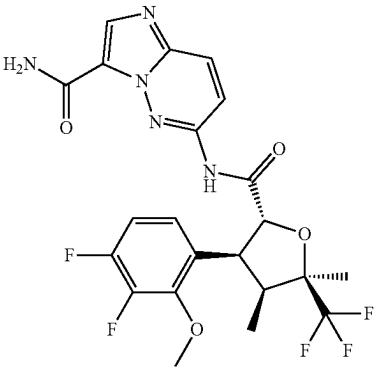

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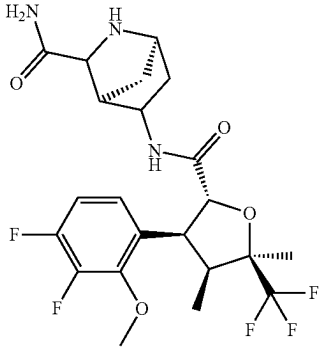

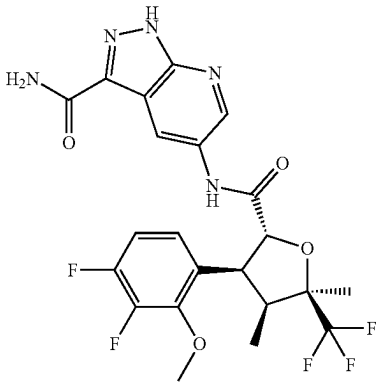

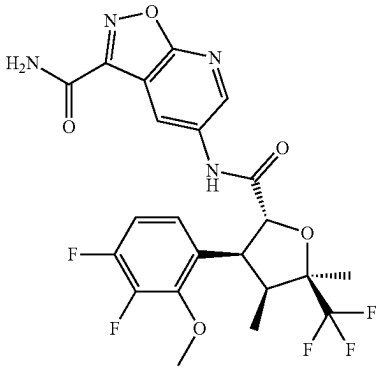

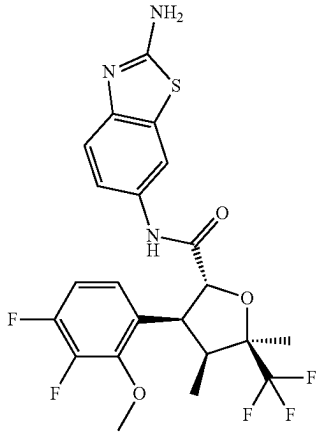

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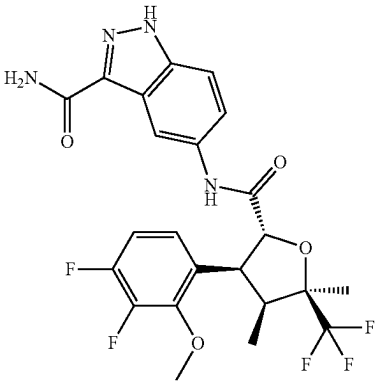

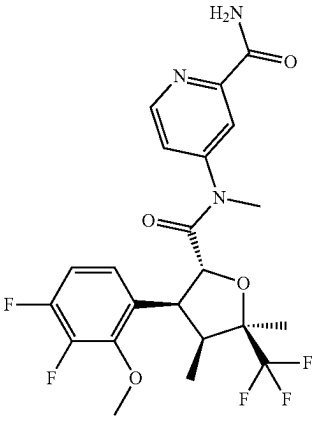

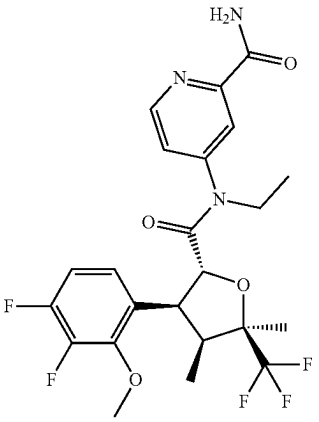

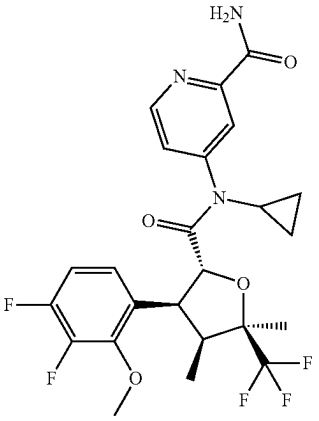

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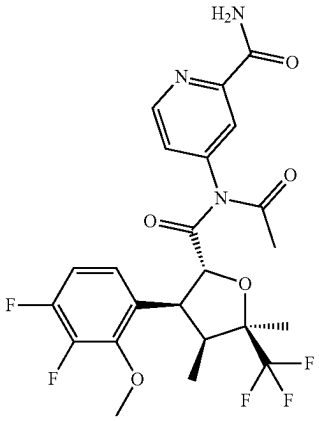

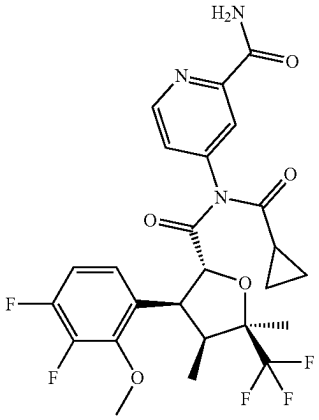

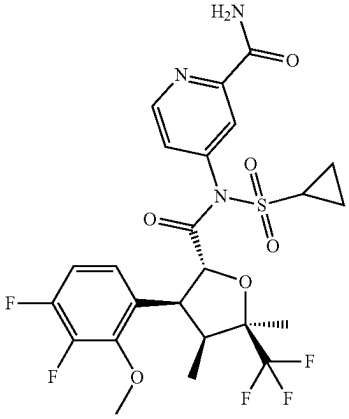

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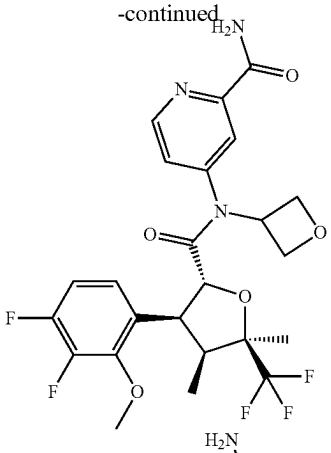

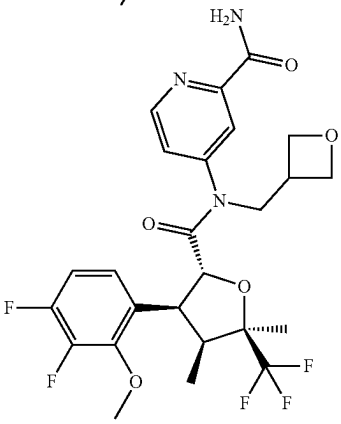

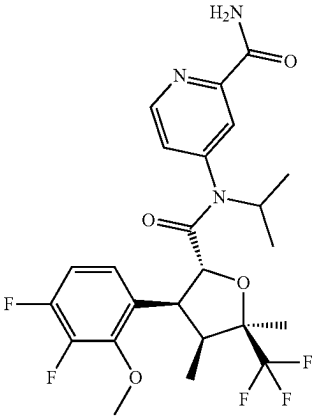

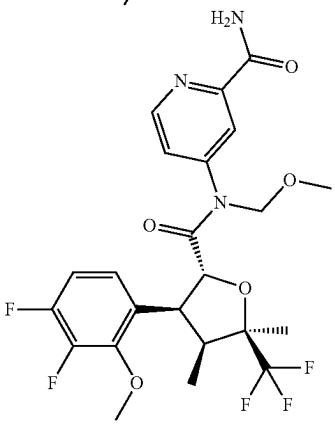

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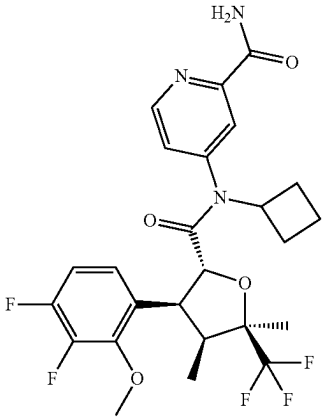

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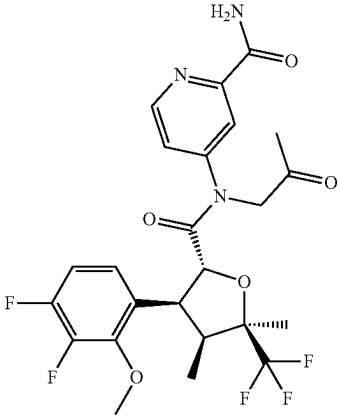

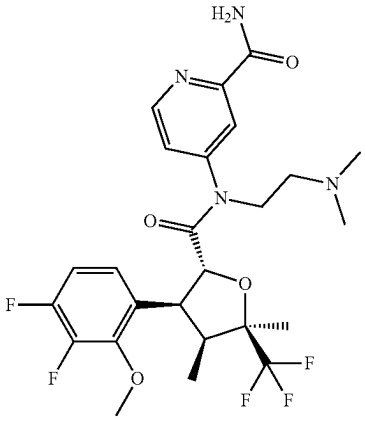

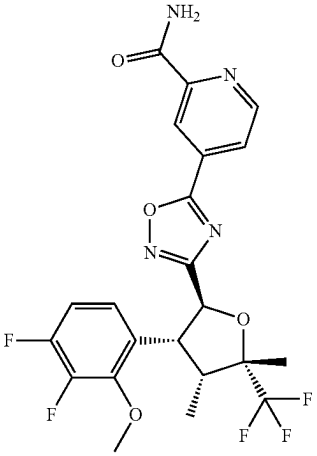

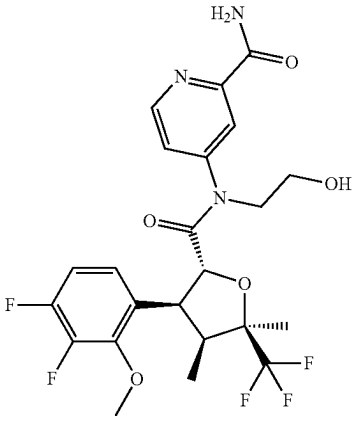

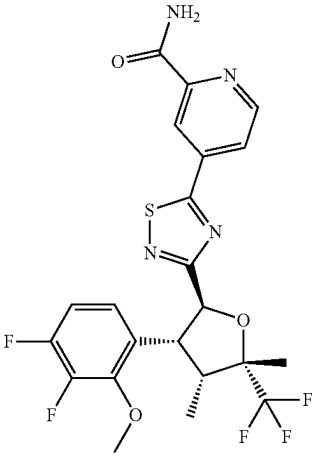

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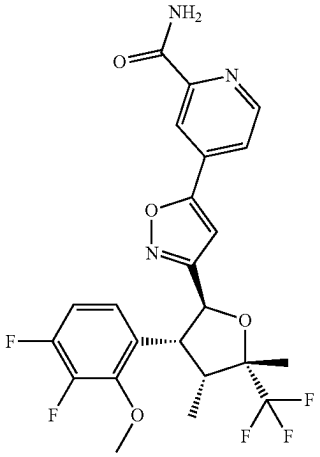

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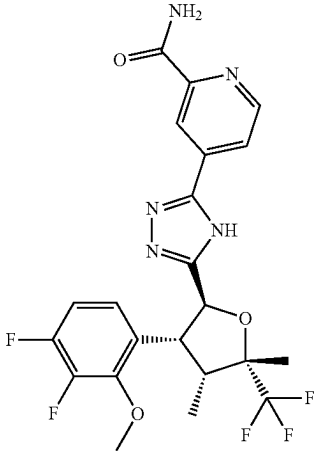

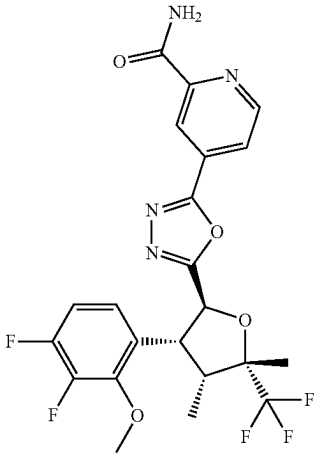

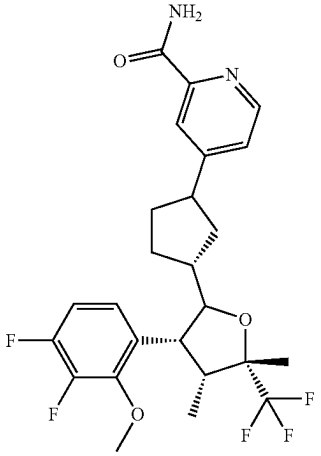

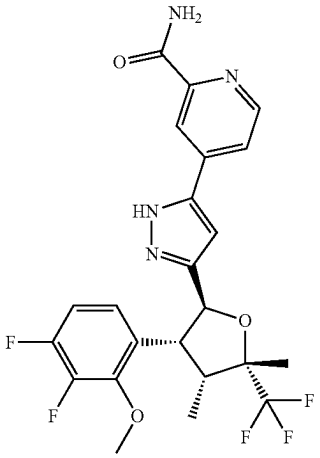

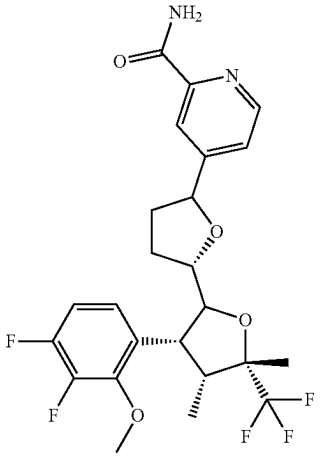

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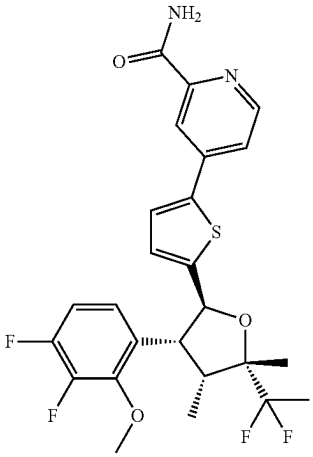

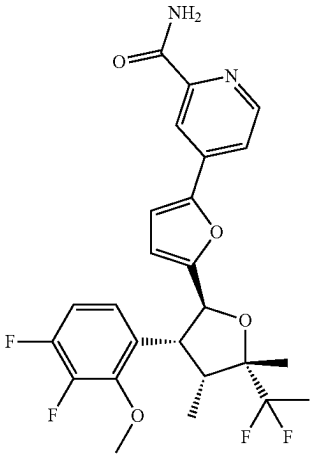

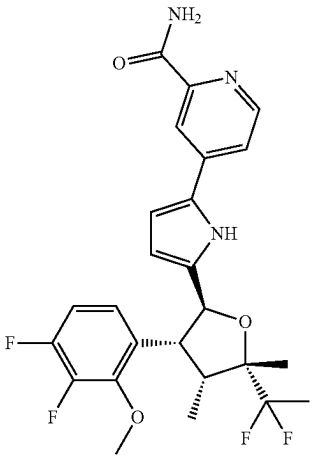

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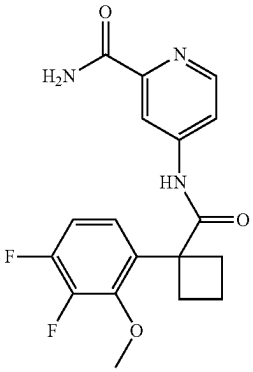

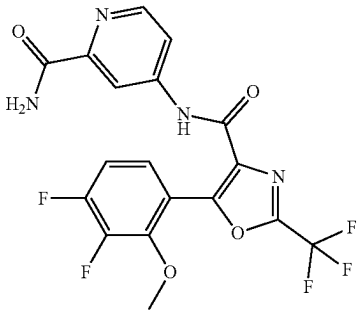

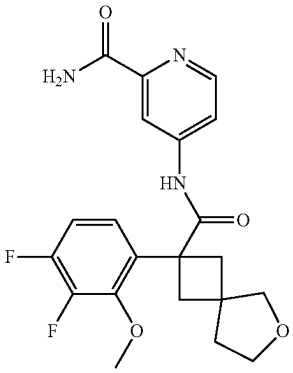

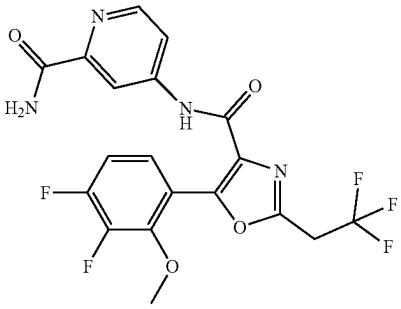

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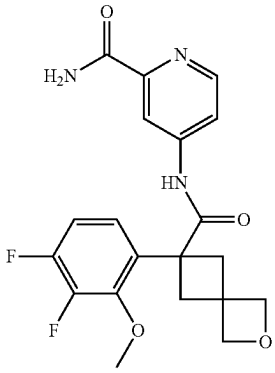

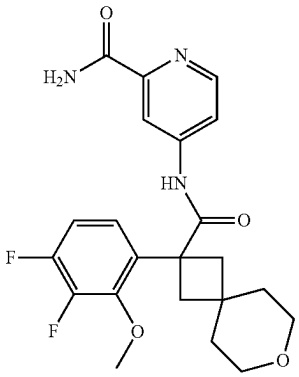

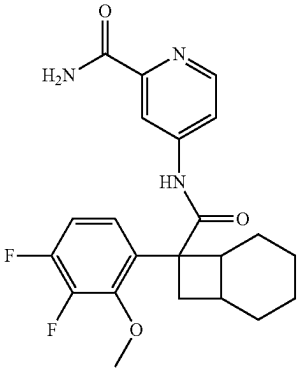

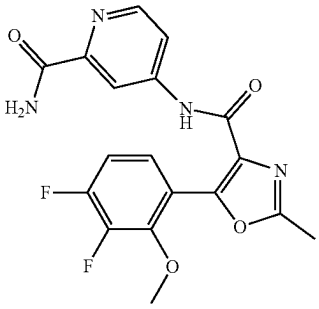

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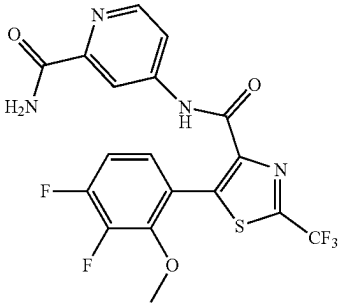

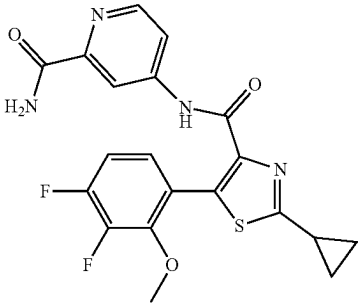

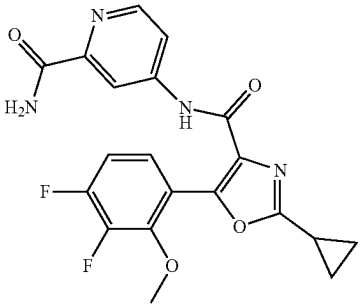

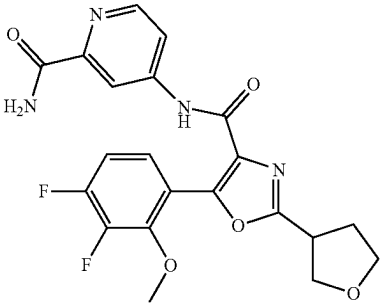

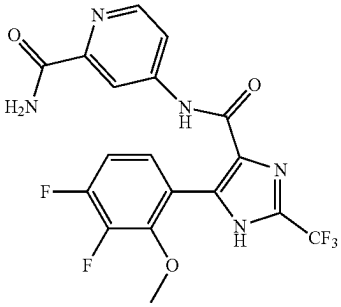

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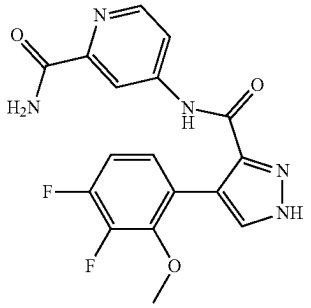

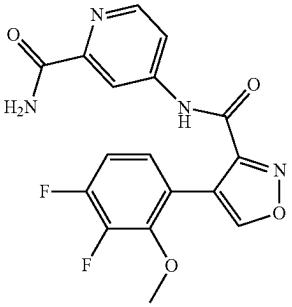

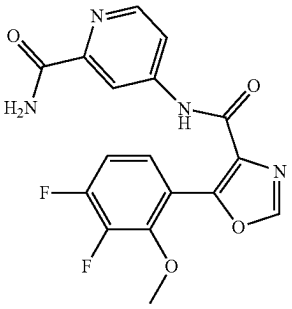

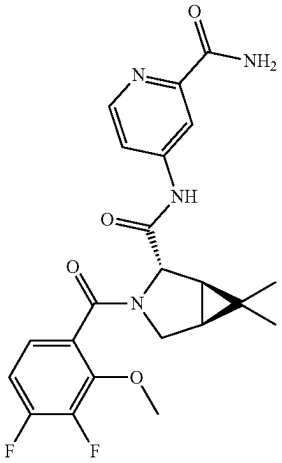

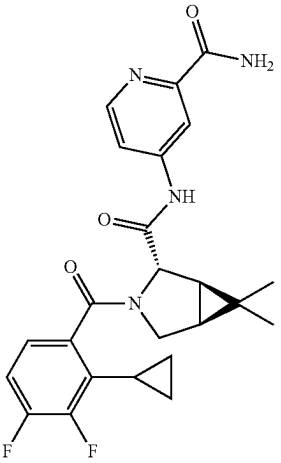

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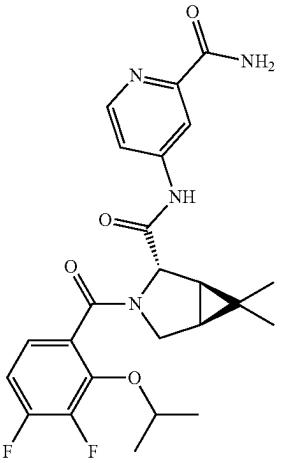

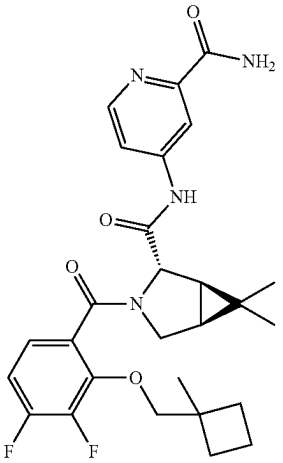

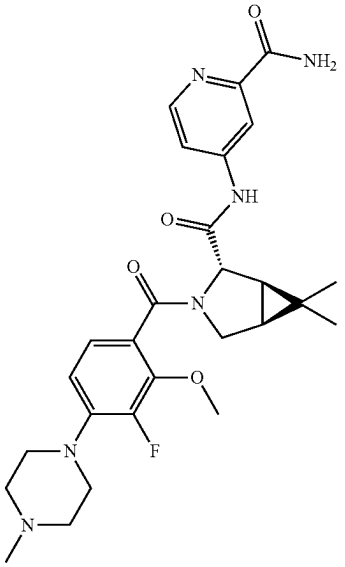

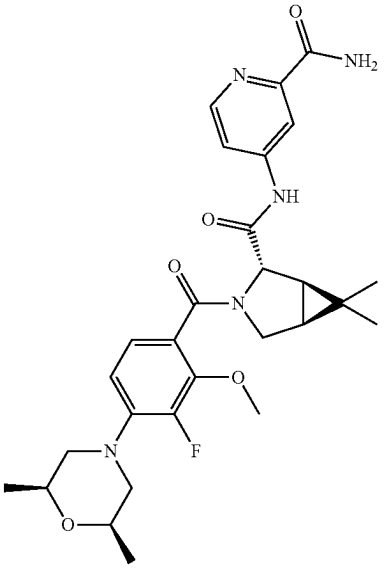

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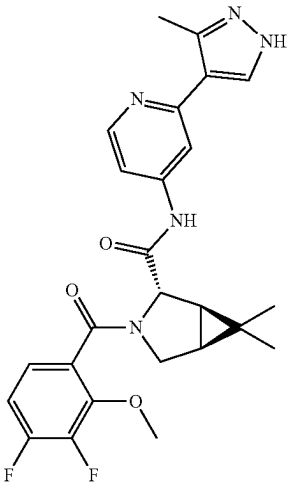

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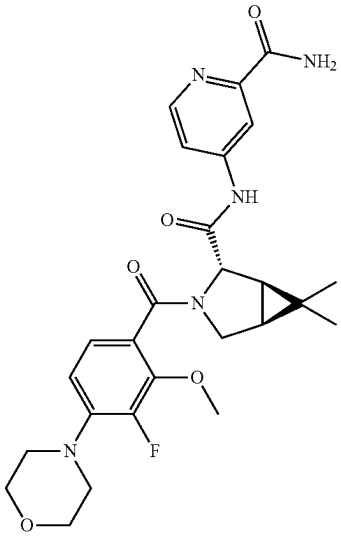

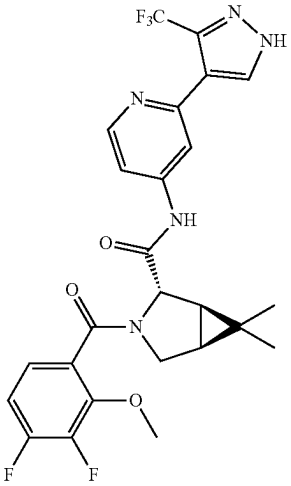

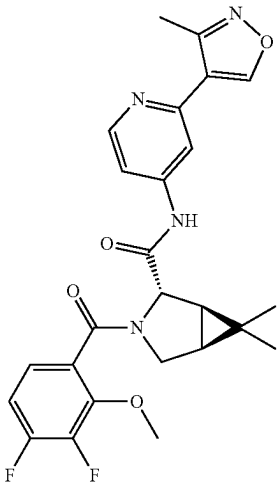

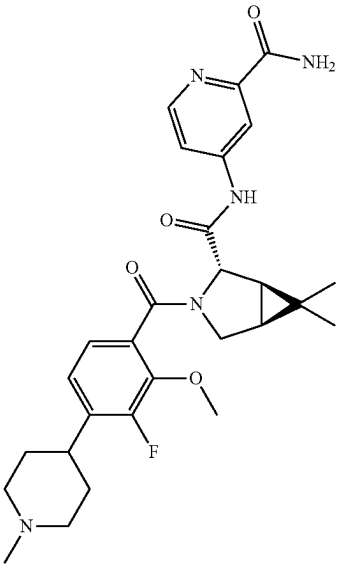

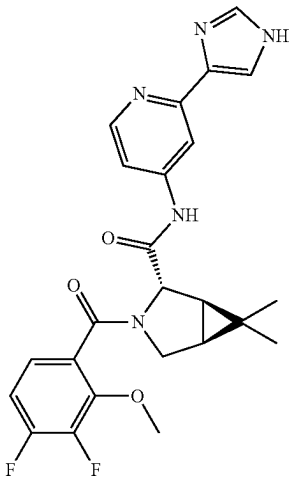

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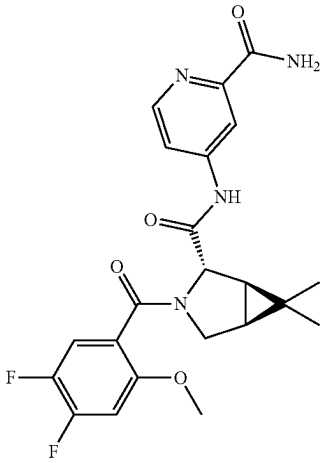

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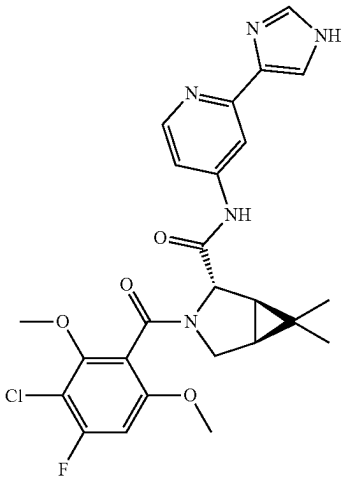

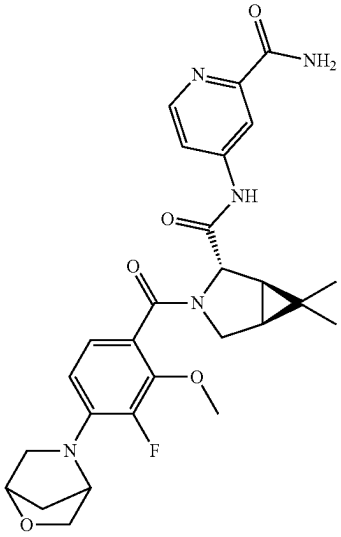

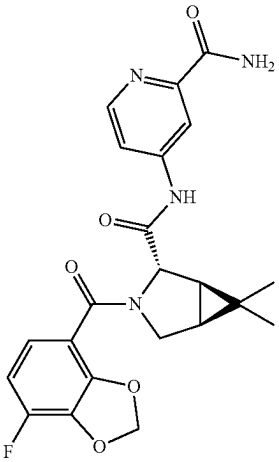

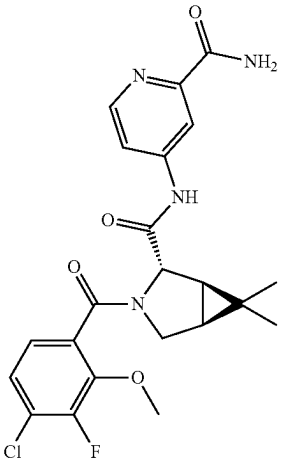

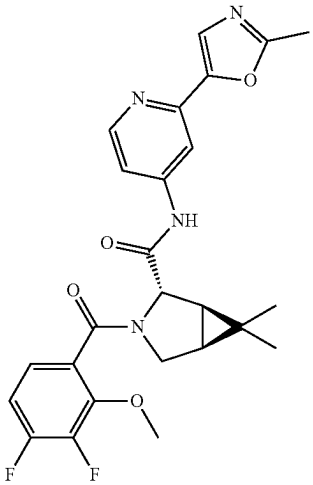

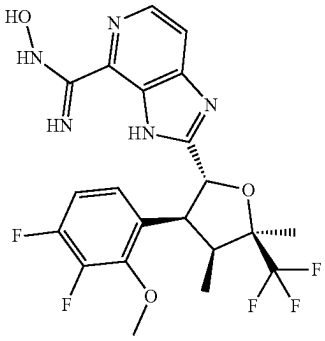

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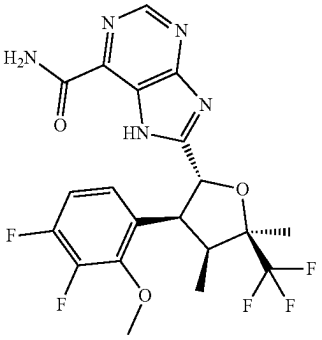

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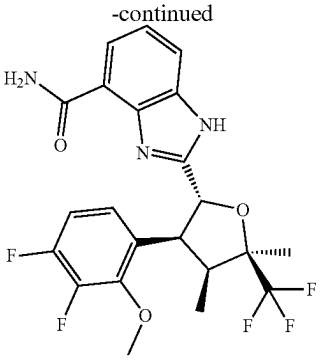

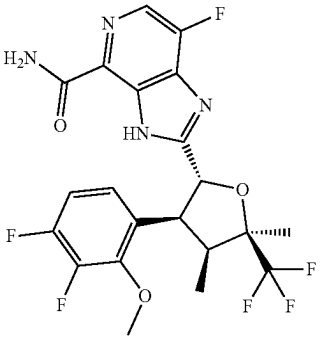

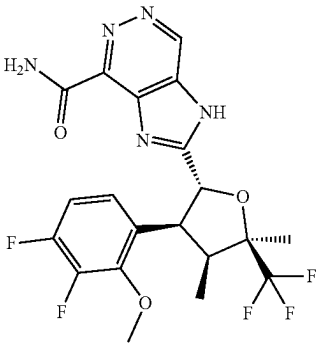

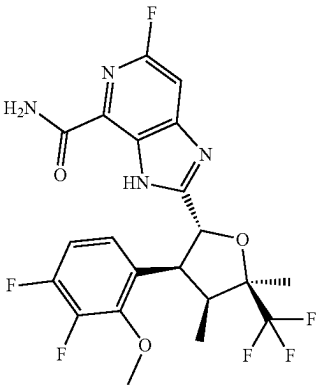

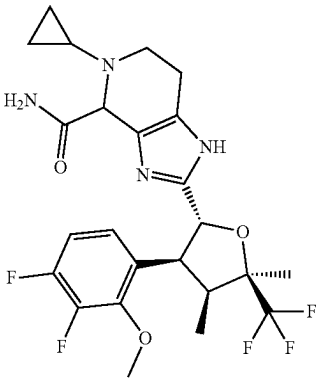

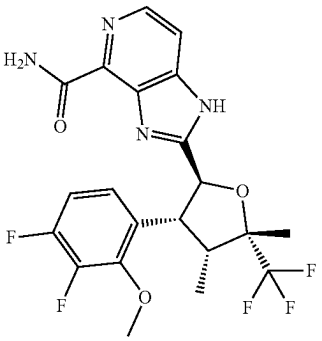

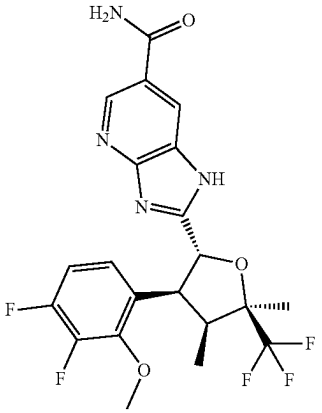

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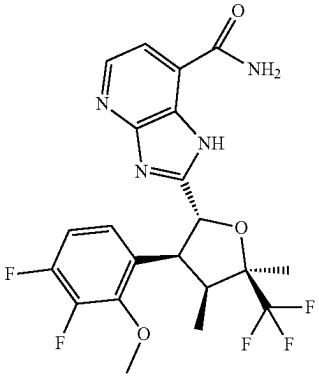

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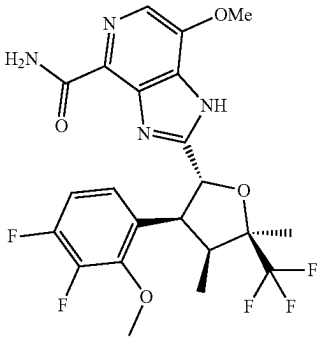

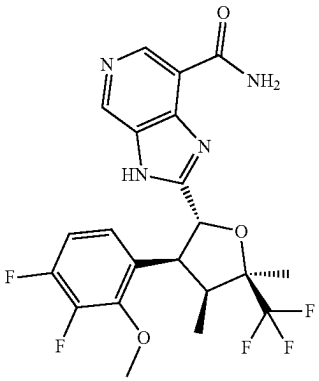

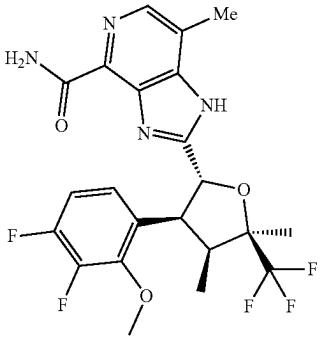

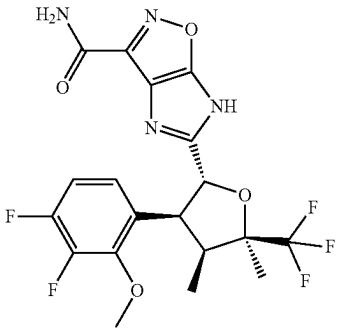

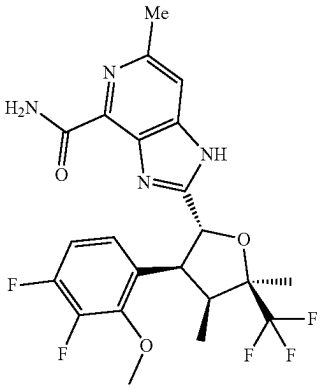

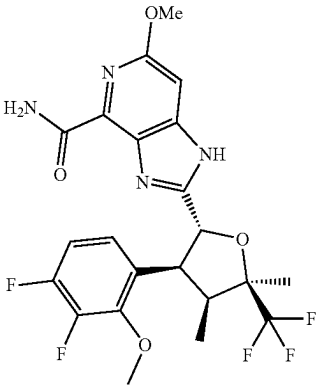

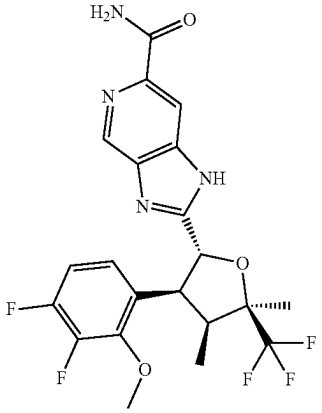

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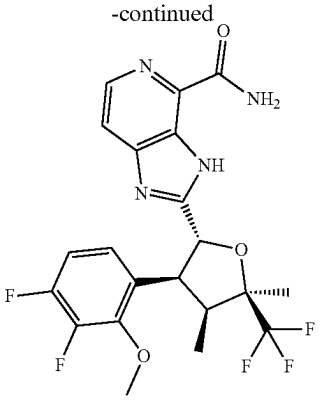

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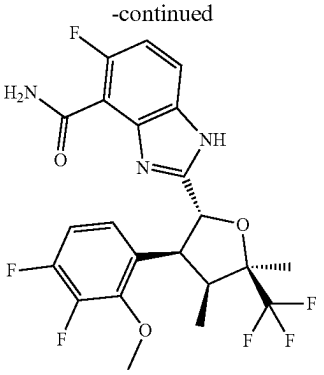

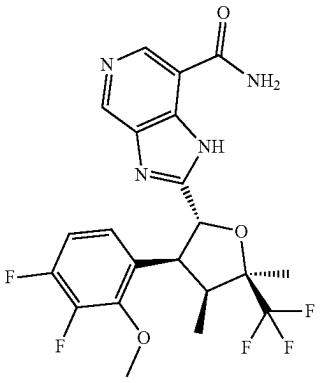

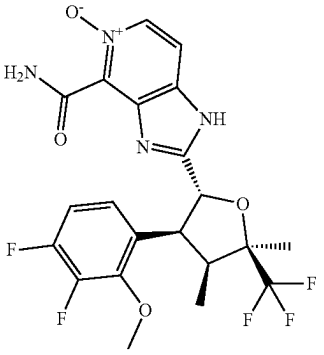

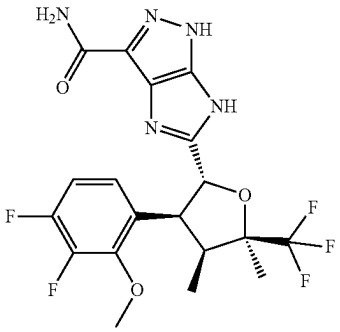

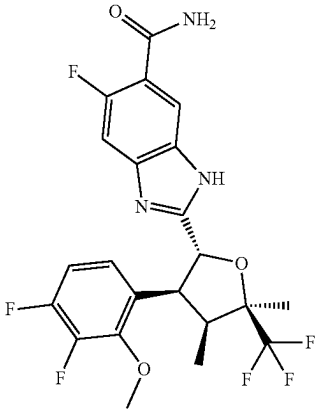

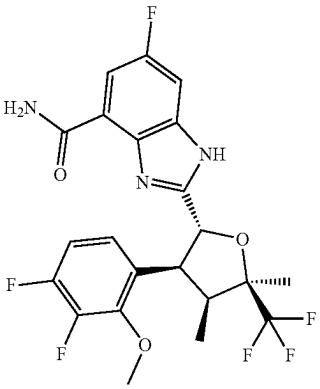

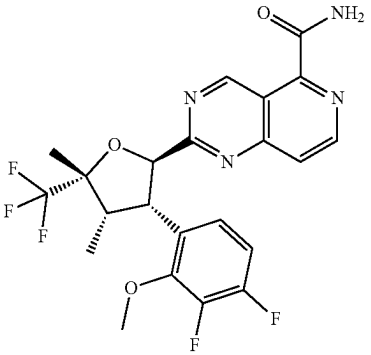

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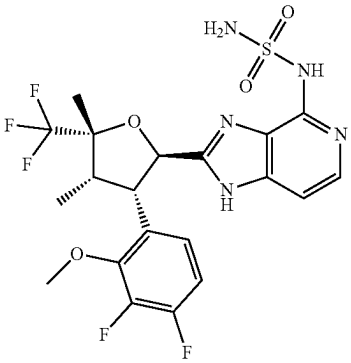

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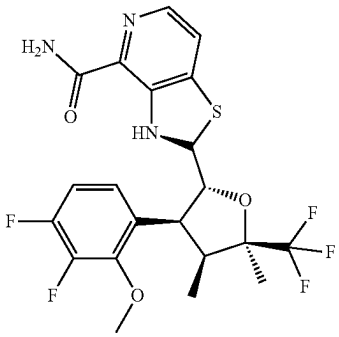

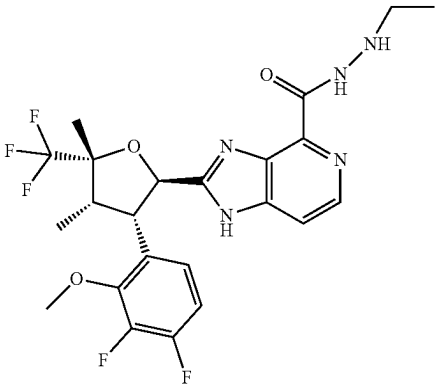

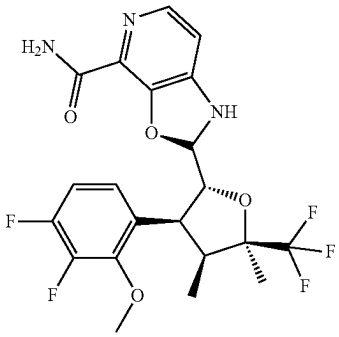

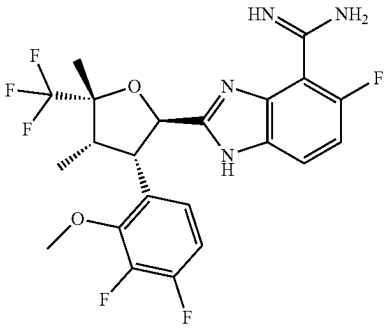

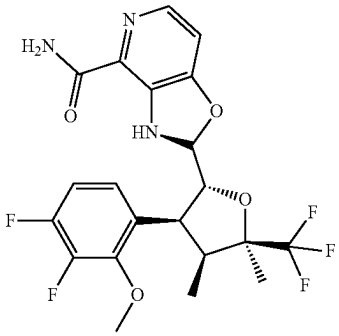

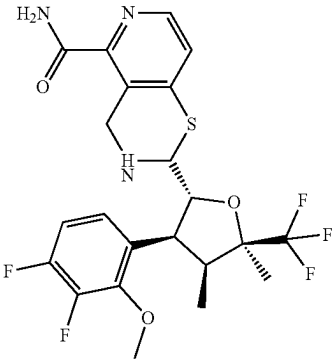

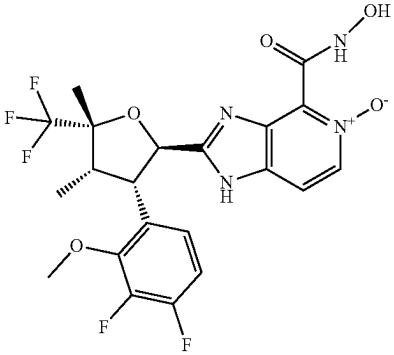

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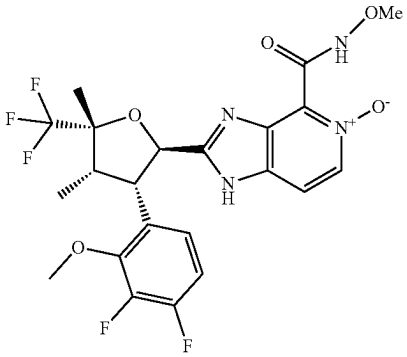

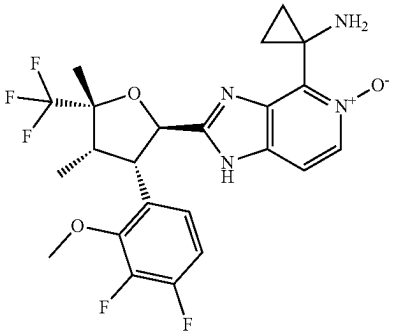

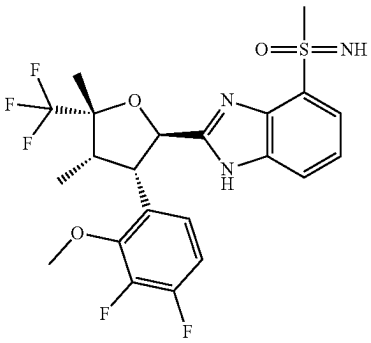

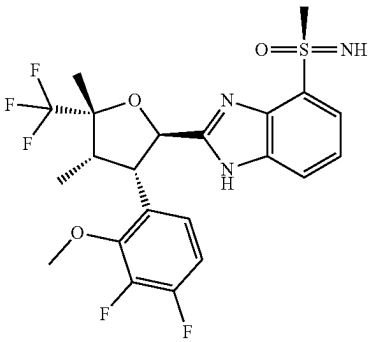

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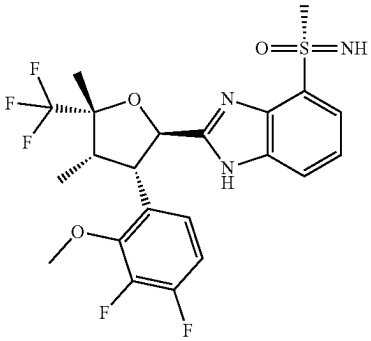

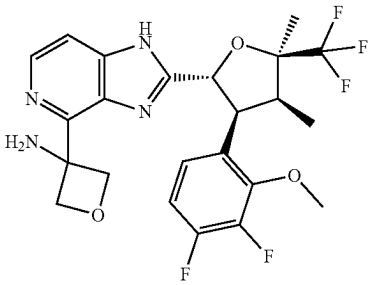

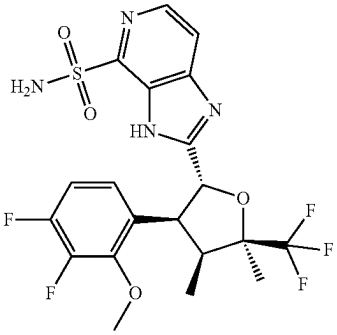

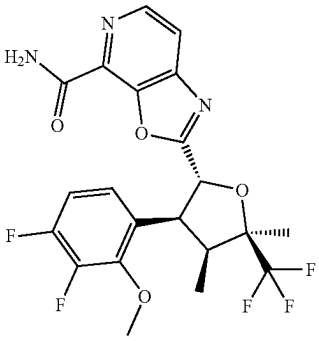

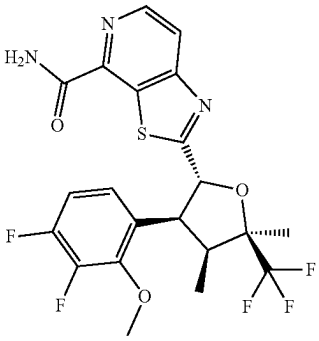

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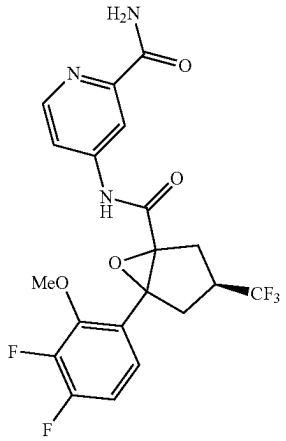

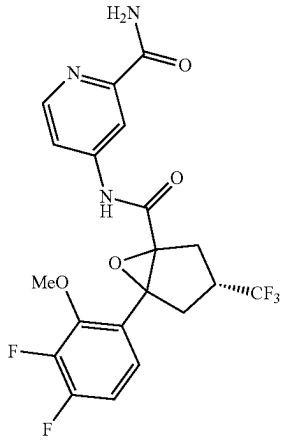

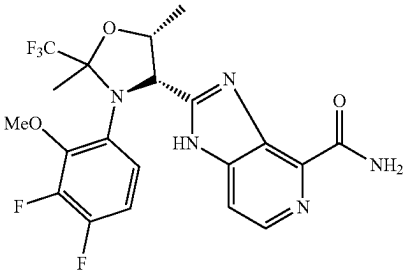

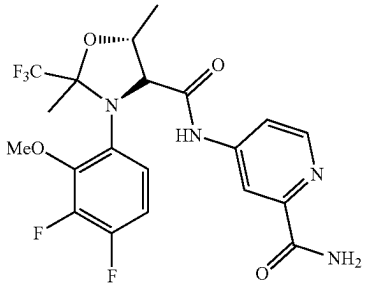

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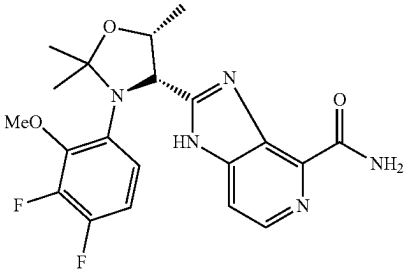

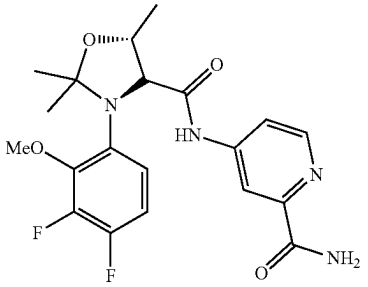

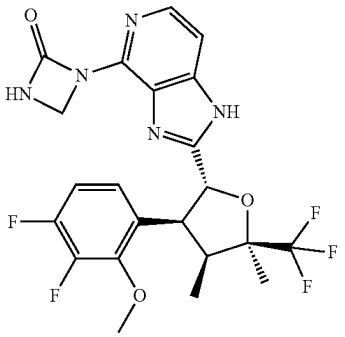

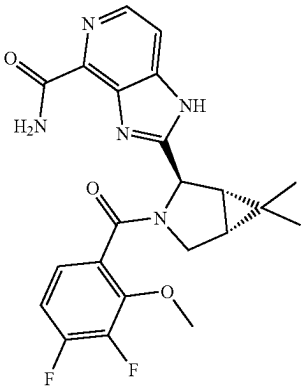

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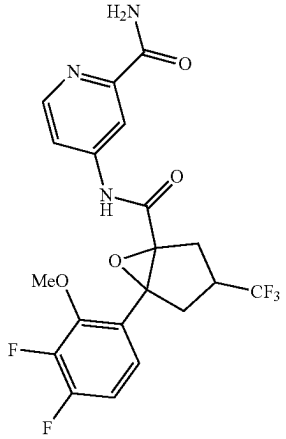

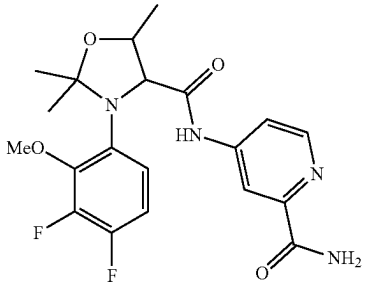

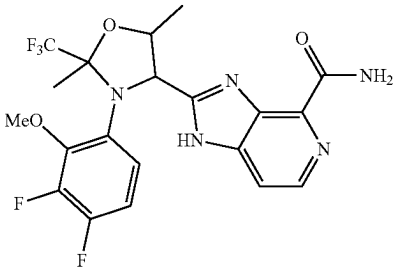

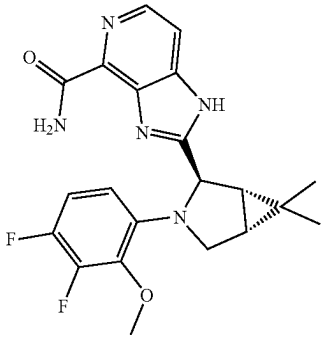

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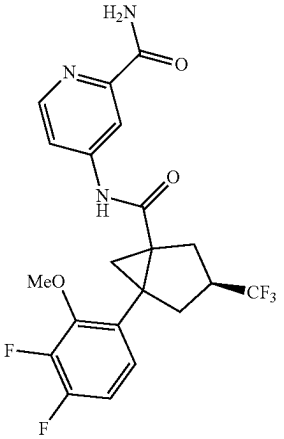

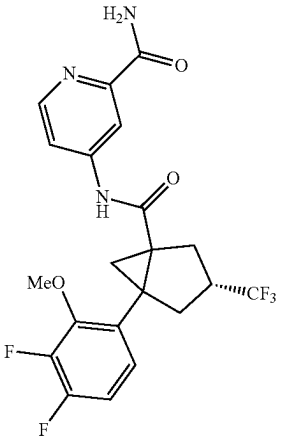

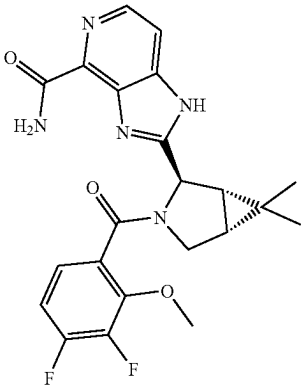

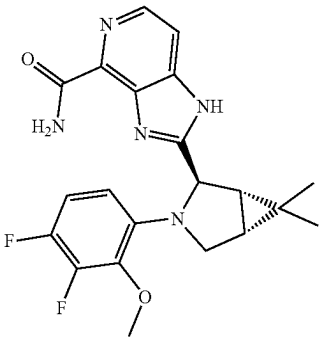

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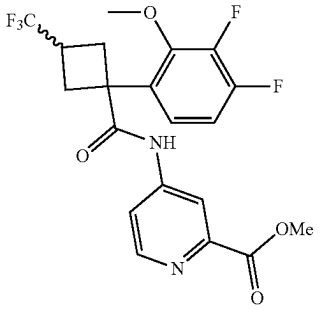

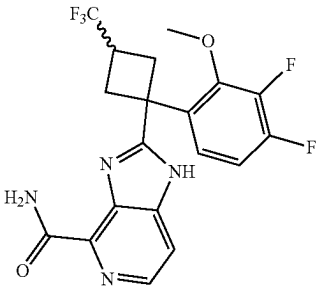

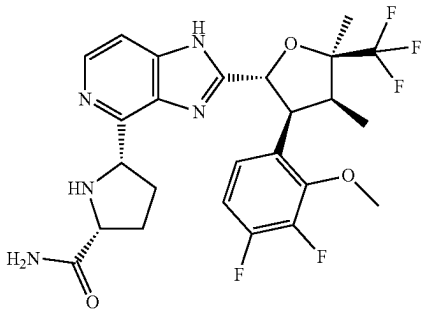

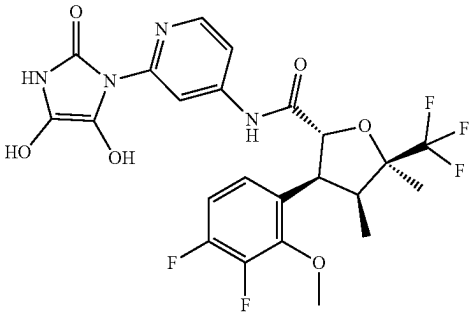

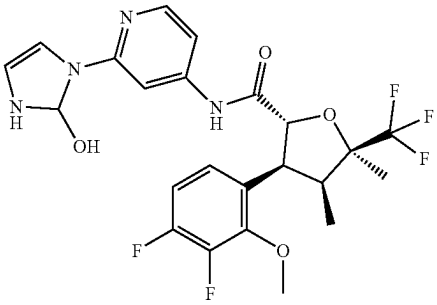

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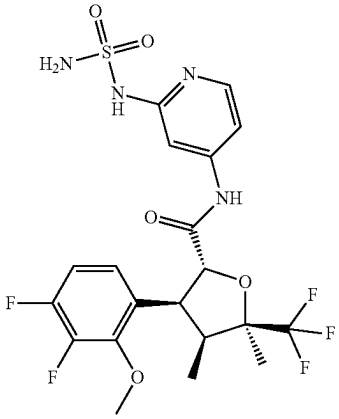

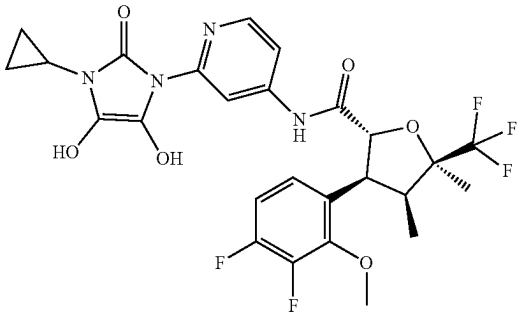

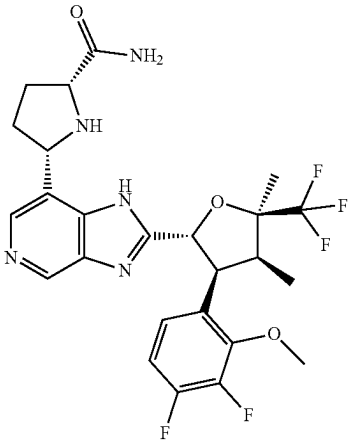

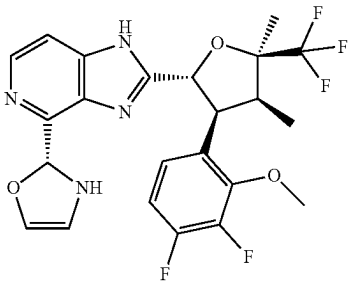

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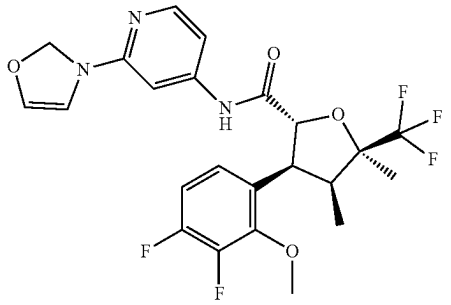

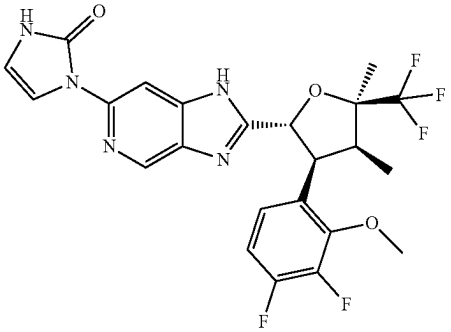

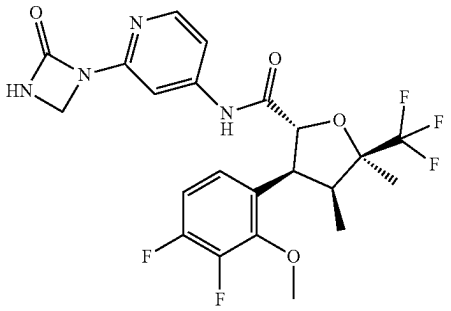

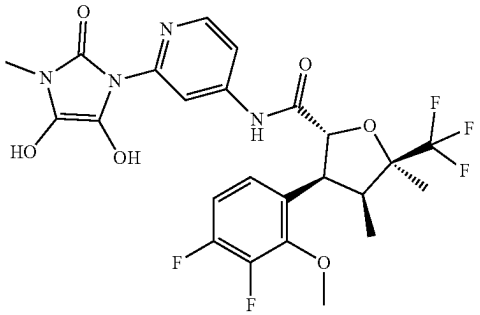

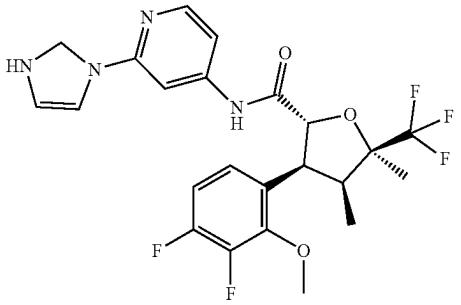

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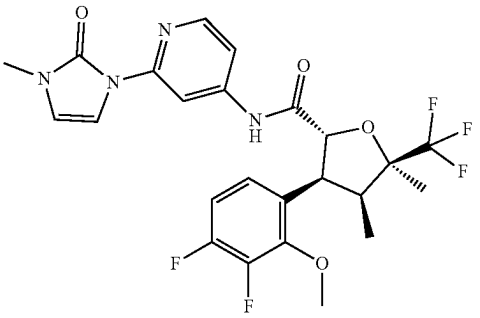

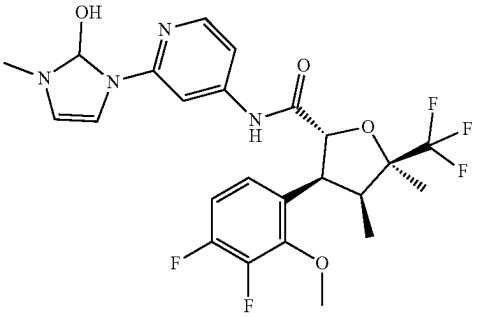

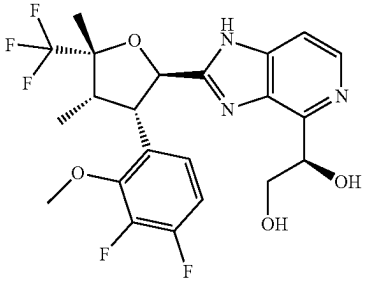

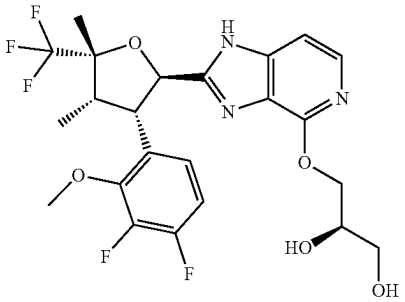

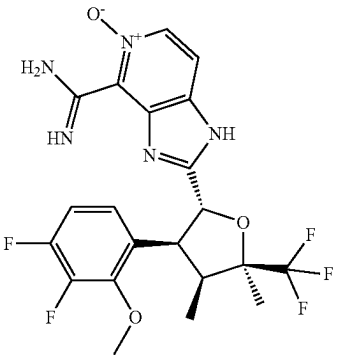

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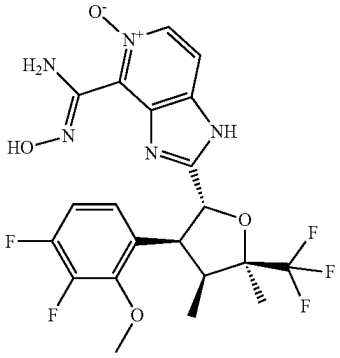

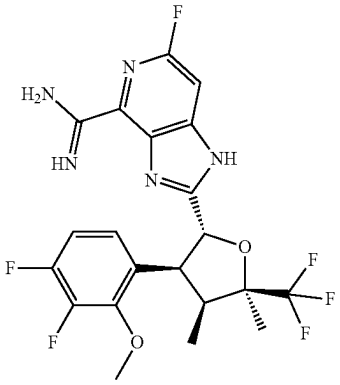

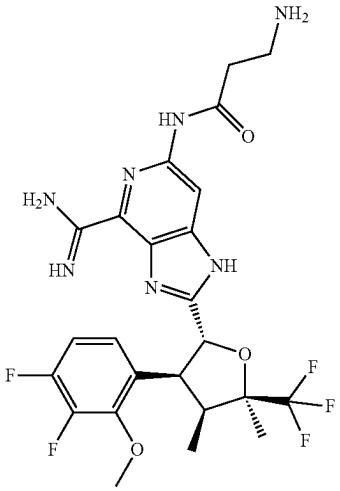

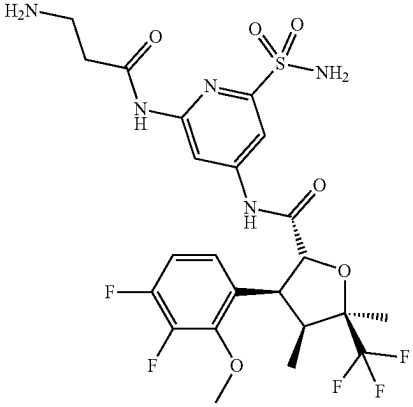

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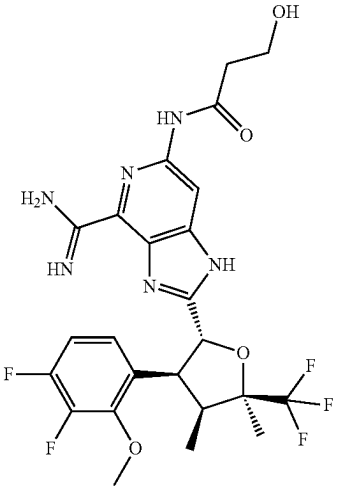

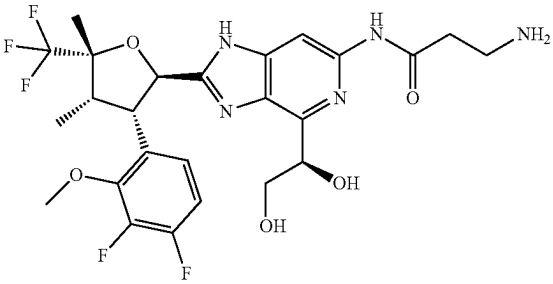

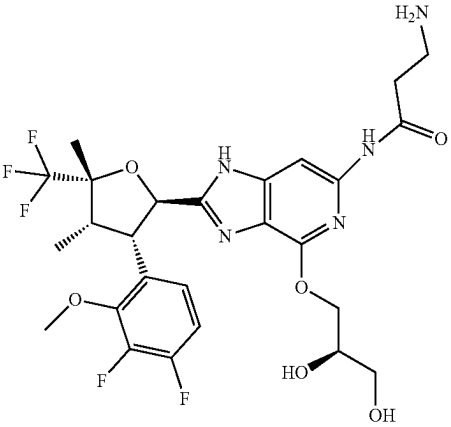

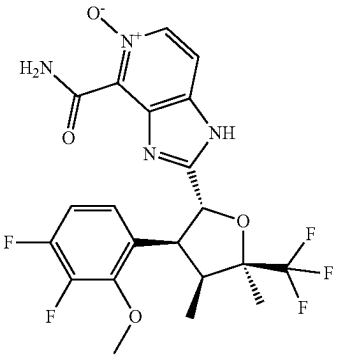

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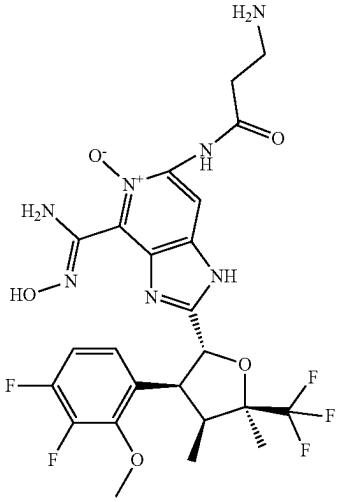

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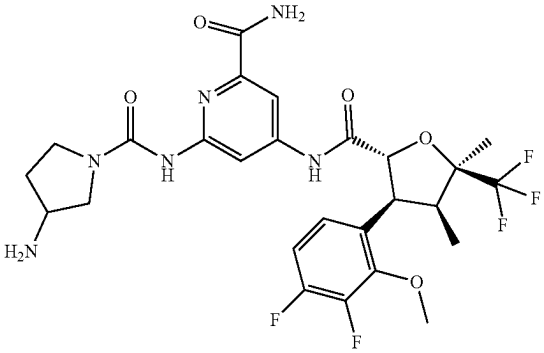

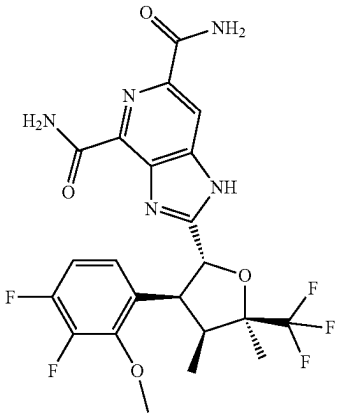

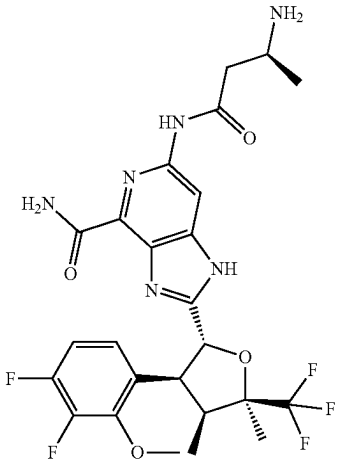

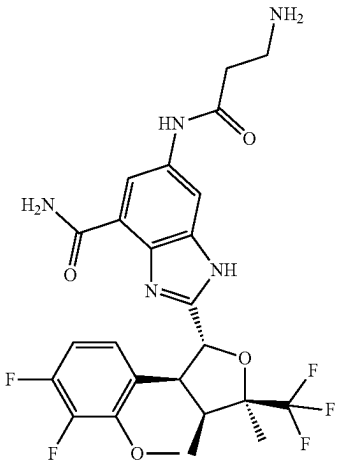

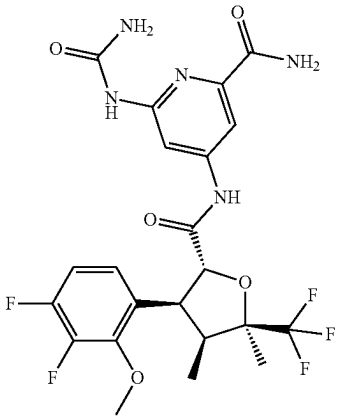

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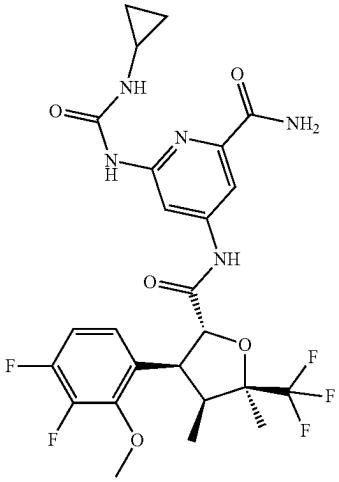

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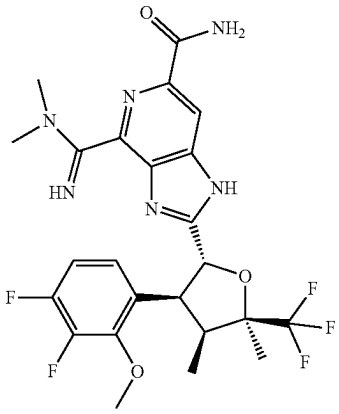

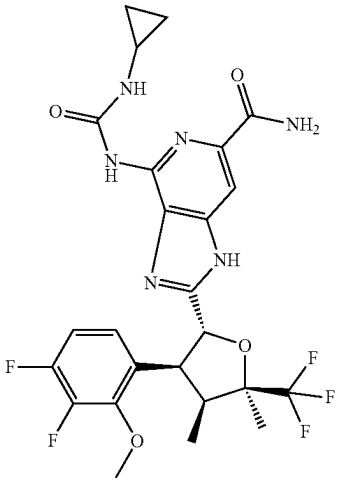

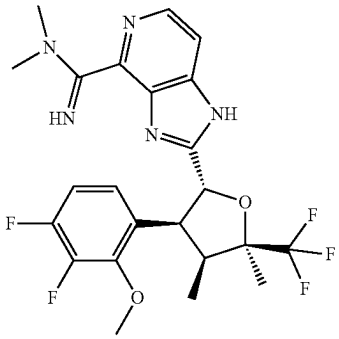

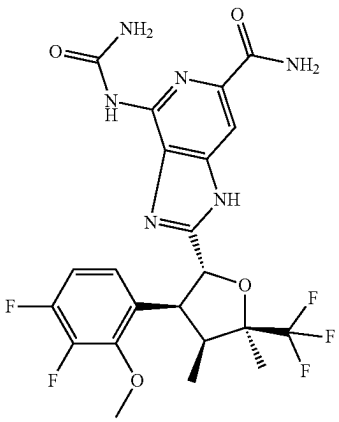

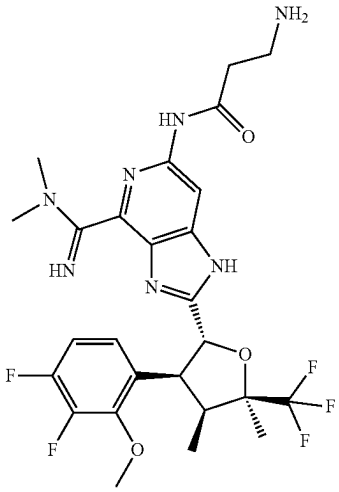

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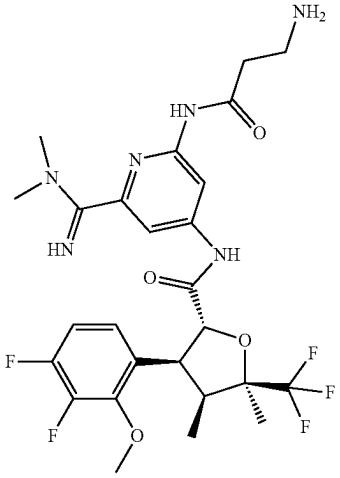

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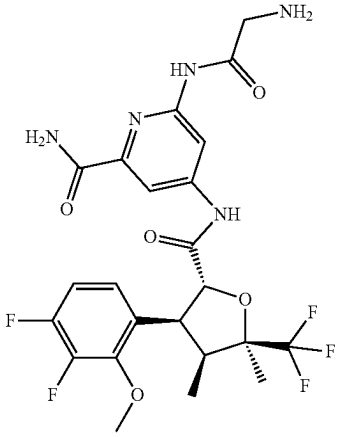

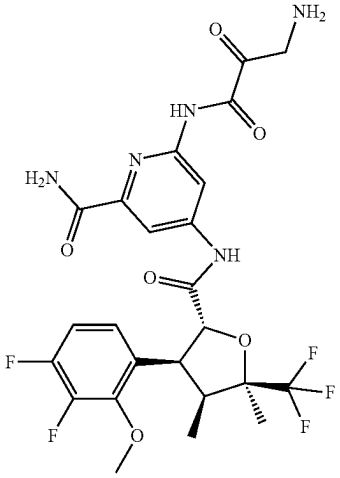

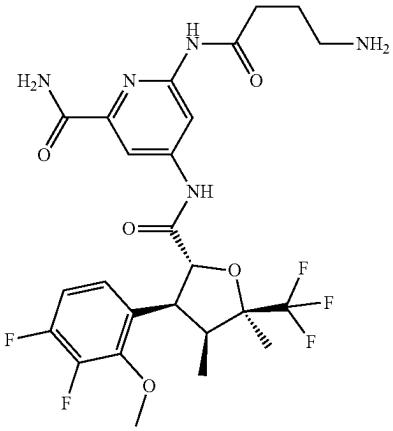

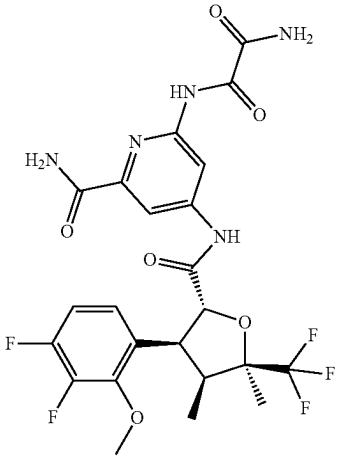

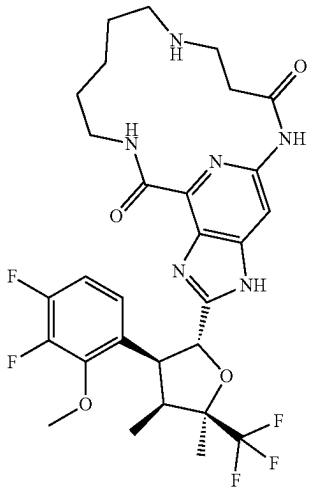

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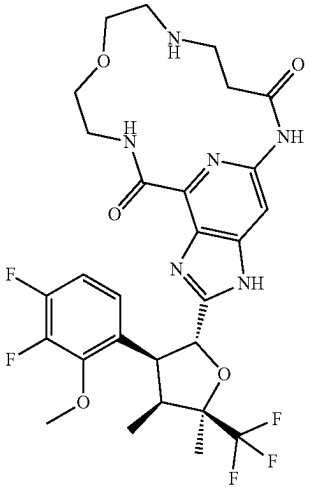

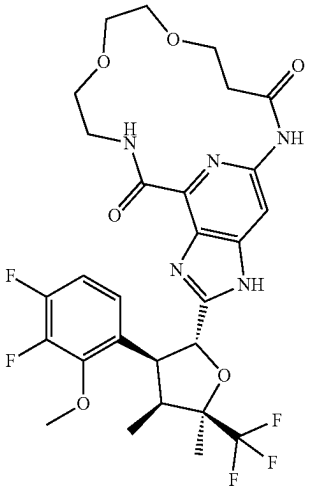

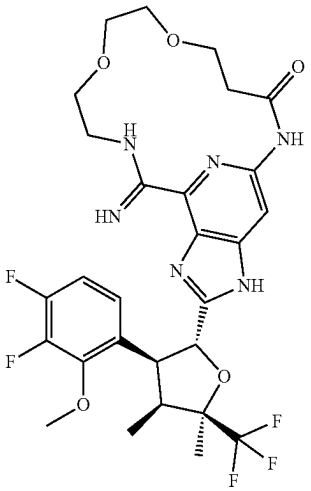

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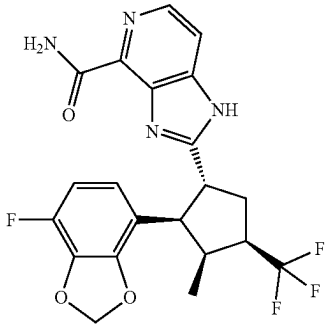

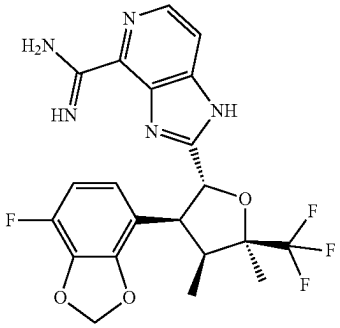

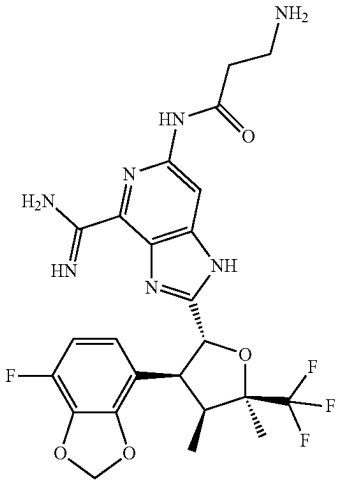

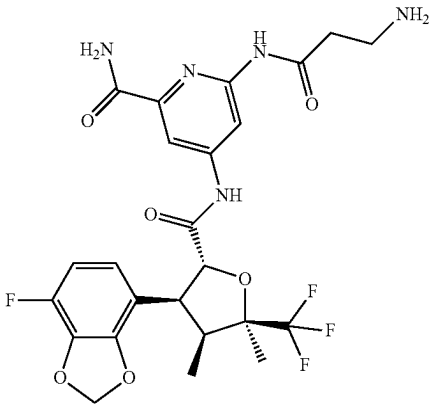

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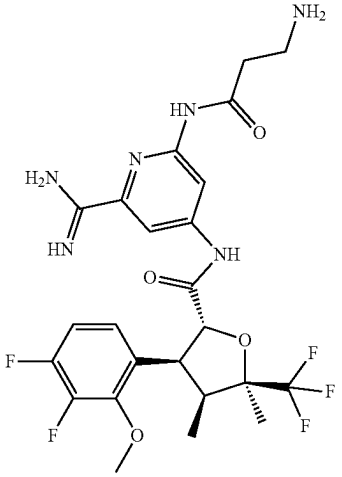

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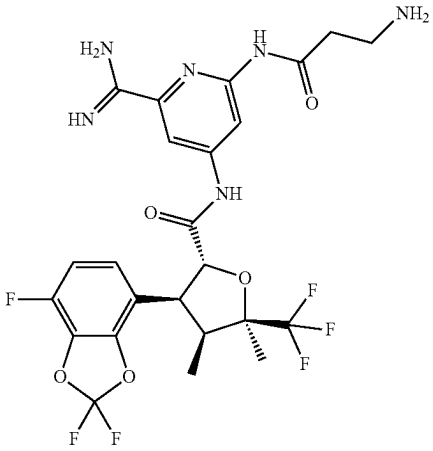

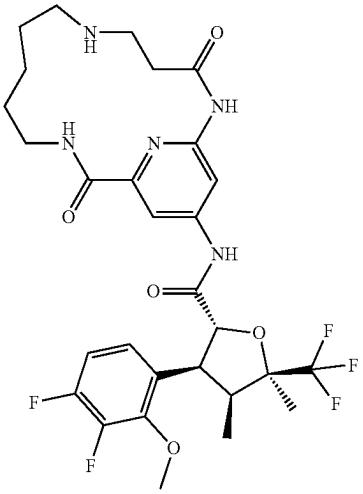

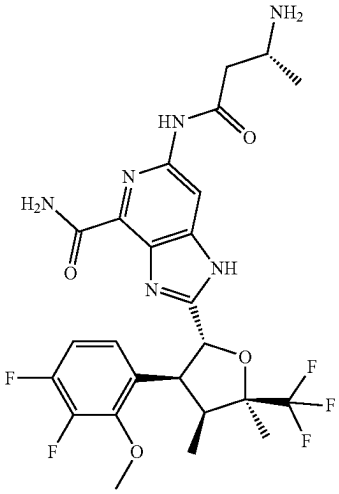

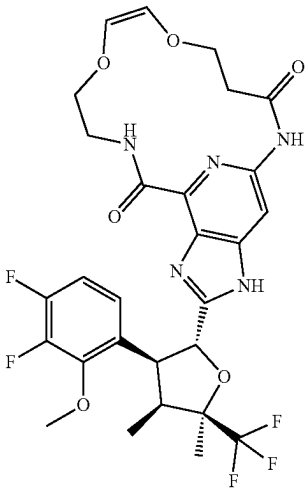

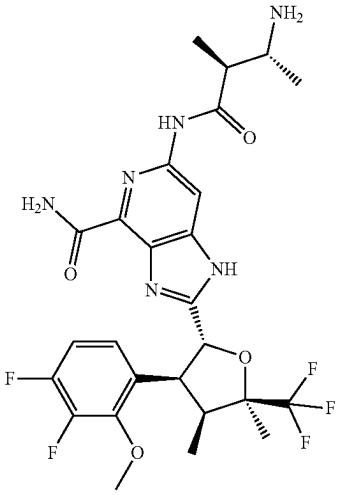

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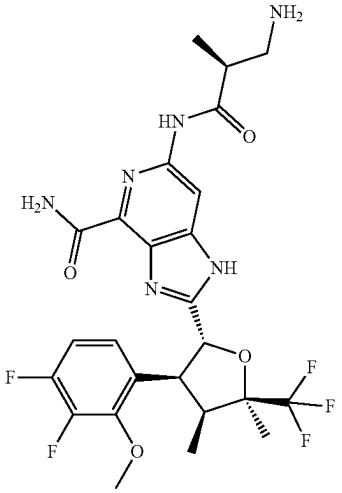

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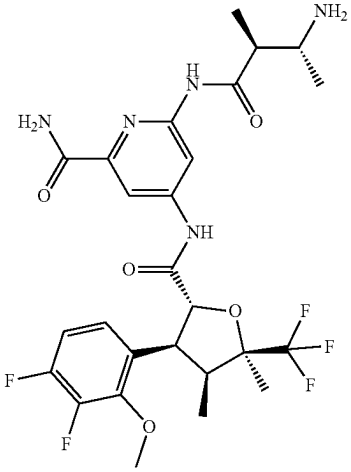

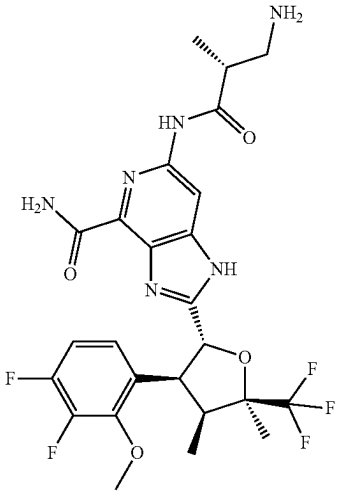

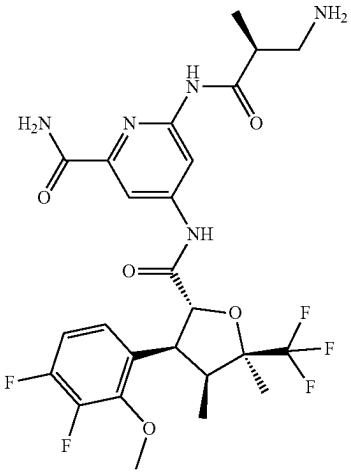

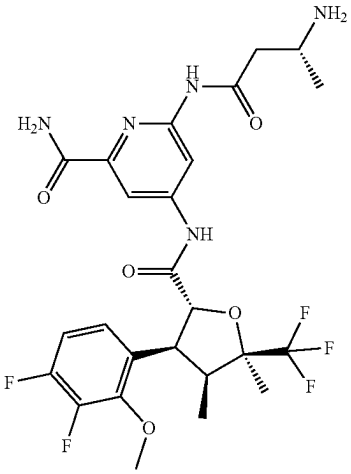

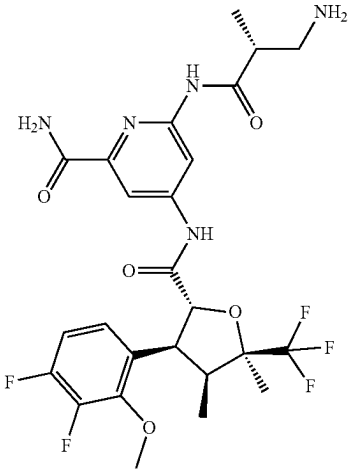

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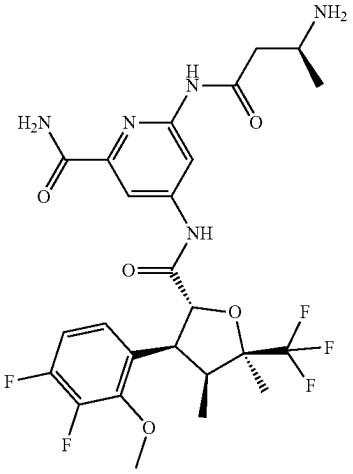

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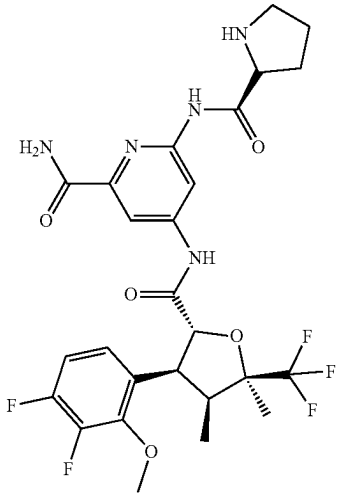

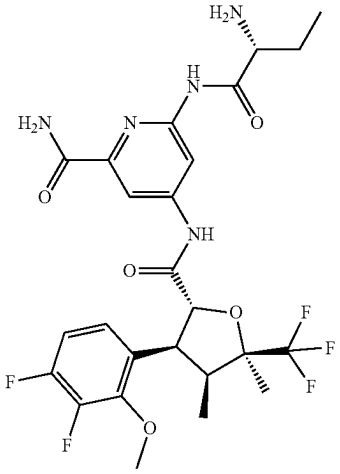

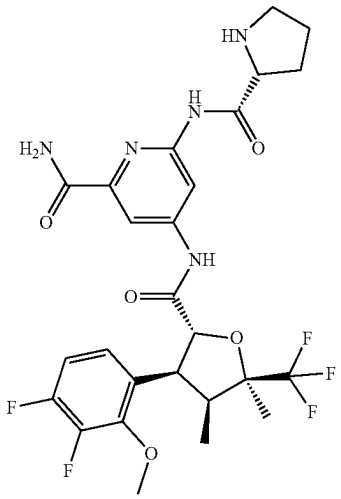

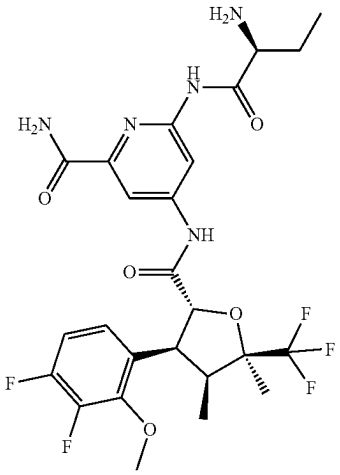

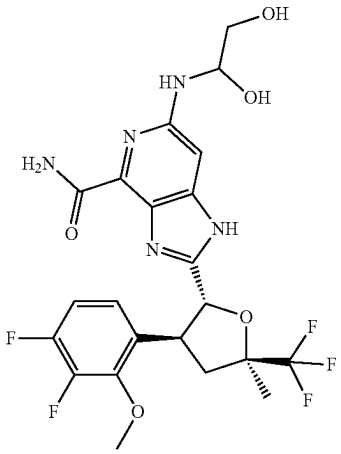

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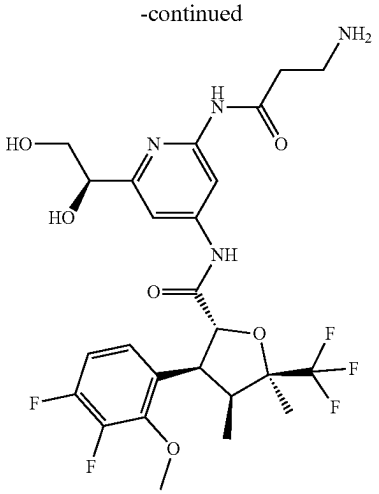

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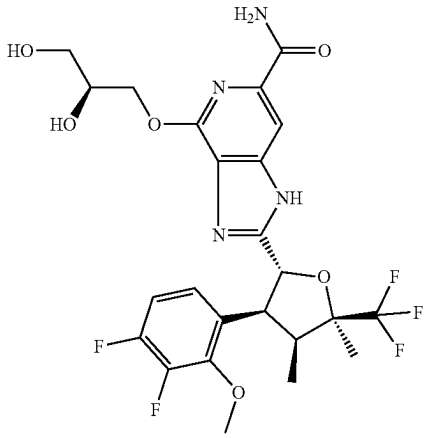

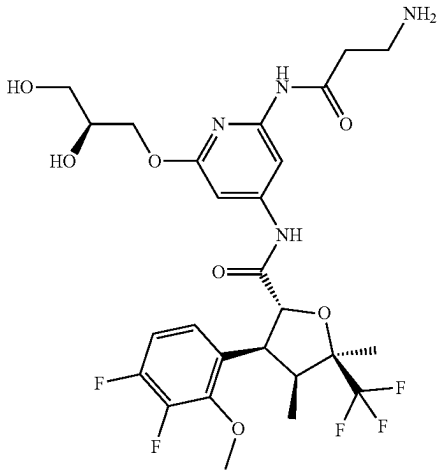

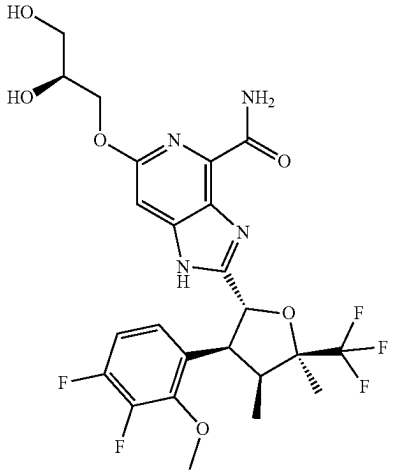

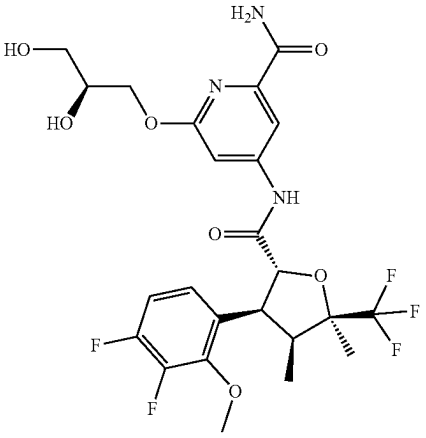

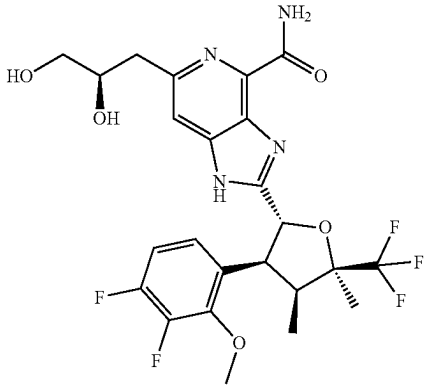

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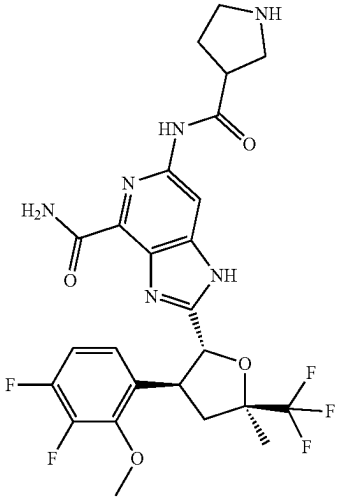

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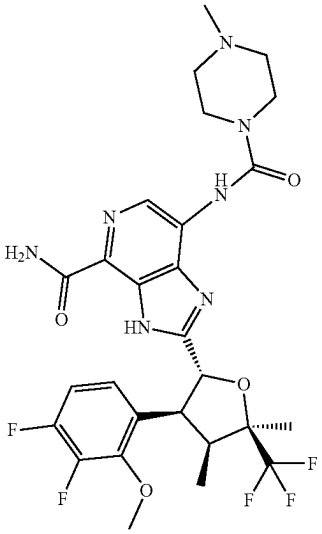

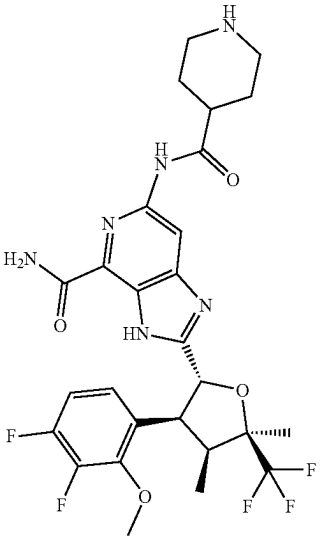

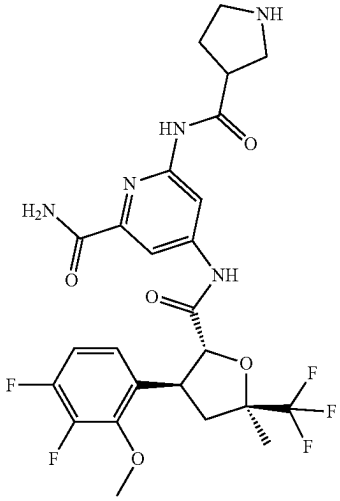

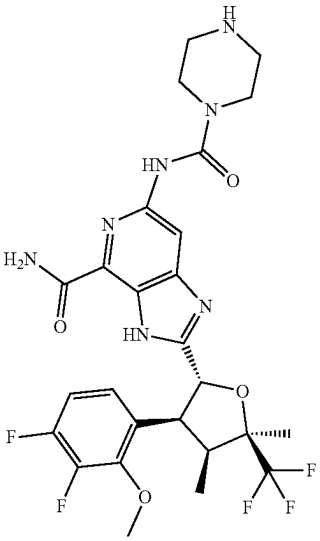

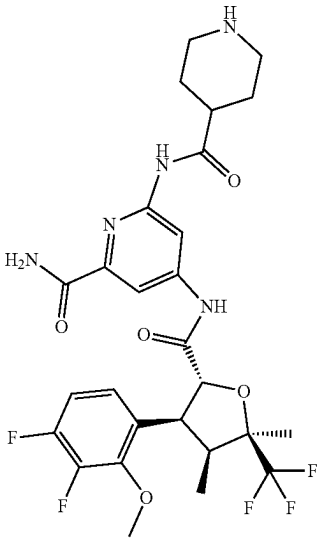

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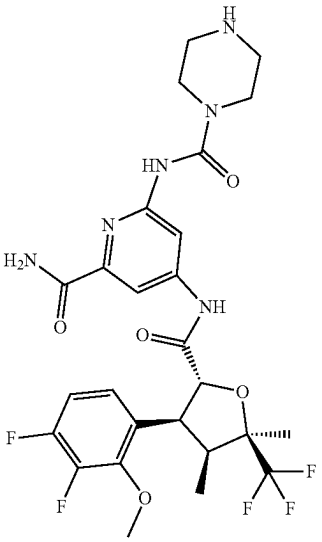

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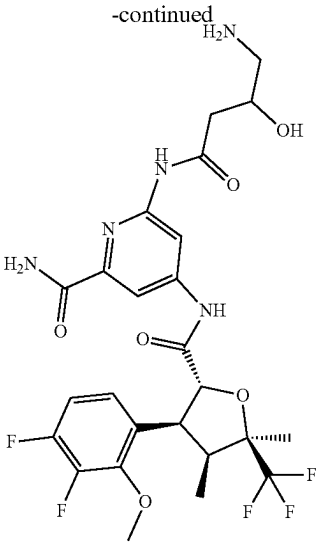

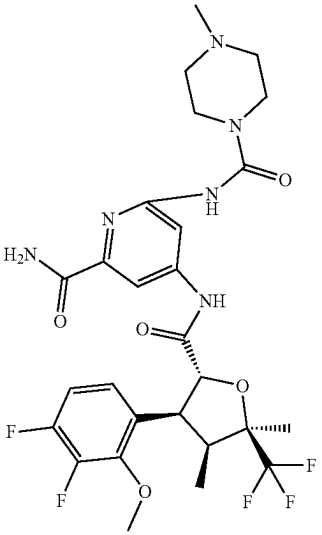

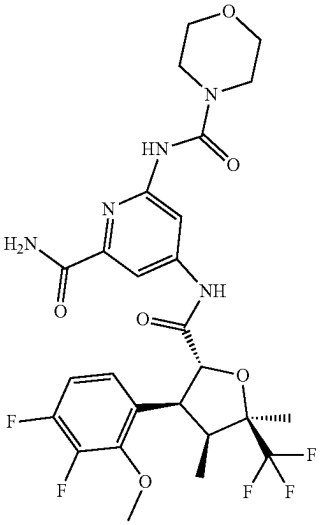

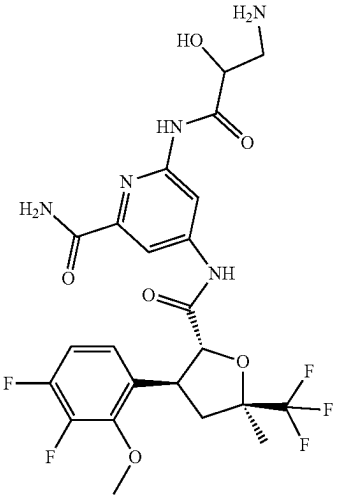

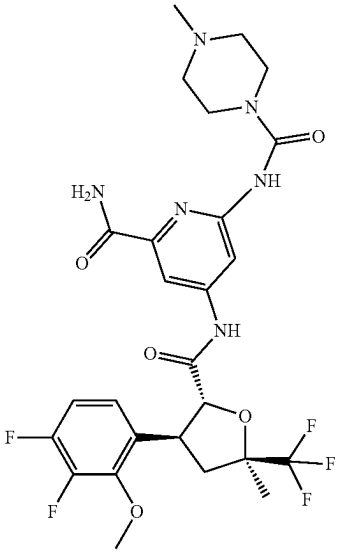

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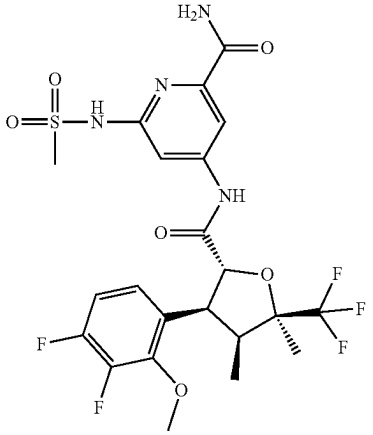

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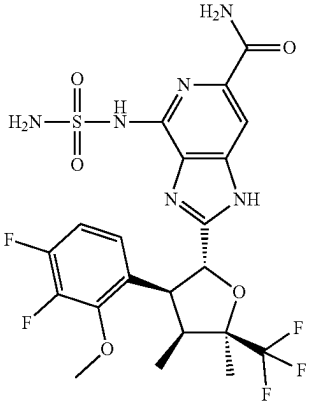

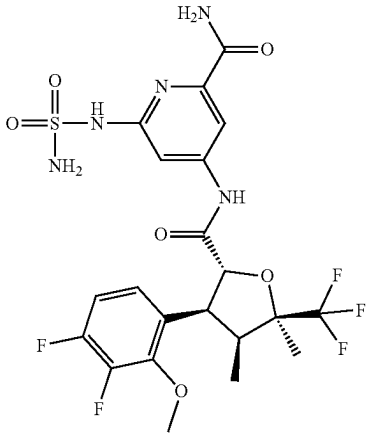

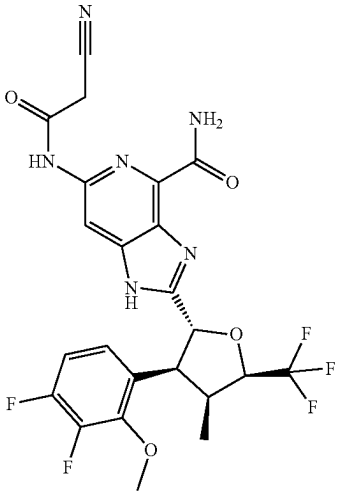

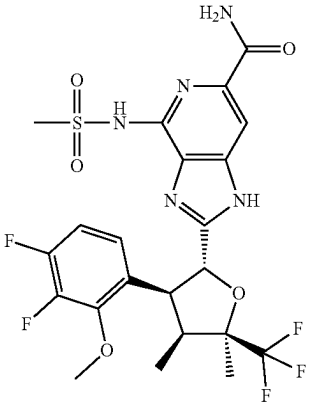

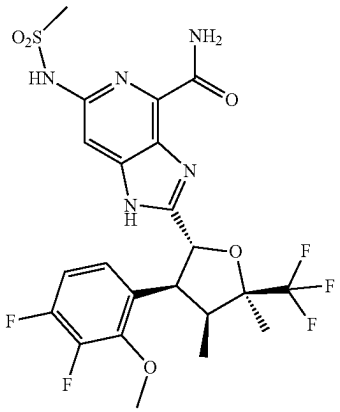

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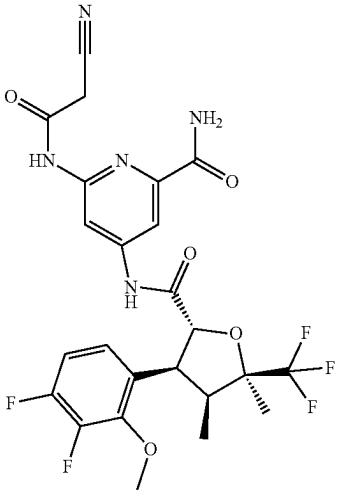

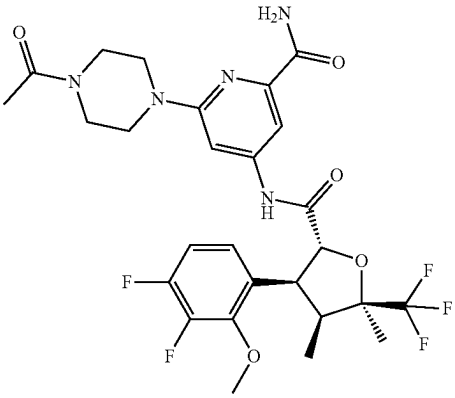

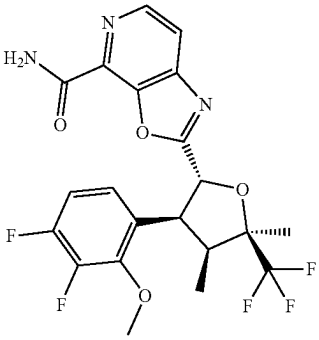

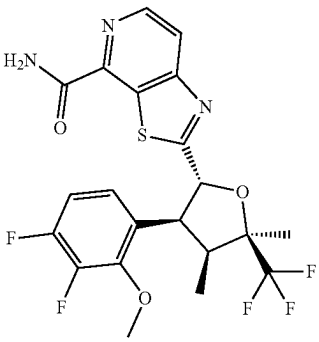

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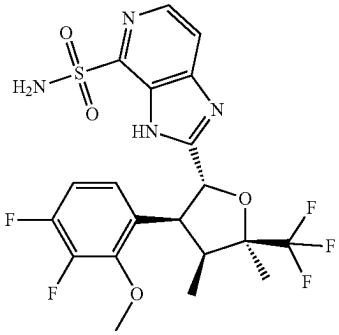

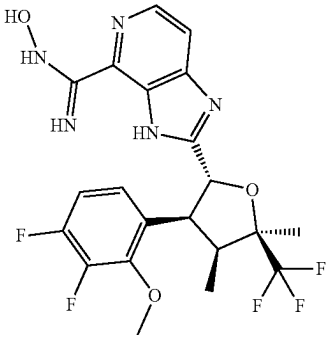

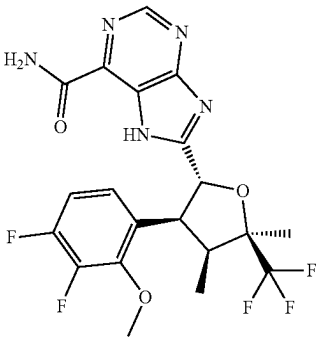

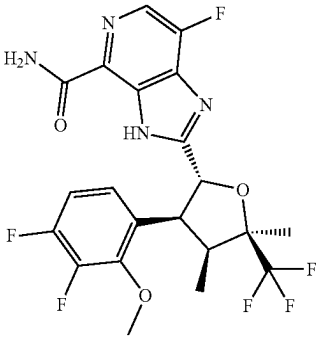

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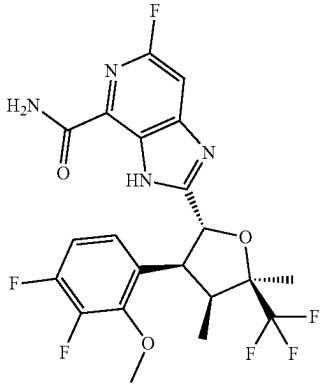

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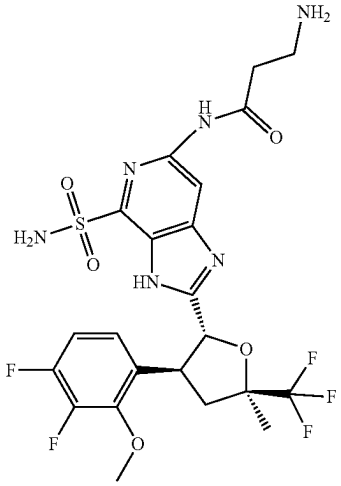

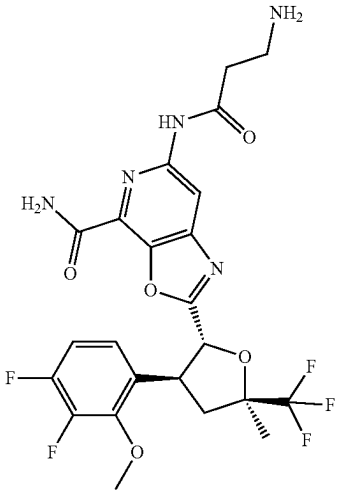

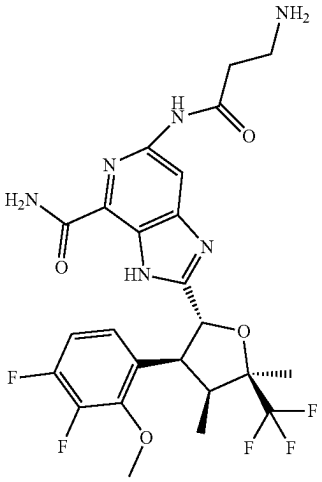

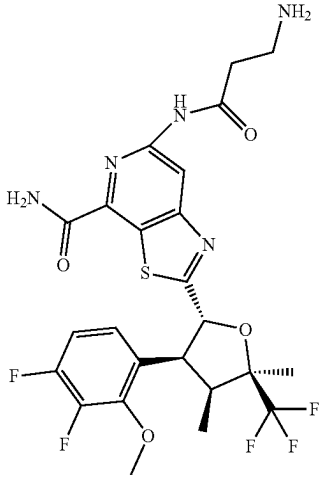

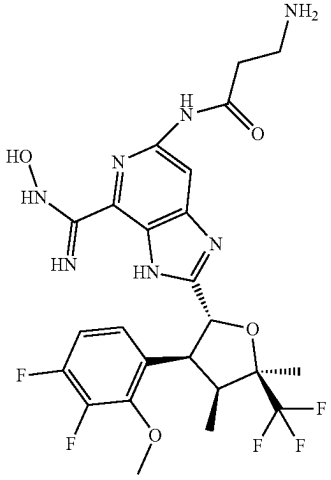

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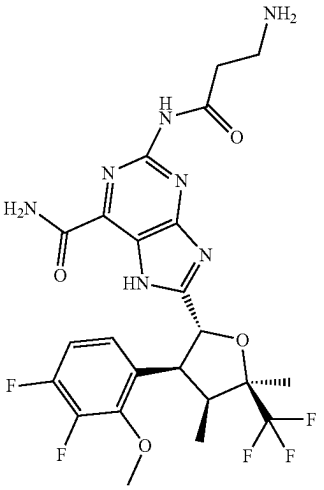

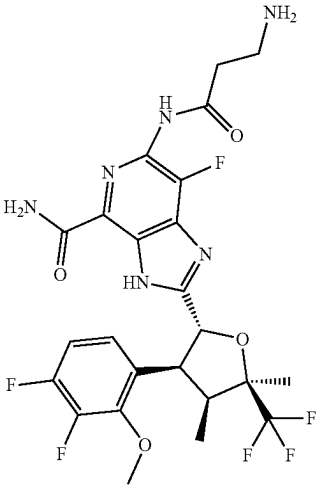

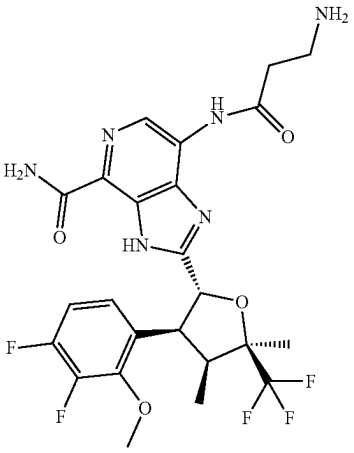

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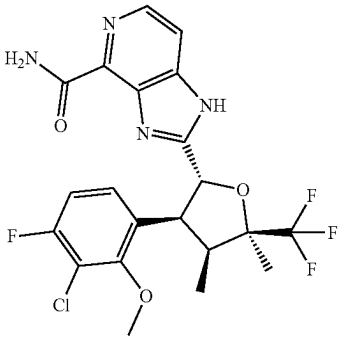

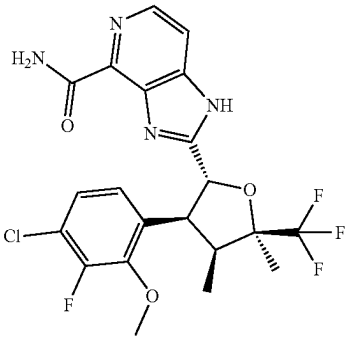

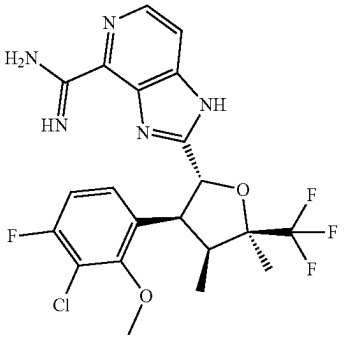

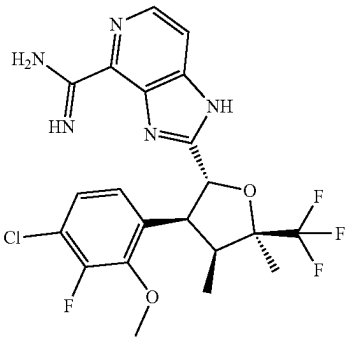

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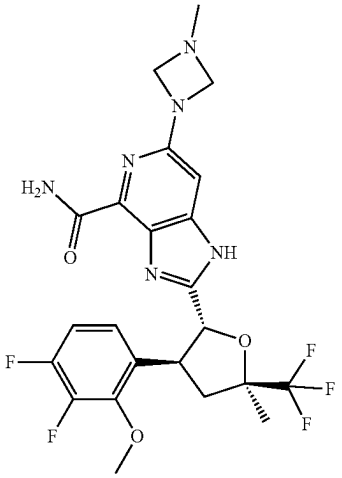

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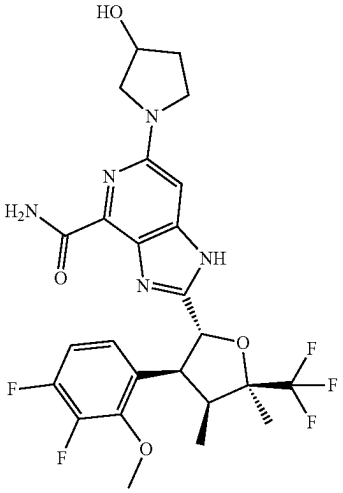

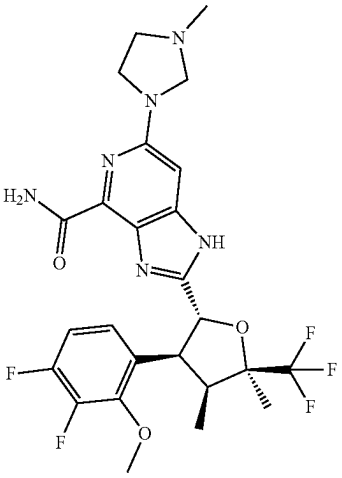

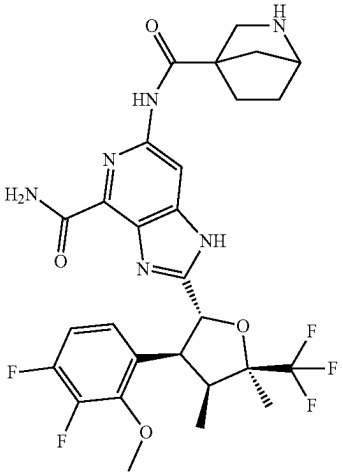

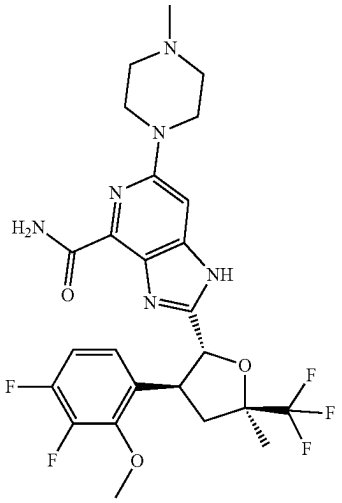

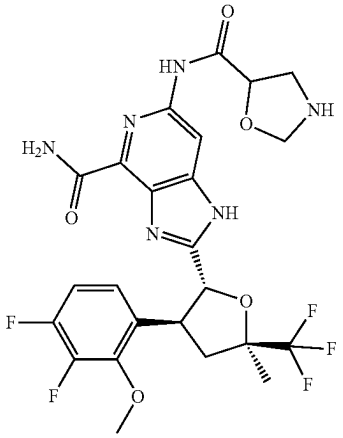

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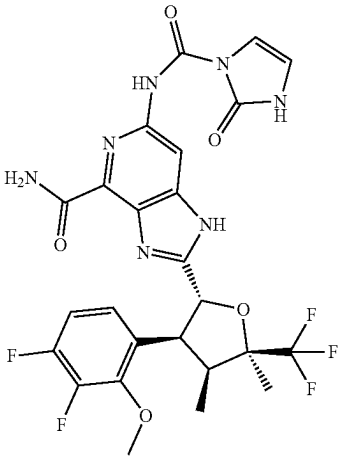

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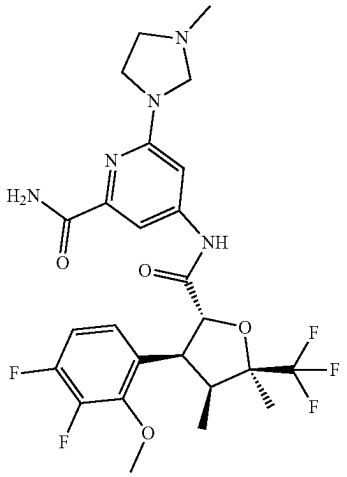

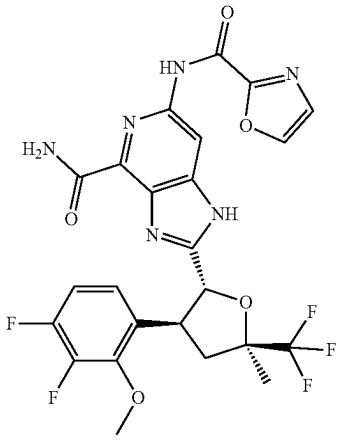

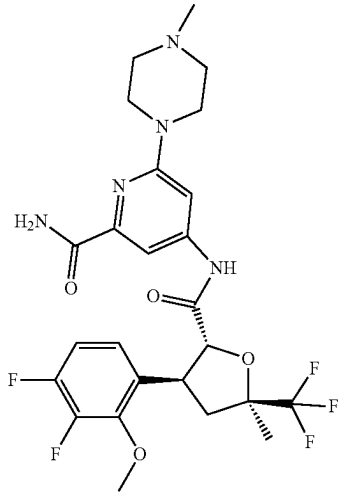

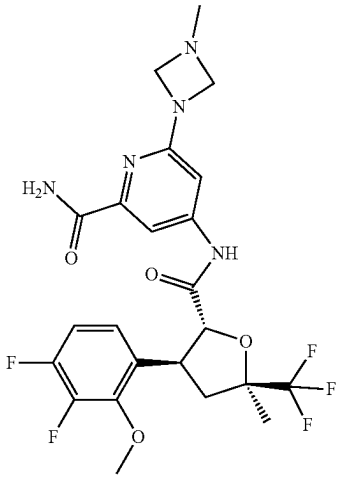

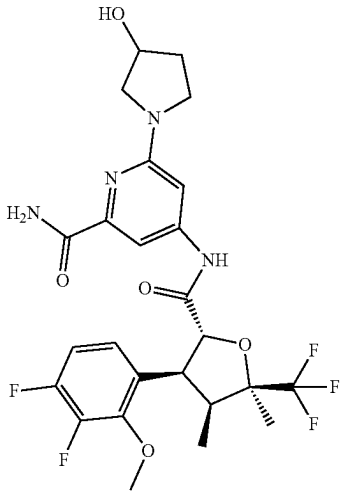

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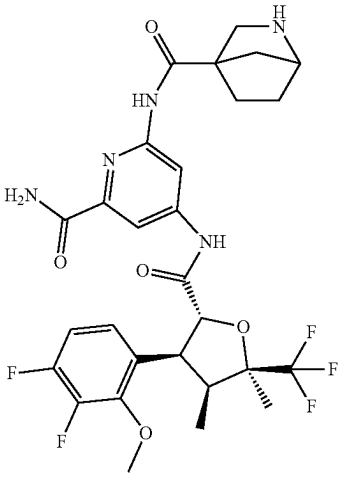

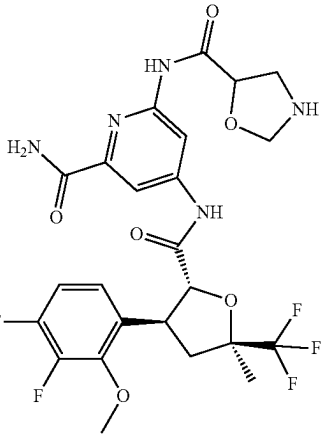

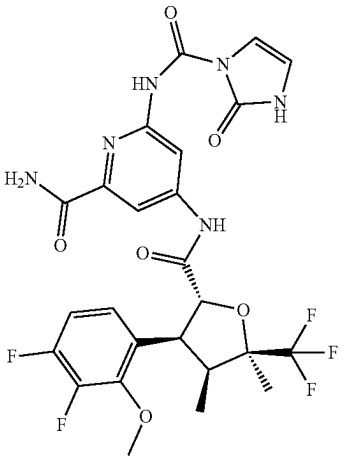

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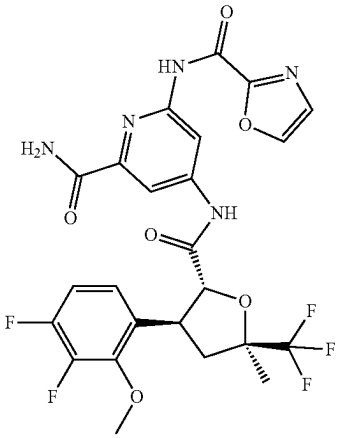

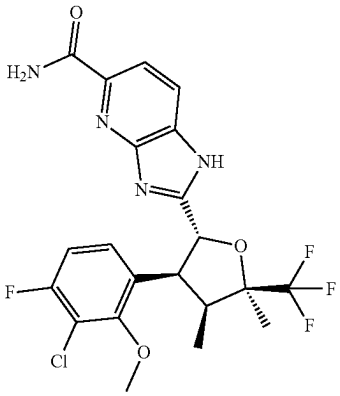

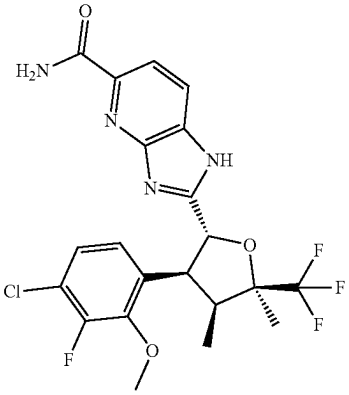

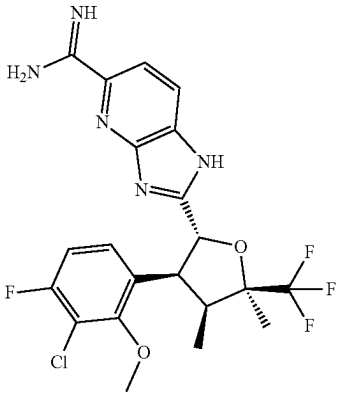

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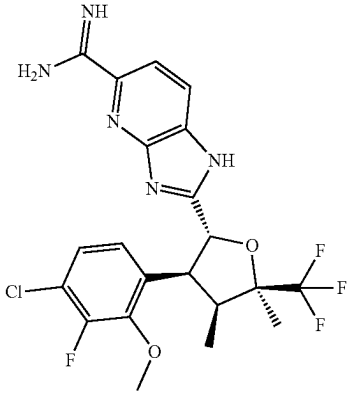

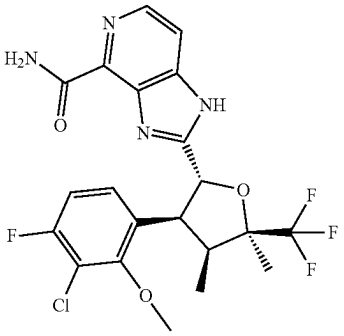

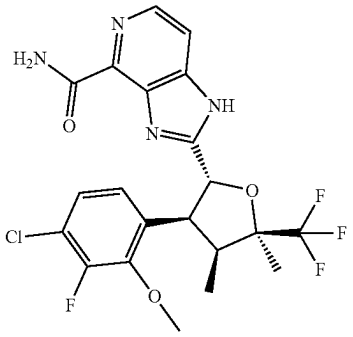

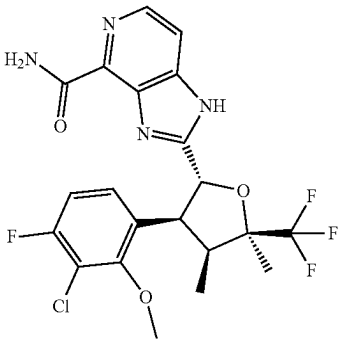

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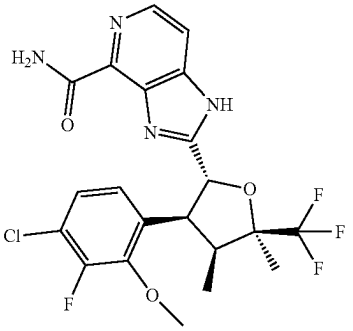

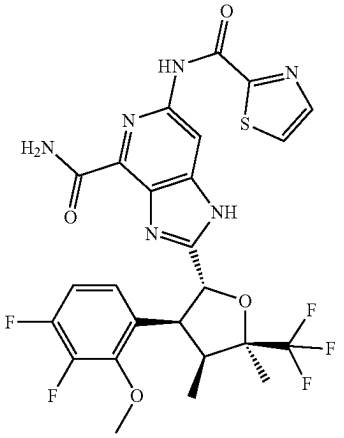

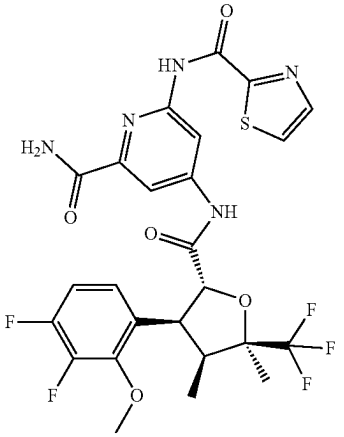

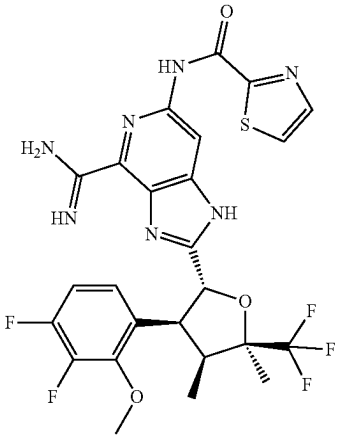

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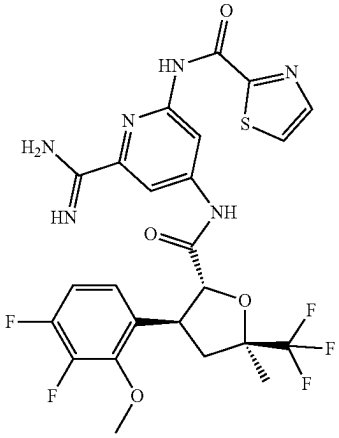

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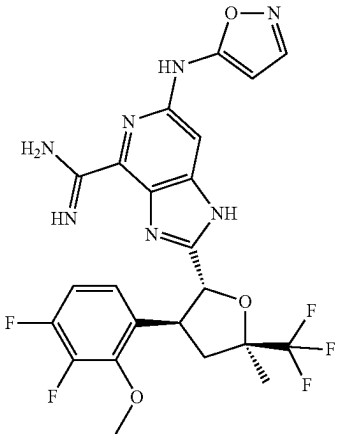

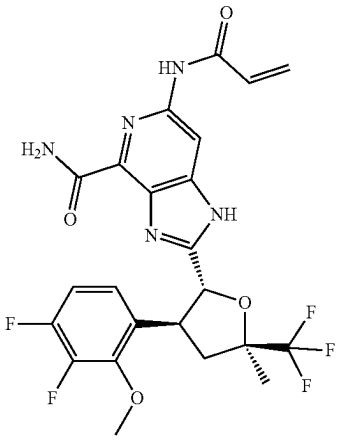

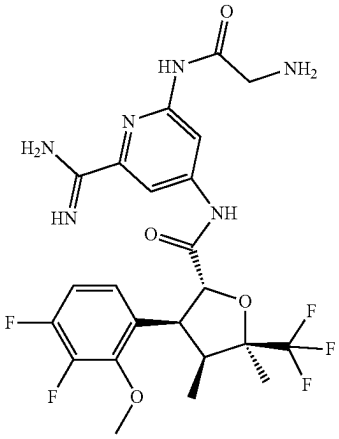

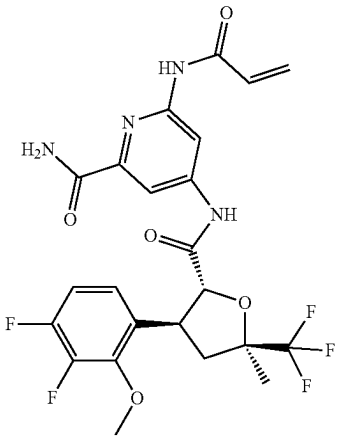

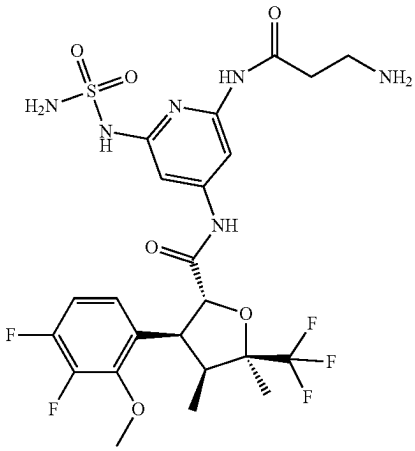

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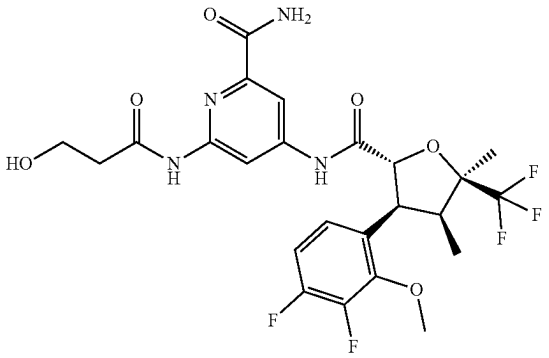

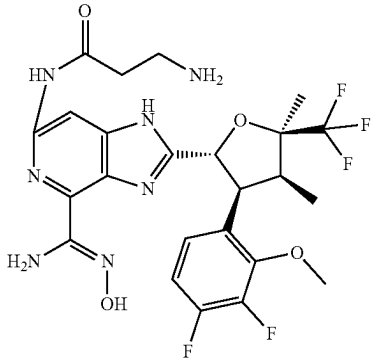

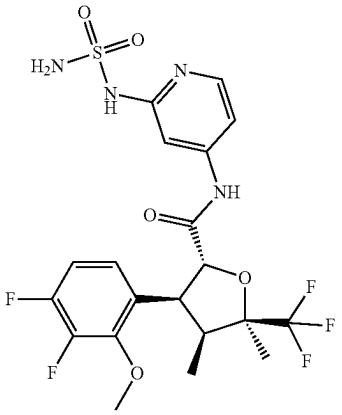

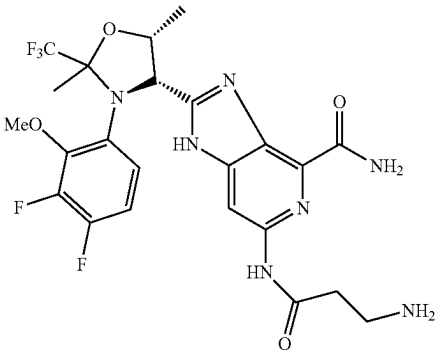

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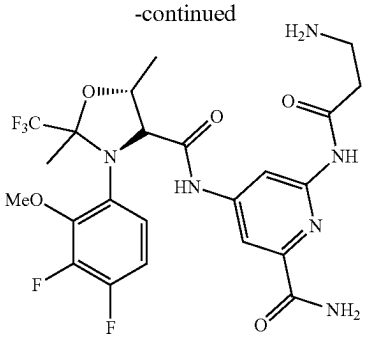

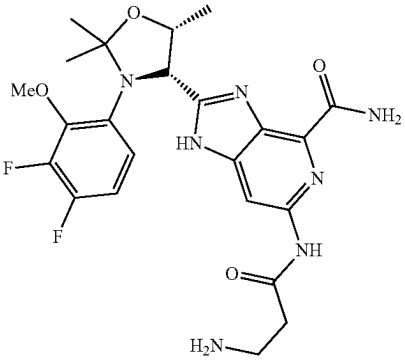

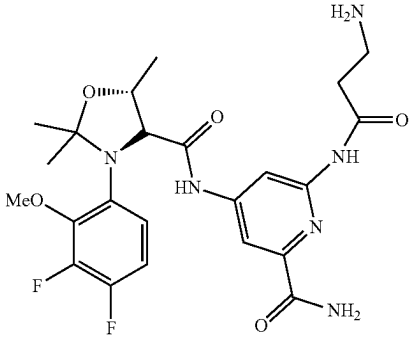

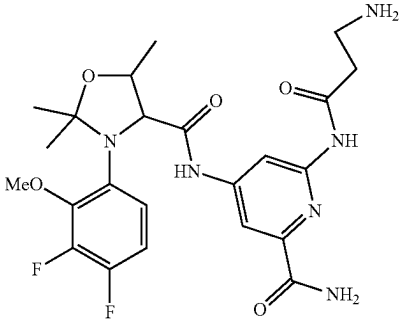

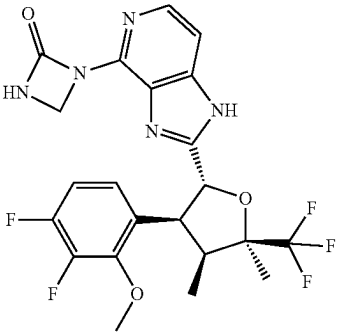

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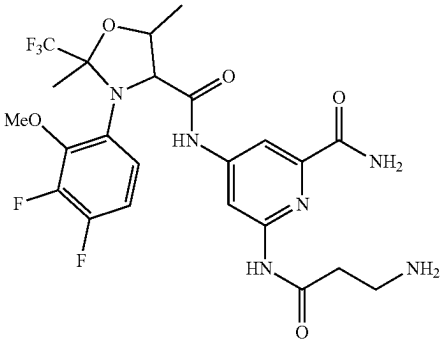

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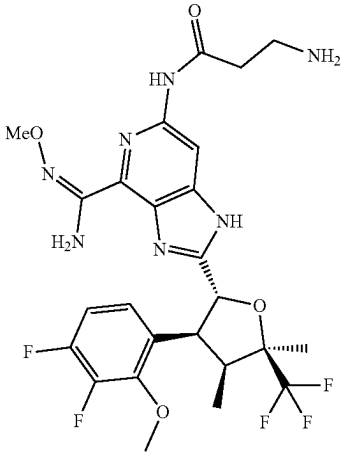

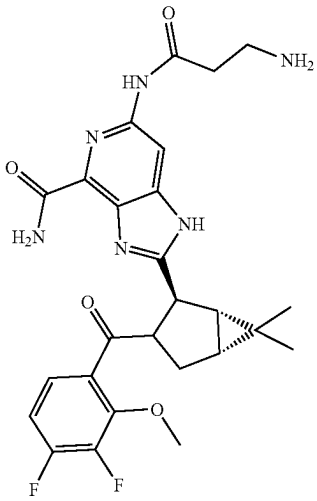

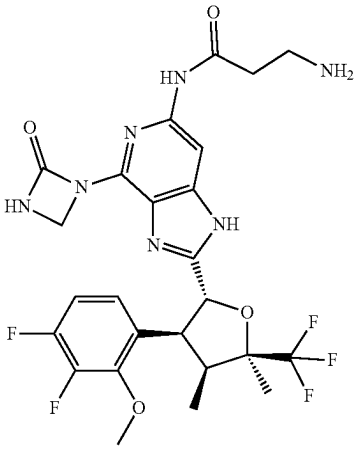

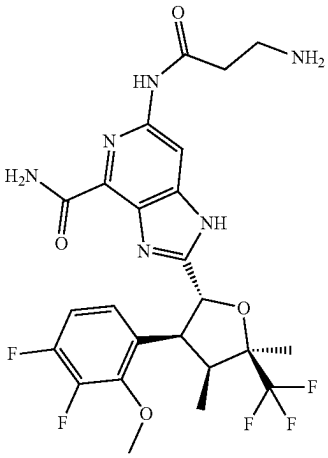

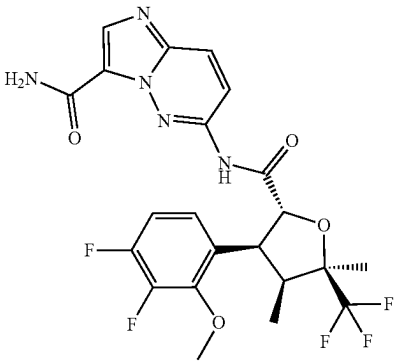

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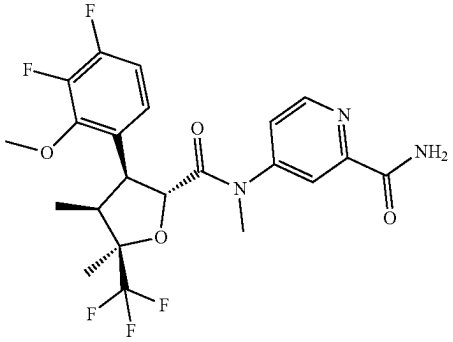

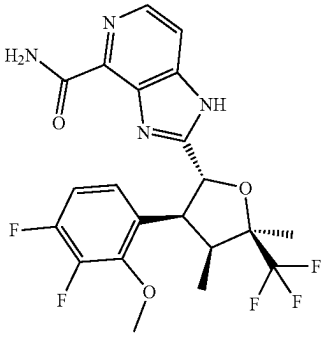

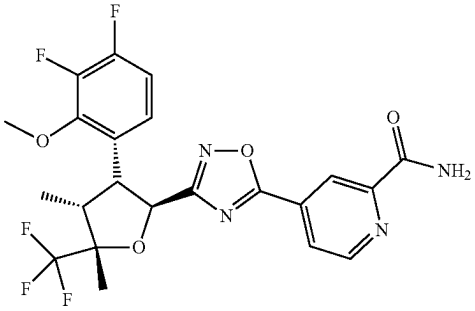

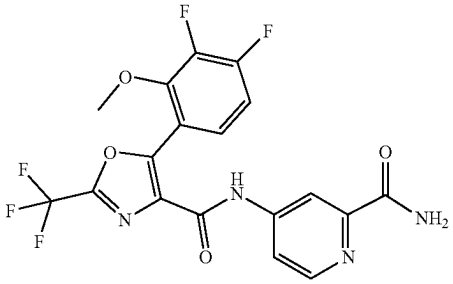

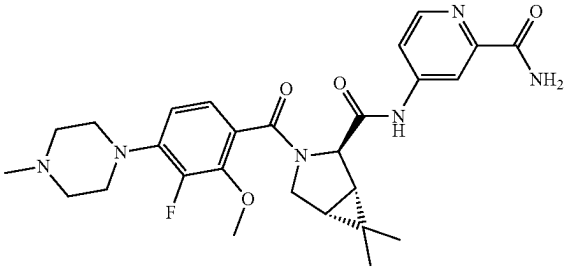

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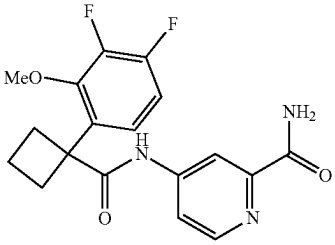

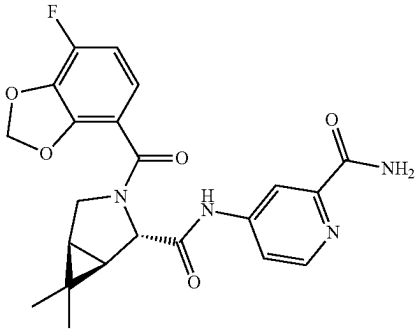

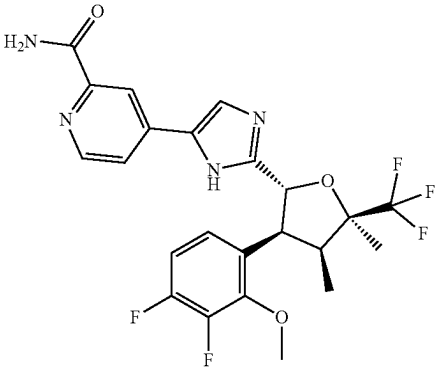

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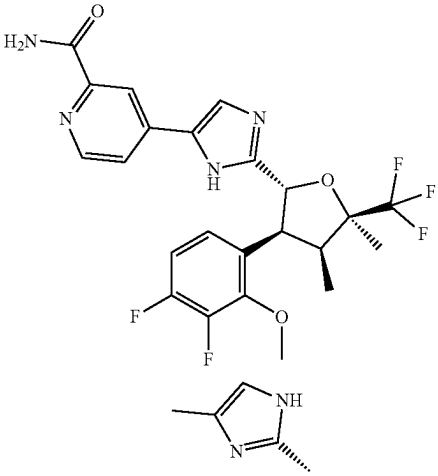

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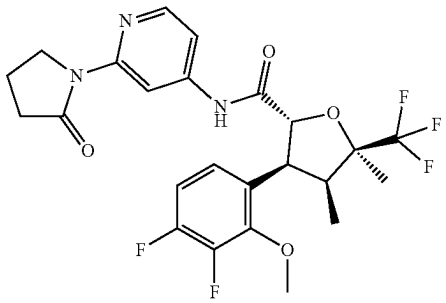

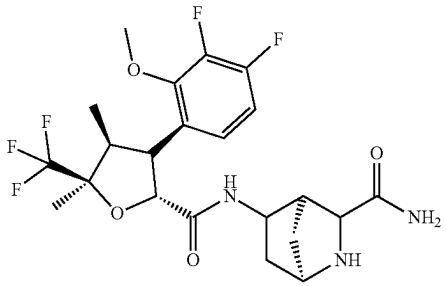

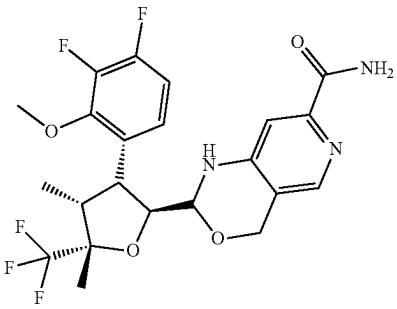

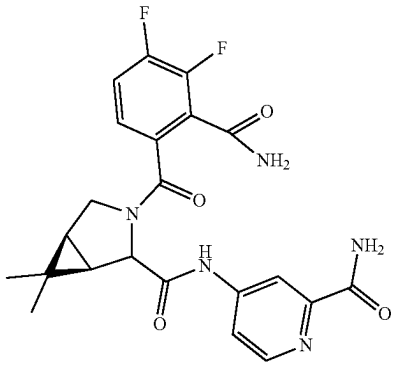

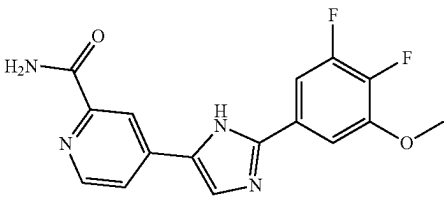

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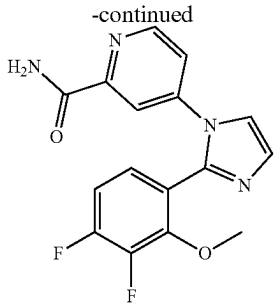

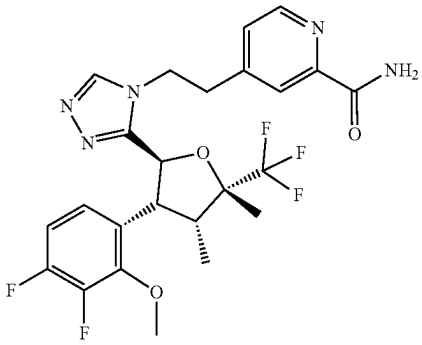

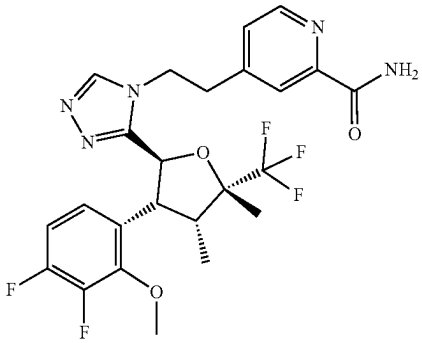

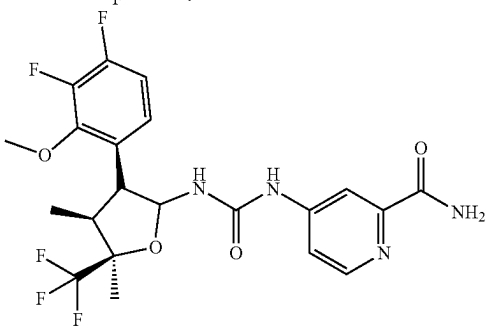

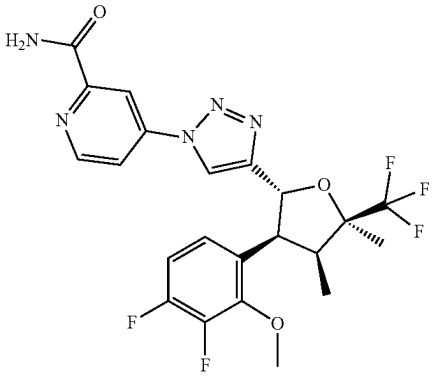

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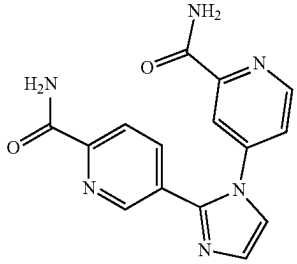

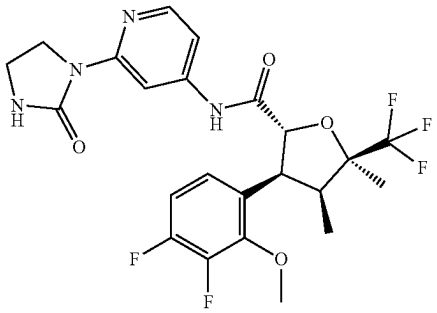

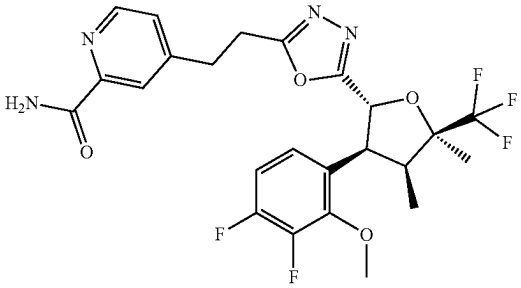

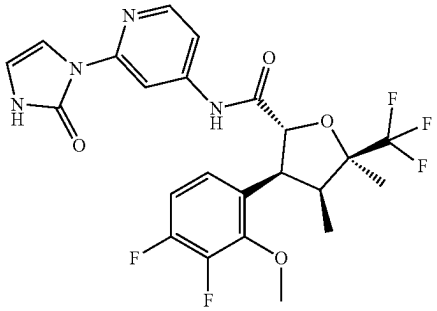

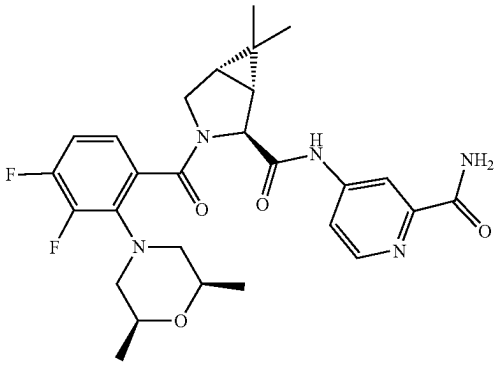

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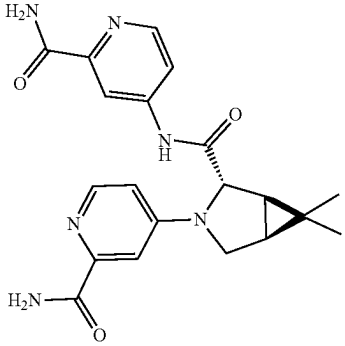

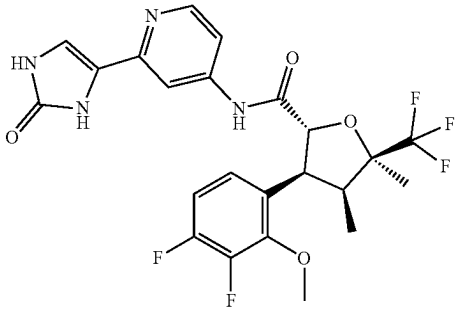

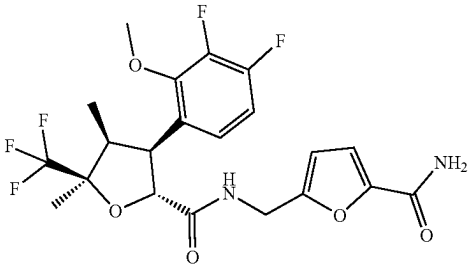

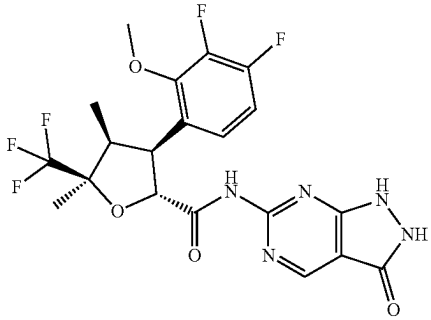

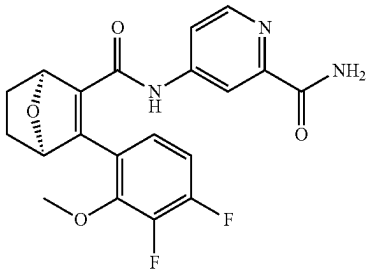

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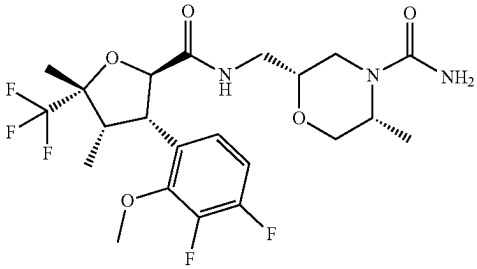

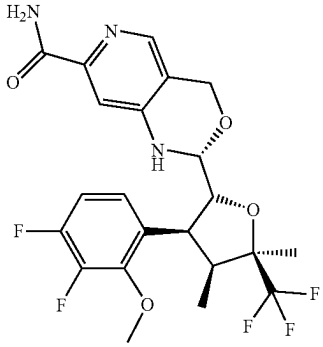

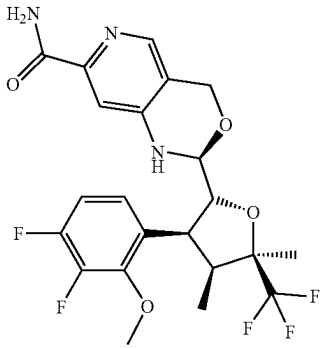

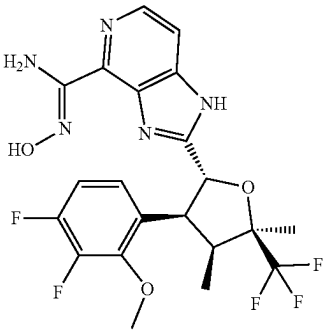

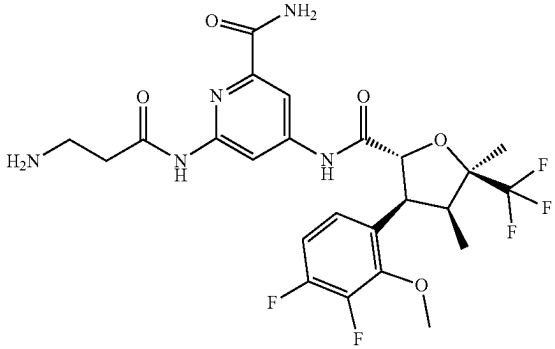

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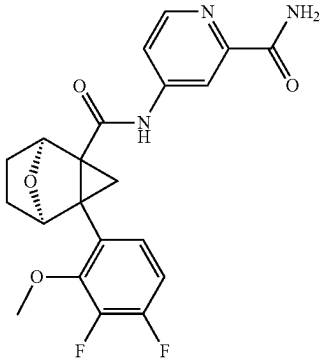

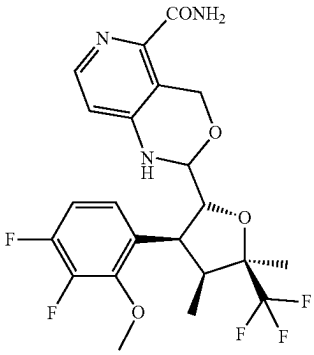

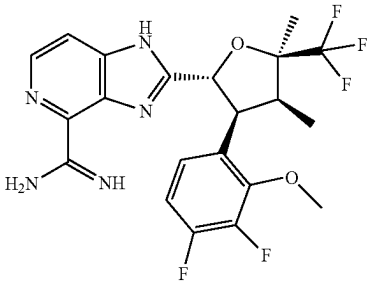

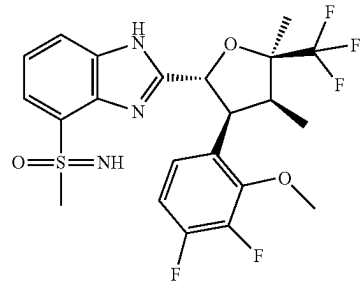

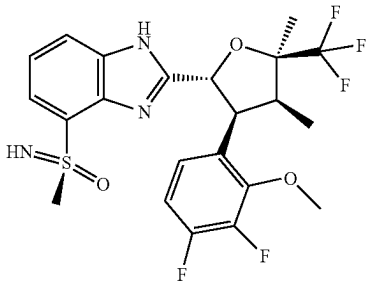

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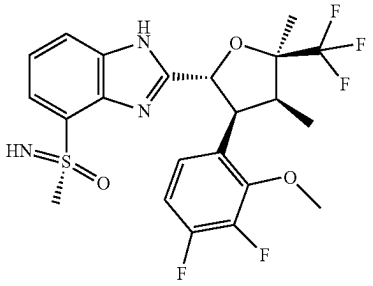

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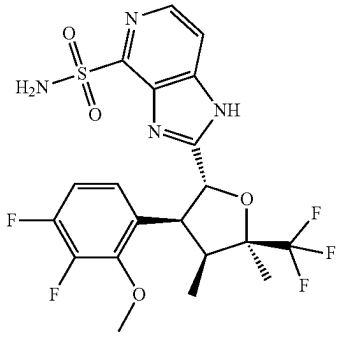

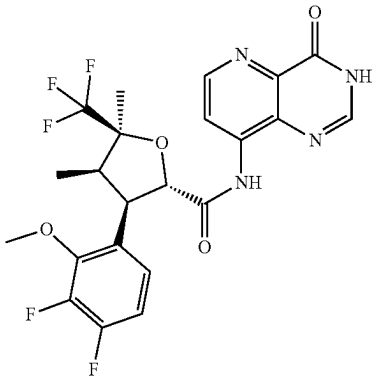

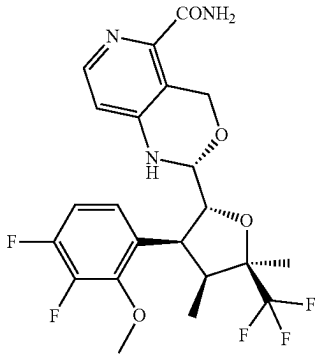

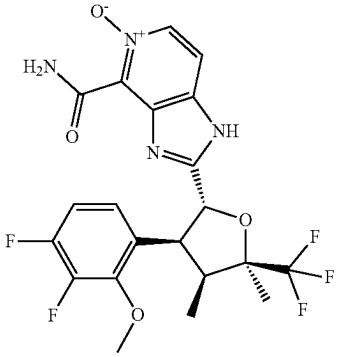

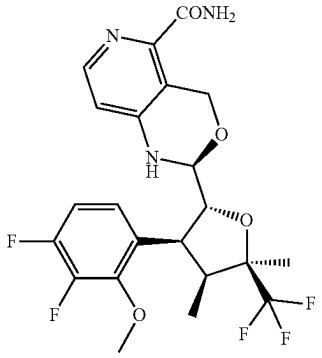

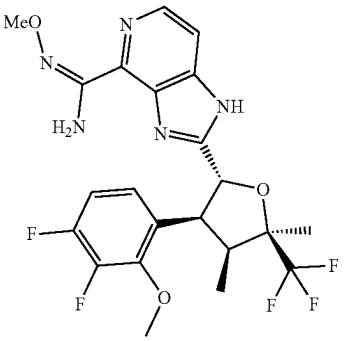

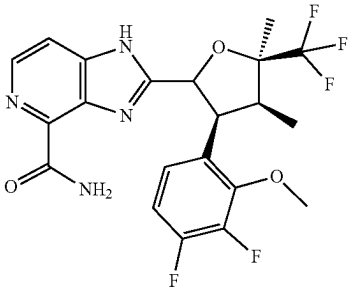

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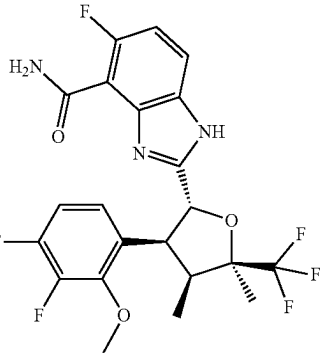

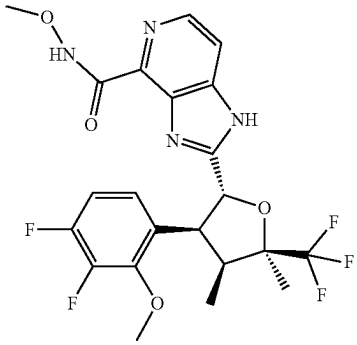

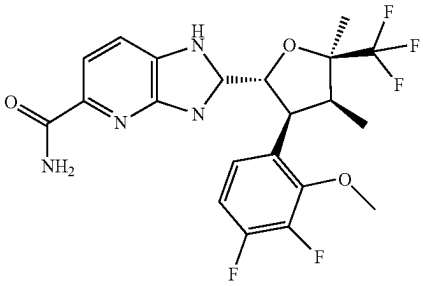

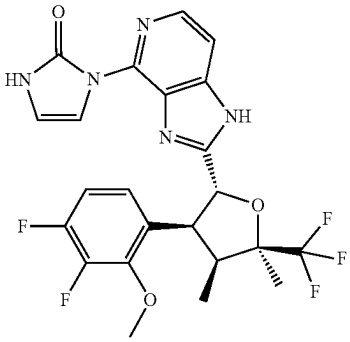

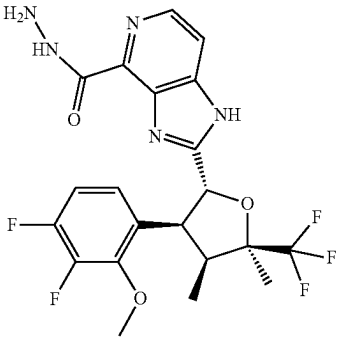

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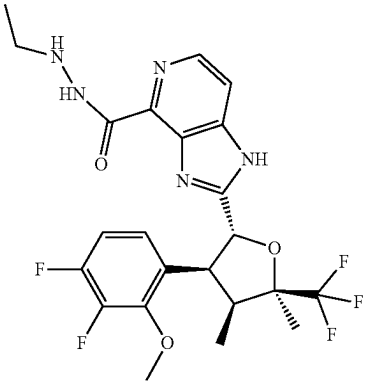

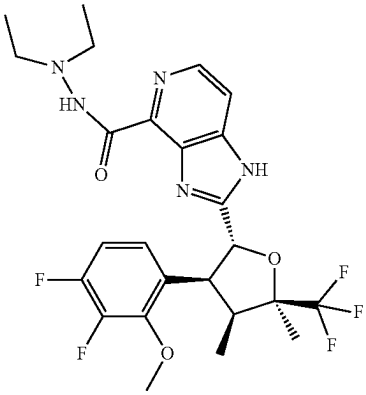

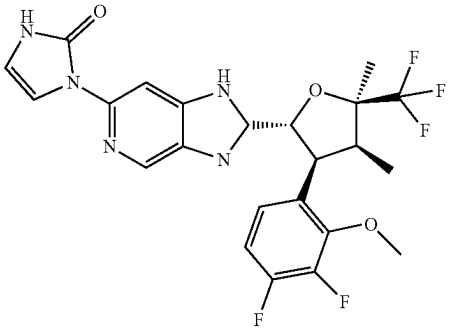

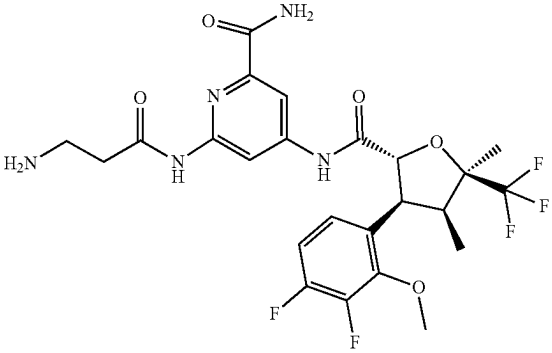

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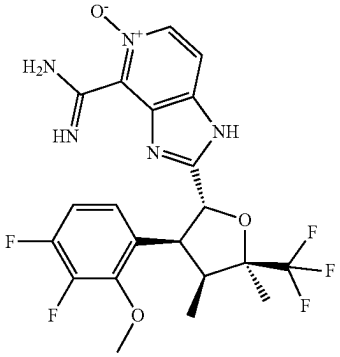

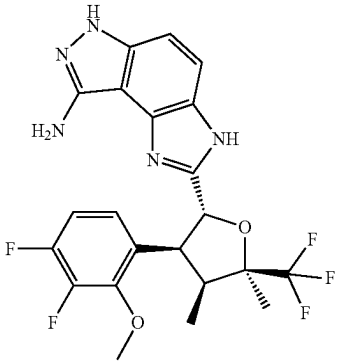

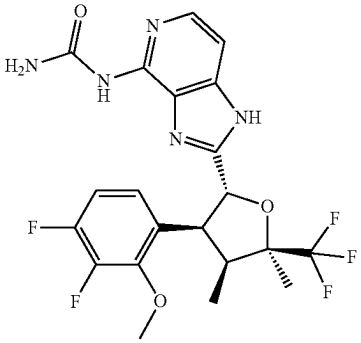

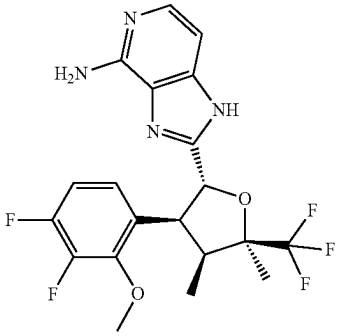

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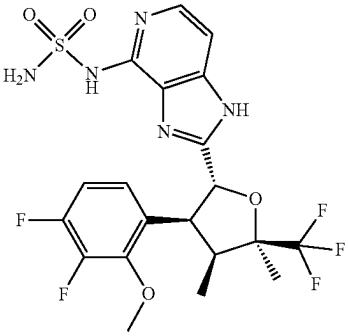

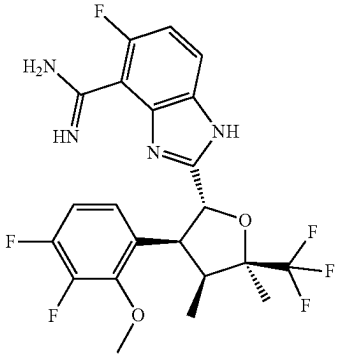

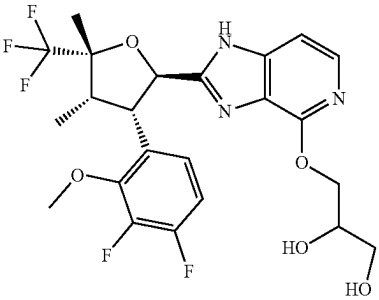

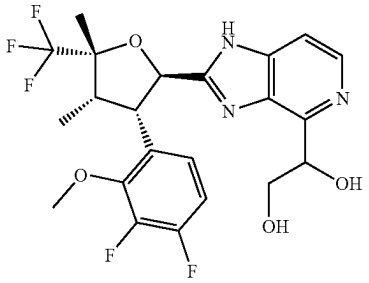

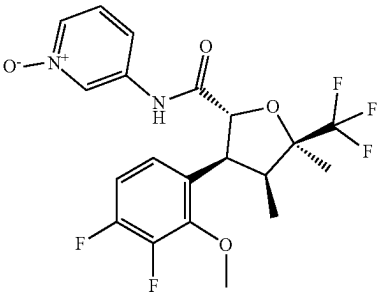

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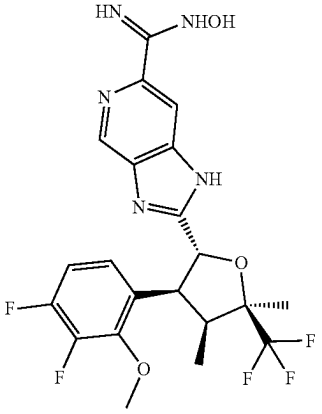

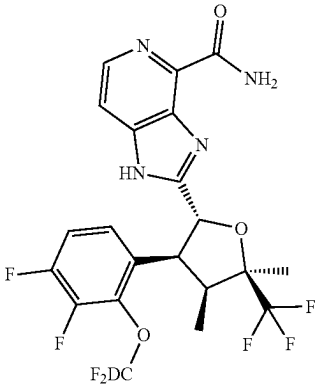

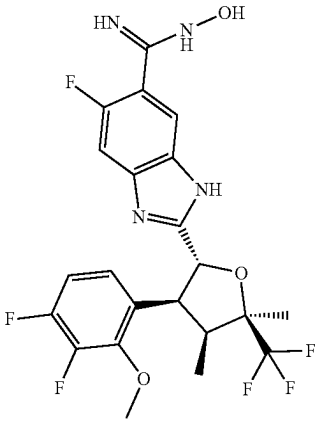

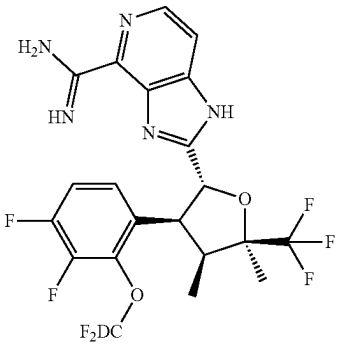

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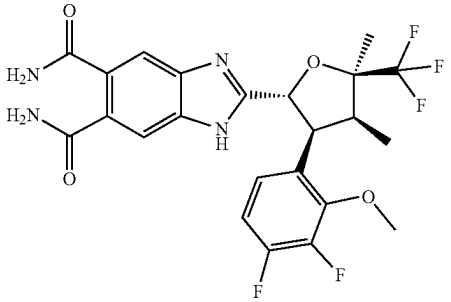

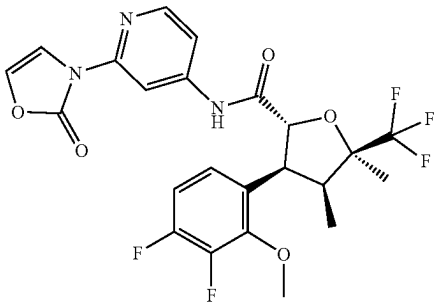

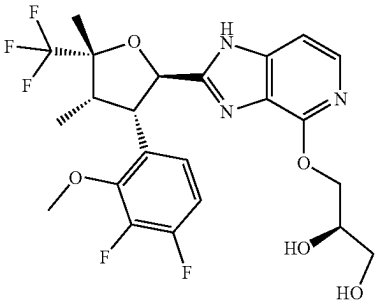

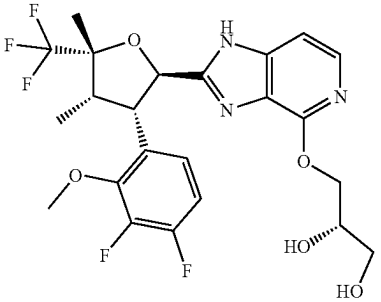

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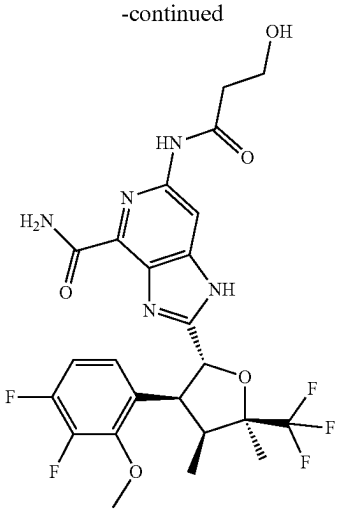

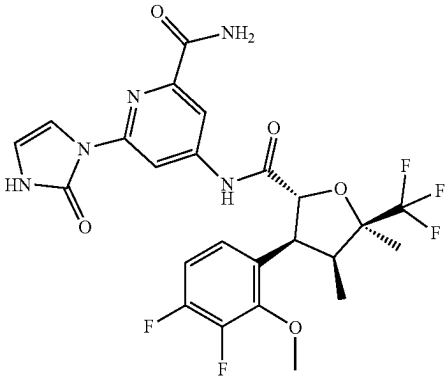

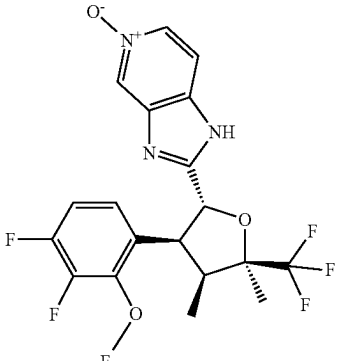

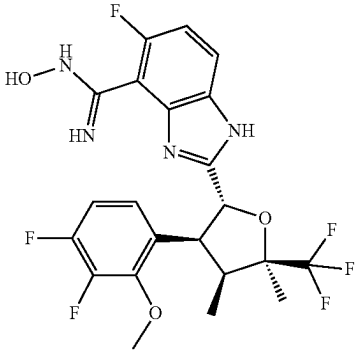

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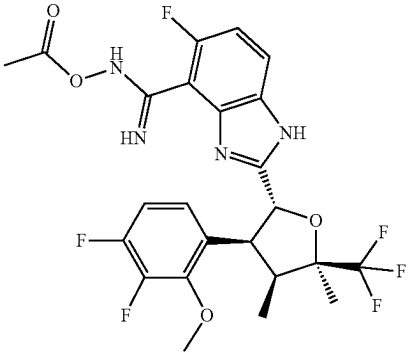

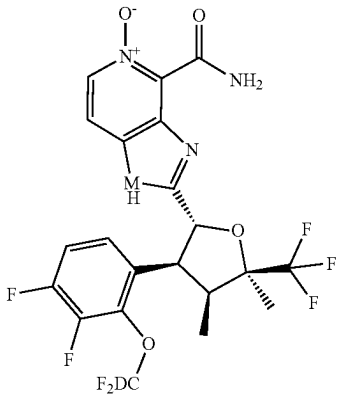

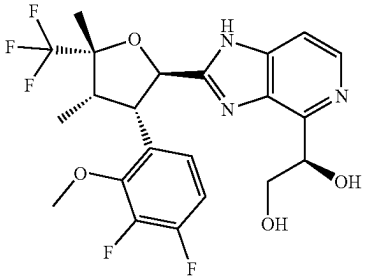

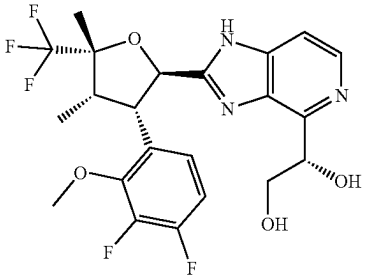

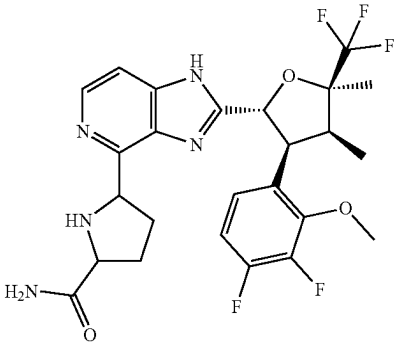

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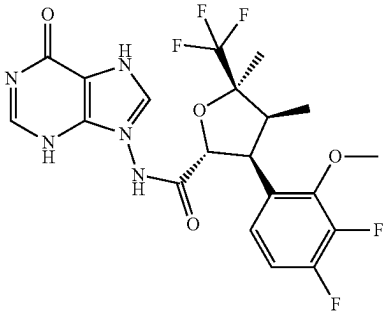

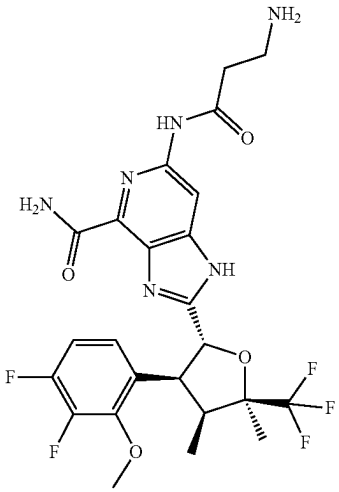

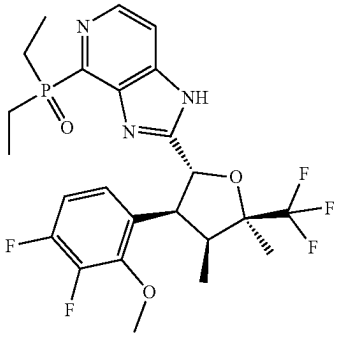

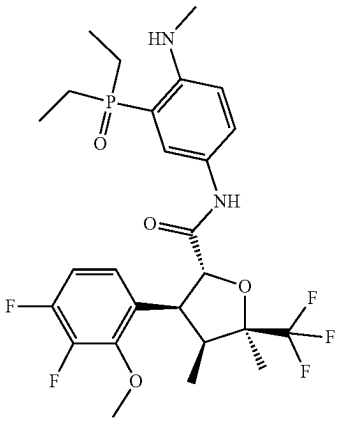

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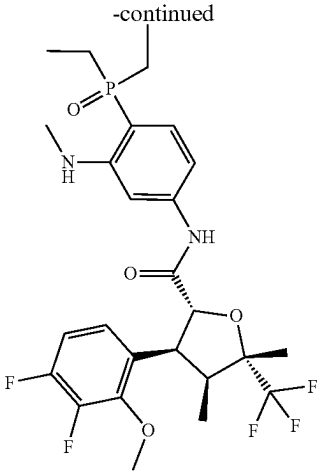

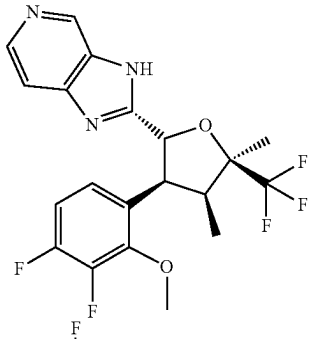

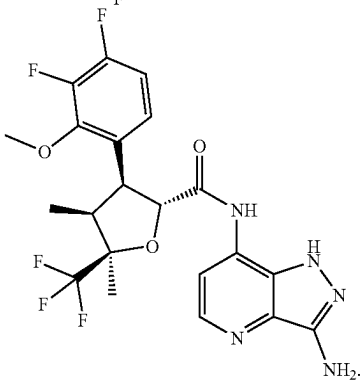

13. A pharmaceutical composition comprising the compound as described in claim **1** or its pharmaceutically acceptable salt, tautomeric isomers, stereoisomers, hydrates, solvates, pharmaceutically acceptable salts, or prodrugs, and pharmaceutically acceptable excipients.

14. A method of treating and/or alleviating symptoms of chronic pain, primary pain, idiopathic pain, gastrointestinal pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer-related pain, idiopathic pain, postoperative pain, visceral pain, multiple sclerosis, Summer-Marr-Tuff syndrome, incontinence, pathological cough, or arrhythmia, the method comprising administering the compound of claim **1** to a subject in need thereof.

15. The method of claim **14**, wherein the pharmaceutical composition is administered subcutaneous, intradermal, intravenous, intramuscular, orally, or intraperitoneal.

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