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(54) EGFR DEGRADATION AGENT

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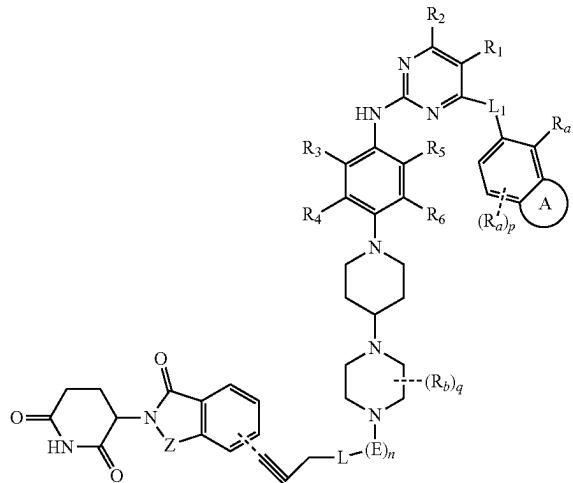
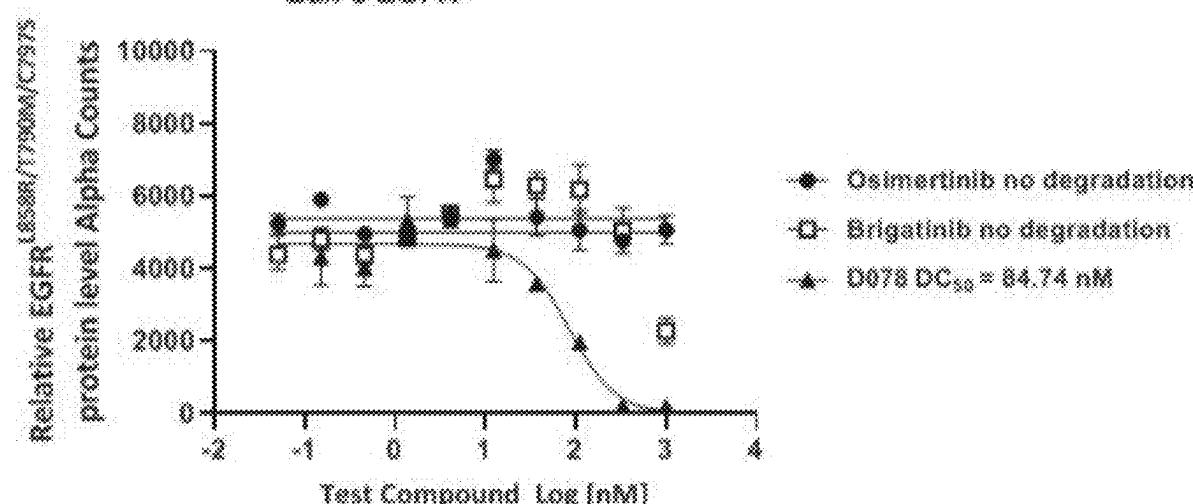
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(57)

ABSTRACT

The present invention relates to a novel compound of general formula (A) capable of inhibiting and inducing degradation of EGFR, and a pharmaceutical composition containing the compound, which can be used for treating diseases associated with EGFR kinase, such as cancer. The present invention further relates to preparation and use of the compound described above.

(A)

Ba/F3 EGFR^{L858R/T790M/C797S}

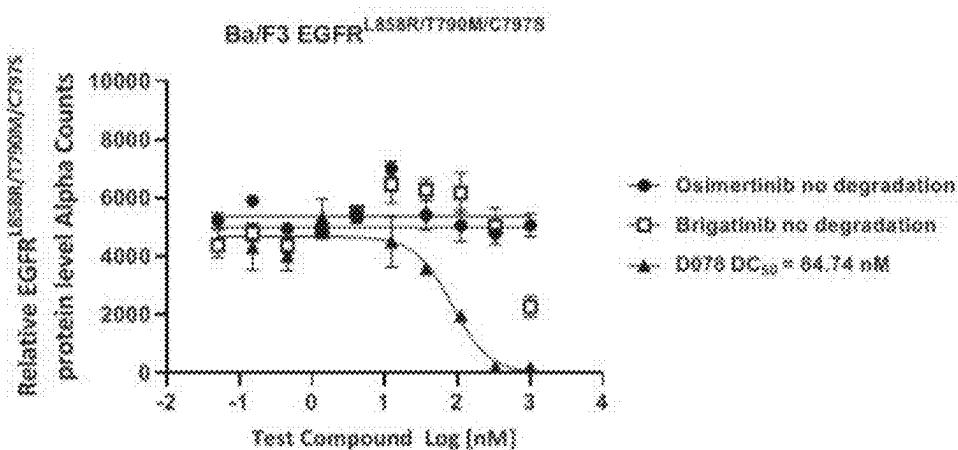


Fig. 1

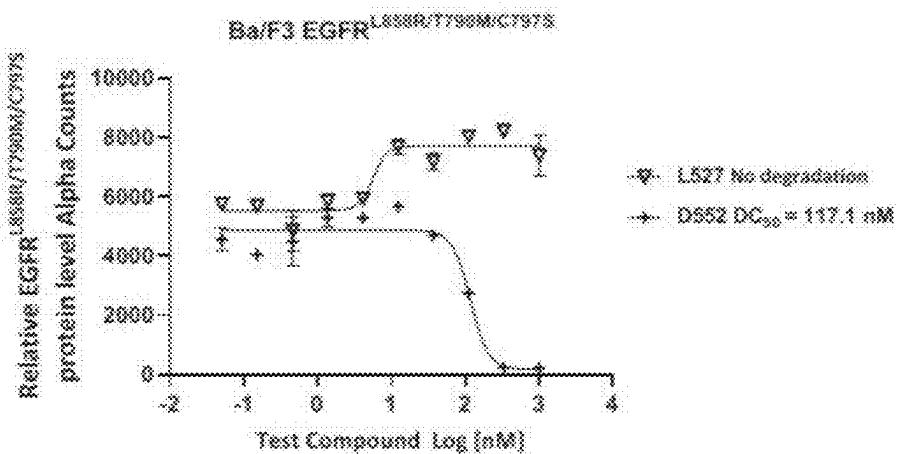


Fig. 2

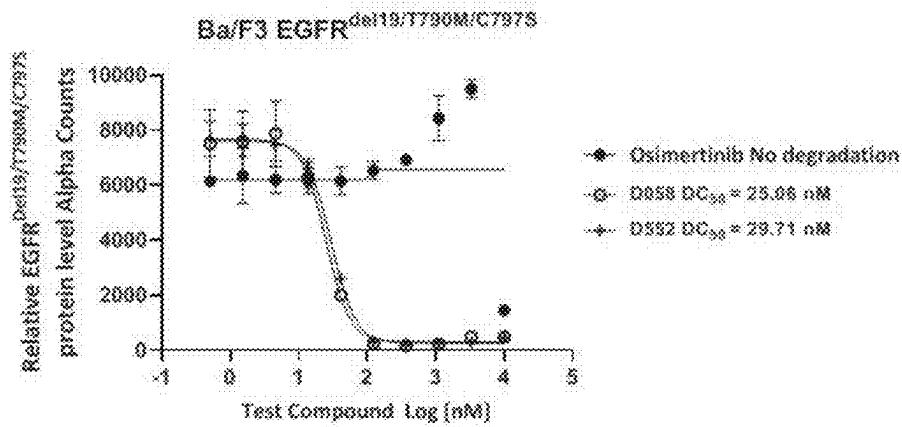


Fig. 3

EGFR DEGRADATION AGENT

[0001] This application is a National Stage filing under 35 U.S.C. 371 of International PCT Application No. PCT/CN2023/088336, filed on Apr. 14, 2023, which claims the priority of Chinese application No. 202210398246.3 filed on Apr. 15, 2022 and Chinese application No. 202310317846.7 filed on Mar. 28, 2023, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present disclosure relates to the field of medicine. Specifically, the present disclosure provides compounds capable of inducing EGFR degradation, and a preparation method and use thereof.

BACKGROUND OF THE INVENTION

[0003] Lung cancer is one of the most common malignant tumors. In 2020, there were 2.2 million new cases of lung cancer and 1.8 million deaths worldwide. Among them, non-small cell lung cancer (NSCLC) accounts for 80%-85% of all lung cancers. In non-small cell lung cancer, about 50% of patients in China and 11-16% of patients in Western countries have EGFR gene mutation, in which the most common types of mutations are exon 19 deletion mutation (del E746-A750) and exon 21 L858R point mutation, accounting for about 90% of all EGFR mutations in populations. EGFR small molecule inhibitors are the standard first-line treatment for non-small cell lung cancer with EGFR gene mutation and have been widely used in the field of lung cancer treatment. They inhibit the activation of tyrosine kinase by competing with endogenous ligands for binding to EGFR, thereby blocking the EGFR signaling pathway, inhibiting the proliferation and metastasis of tumor cells and promoting a series of biological effects such as tumor cell apoptosis.

[0004] Currently, there are five EGFR small molecule inhibitors approved by the FDA for the treatment of non-small cell lung cancer, namely Gefitinib, Erlotinib, Afatinib, Dacomitinib and Osimertinib. The first-generation EGFR small-molecule inhibitors Gefitinib and Erlotinib have been used to treat advanced non-small cell lung cancer with activating EGFR mutations (L858R, del E746-A750). However, patients develop resistance after 10-12 months of administration of Gefitinib and Erlotinib, wherein more than 50% of drug-resistant patients are due to the secondary mutation of T790M in EGFR. Afatinib, a second-generation irreversible EGFR inhibitor, is effective for advanced non-small cell lung cancer patients with activating EGFR mutations (L858R, or del E746-A750), but cannot resolve the clinical drug resistance caused by EGFR T790M mutation. Moreover, Afatinib lacks selectivity to wild-type EGFR and has great toxicity. Osimertinib, a third-generation irreversible inhibitor, overcomes the drug resistance caused by EGFR T790M and can effectively treat advanced non-small cell lung cancer patients with drug resistance caused by EGFR T790M mutation. Although Osimertinib has achieved great success in the clinical treatment of non-small cell lung cancer with EGFR T790M mutant, some patients who benefits from the treatment develops drug resistance after 9-14 months of treatment. Studies have shown that 15-22% of patients with drug resistance of Osimertinib are due to EGFR C797S mutation. As a type of cancer with high morbidity and mortality, lung cancer has a huge and unmet

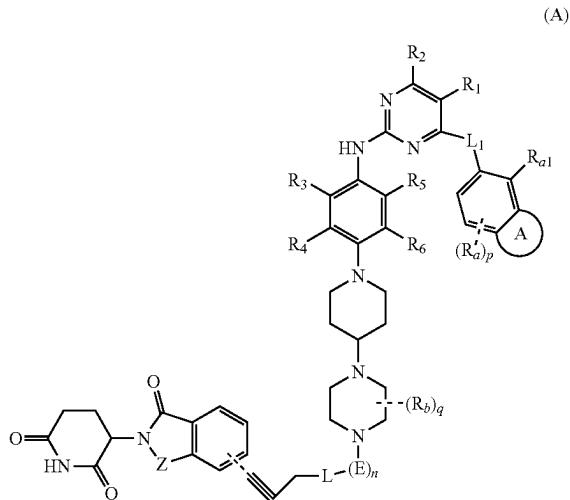
demand for clinical drugs. Therefore, the development of new lung cancer drugs to meet clinical treatment needs is an urgent problem to be solved.

[0005] Ubiquitin-proteasome system (UPS) is a multi-component system for intracellular protein degradation, which is involved in important physiological and biochemical processes such as cell growth and differentiation, DNA replication and repair, cell metabolism, immune response and so on. Protein degradation mediated by the ubiquitin-proteasome pathway is an important mechanism of the body for regulating intracellular protein level and function, and plays an important role in maintaining protein homeostasis in vivo. Inducing the degradation of EGFR through the intracellular ubiquitin-proteasome pathway provides a new idea for the treatment of cancers.

[0006] The present disclosure provides compounds capable of inducing degradation of EGFR, and preparation methods and use thereof.

SUMMARY OF THE INVENTION

[0007] In one aspect, the present disclosure provides a compound of formula (A) or (X), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug, or isotopic variant thereof, or a mixture thereof, which can be used to treat EGFR kinase-mediated diseases, such as diseases.



[0008] wherein

[0009] represents that the point of attachment to the rest of the molecule can be located at an available point of a ring where it is located;

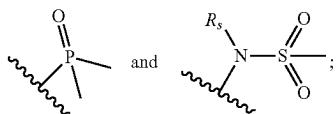
[0010] Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;

[0011] R₁ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0012] R₂ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0013] R₃ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OC₁₋₆ alkyl, —OC₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

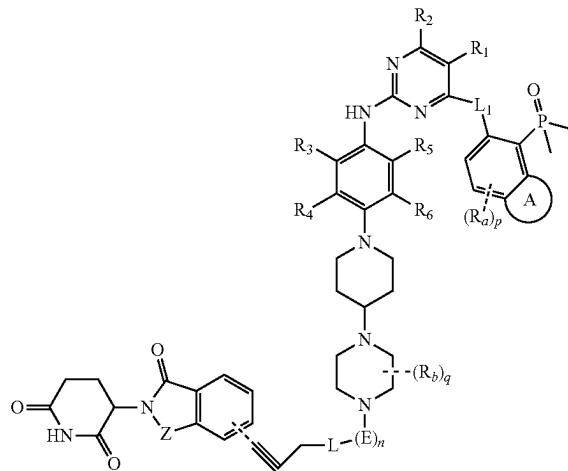
- [0014] R_4 is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0015] R_5 is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0016] R_6 is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';
- [0017] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;
- [0018] R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0019] Z is CH₂, C=O, C=S or C=NH;
- [0020] R_{a1} is selected from



- [0021] R_s is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0022] R_a is selected from H, halogen, —OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;
- [0023] alternatively, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C₄₋₁₀ cycloalkyl, a 5-8 membered heterocyclyl, a C₆₋₁₀ aryl or a 5-10 membered heteroaryl;
- [0024] R_b is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;
- [0025] alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C₃₋₁₀ cycloalkyl, a 3-10 membered heterocyclyl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;
- [0026] R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0027] R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0028] alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocyclyl;
- [0029] L is selected from a chemical bond, —O—, —NR#, —CR#R#, —S—, —SO— and —S(O)₂—;
- [0030] L₁ is selected from a chemical bond, —O—, —NR#, —CR#R#, —S—, —SO— and —S(O)₂—;
- [0031] E is selected from a chemical bond and —CR#R#—;

- [0032] wherein R # and R #[#] are independently selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;
- [0033] p is 0, 1, 2, 3, or 4;
- [0034] q is 0, 1, 2, 3, or 4;
- [0035] n is 0, 1, 2, 3, 4, or 5.

(X)



- [0036] wherein
- [0037] ___ represents that the point of attachment to the rest of the molecule can be located at an available point of a ring where it is located;
- [0038] Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;
- [0039] R₁ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0040] R₂ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0041] R₃ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OC₁₋₆ alkyl, —OC₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;
- [0042] R₄ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0043] R₅ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0044] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';
- [0045] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;
- [0046] R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0047] Z is CH₂, C=O, C=S or C=NH;

- [0048] R_a is selected from H, halogen, —OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;
- [0049] alternatively, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C_{4-10} cycloalkyl, a 5-8 membered heterocycl, a C_{6-10} aryl, or a 5-10 membered heteroaryl;
- [0050] R_b is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;
- [0051] alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C_{3-10} cycloalkyl, a 3-10 membered heterocycl, a C_{6-10} aryl, or a 5-10 membered heteroaryl;
- [0052] R_c is selected from H, —OH, —NH₂, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocycl, C_{6-10} aryl and 5-10 membered heteroaryl;
- [0053] R_d is selected from H, —OH, —NH₂, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocycl, C_{6-10} aryl and 5-10 membered heteroaryl;
- [0054] alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocycl;
- [0055] L is selected from a chemical bond, —O—, —NR #, —CR #R #'-, —S—, —SO— and —S(O)₂—;
- [0056] L₁ is selected from a chemical bond, —O—, —NR #, —CR #R #'-, —S—, —SO— and —S(O)₂—;
- [0057] E is selected from a chemical bond and —CR #R #'-;
- [0058] wherein R # and R #' are independently selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;
- [0059] p is 0, 1, 2, 3, or 4;
- [0060] q is 0, 1, 2, 3, or 4;
- [0061] n is 0, 1, 2, 3, 4, or 5.
- [0062] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein, and optionally a pharmaceutically acceptable excipient.
- [0063] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, which further comprises other therapeutic agent(s).
- [0064] In another aspect, the present disclosure provides a kit comprising a compound disclosed herein, other therapeutic agent(s), and a pharmaceutically acceptable carrier, adjuvant or vehicle.
- [0065] In another aspect, the present disclosure provides a use of a compound disclosed herein in the manufacture of a medicament for treating and/or preventing a disease mediated by EGFR kinase.
- [0066] In another aspect, the present disclosure provides a method of treating and/or preventing a disease mediated by EGFR kinase in a subject, comprising administering to the subject a compound disclosed herein or a composition disclosed herein.
- [0067] In another aspect, the present disclosure provides a compound disclosed herein or a composition disclosed herein, for use in treating and/or preventing a disease mediated by EGFR kinase.

[0068] In a specific embodiment, the diseases treated by the present disclosure include cancer, such as ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukemia, lymphoma, non-Hodgkin's lymphoma, gastric cancer, lung cancer, hepatocellular cancer, stomach cancer, gastrointestinal stromal tumor (GIST), thyroid cancer, cancer of bile duct, endometrial cancer, kidney cancer, anaplastic large cell lymphoma, acute myeloid leukemia (AML), multiple myeloma, melanoma, and mesothelioma.

[0069] Other objects and advantages of the present disclosure will be apparent to those skilled in the art from specific embodiments, examples and claims below.

Definition

Chemical Definitions

[0070] Definitions of specific functional groups and chemical terms are described in more detail below.

[0071] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “ C_{1-6} alkyl” is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_{1-6} , C_{1-5} , C_{1-4} , C_{1-3} , C_{1-2} , C_{2-6} , C_{2-5} , C_{2-4} , C_{2-3} , C_{3-6} , C_{3-5} , C_{3-4} , C_{4-6} , C_{4-5} and C_{5-6} alkyl.

[0072] “ C_{1-6} alkyl” refers to a radical of a straight or branched, saturated hydrocarbon group having 1 to 6 carbon atoms. In some embodiments, C_{1-4} alkyl is alternative. Examples of C_{1-6} alkyl include methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), tert-butyl (C_4), sec-butyl (C_4), iso-butyl (C_4), n-pentyl (C_5), 3-pentyl (C_5), pentyl (C_5), neopentyl (C_5), 3-methyl-2-butyl (C_5), tert-pentyl (C_5) and n-hexyl (C_6). The term “ C_{1-6} alkyl” also includes heteroalkyl, wherein one or more (e.g., 1, 2, 3 or 4) carbon atoms are substituted with heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus). Alkyl groups can be optionally substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent. Conventional abbreviations of alkyl include Me (—CH₃), Et (—CH₂CH₃), iPr (—CH(CH₃)₂), nPr (—CH₂CH₂CH₃), n-Bu (—CH₂CH₂CH₂CH₃) or i-Bu (—CH₂CH(CH₃)₂).

[0073] “ C_{2-6} alkenyl” refers to a radical of a straight or branched hydrocarbon group having 2 to 6 carbon atoms and at least one carbon-carbon double bond. In some embodiments, C_{2-4} alkenyl is alternative. Examples of C_{2-6} alkenyl include vinyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), etc. The term “ C_{2-6} alkenyl” also includes heteroalkenyl, wherein one or more (e.g., 1, 2, 3 or 4) carbon atoms are replaced by heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus). The alkenyl groups can be optionally substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0074] “ C_{2-6} alkynyl” refers to a radical of a straight or branched hydrocarbon group having 2 to 6 carbon atoms, at least one carbon-carbon triple bond and optionally one or more carbon-carbon double bonds. In some embodiments, C_{2-4} alkynyl is alternative. Examples of C_{2-6} alkynyl include, but are not limited to, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), hexynyl (C_6), etc. The term “ C_{2-6} alkynyl” also includes heteroalkynyl, wherein one or more (e.g., 1, 2, 3 or 4) carbon atoms are replaced by heteroatoms (e.g., oxygen,

sulfur, nitrogen, boron, silicon, phosphorus). The alkynyl groups can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0075] "Halo" or "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[0076] Thus, " C_{1-6} haloalkyl" refers to the above " C_{1-6} alkyl", which is substituted with one or more halogen. In some embodiments, C_{1-4} haloalkyl is yet alternative, and still alternatively C_{1-2} haloalkyl. Exemplary haloalkyl groups include, but are not limited to, $-CF_3$, $-CH_2F$, $-CHF_2$, $-CHFC_2F$, $-CH_2CHF_2$, $-CF_2CF_3$, $-CCl_3$, $-CH_2Cl$, $-CHCl_2$, 2,2,2-trifluoro-1,1-dimethyl-ethyl, and the like. The haloalkyl can be substituted at any available point of attachment, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0077] " C_{3-10} cycloalkyl" refers to a radical of an aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms. In some embodiments, C_{4-10} cycloalkyl, C_{3-7} cycloalkyl and C_{3-6} cycloalkyl are yet alternative, and still alternatively C_{5-6} cycloalkyl. The cycloalkyl also includes a ring system in which the cycloalkyl described herein is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the cycloalkyl ring, and in such case, the number of carbon atoms continues to represent the number of carbon atoms in the cycloalkyl system. Exemplary cycloalkyl groups include, but are not limited to, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), etc. The cycloalkyl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0078] "3-10 membered heterocyclyl" refers to a radical of 3-10 membered non-aromatic ring system having ring carbon atoms and 1 to 5 ring heteroatoms, wherein each of the heteroatoms is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus and silicon. In the heterocyclyl containing one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom as long as the valence permits. In some embodiments, 3-7 membered heterocyclyl is alternative, which is a radical of 3-7 membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms. 3-6 membered heterocyclyl is alternative, which is a radical of 3-6 membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. 5-8 membered heterocyclyl is alternative, which is a radical of 5-8 membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. 5-6 membered heterocyclyl is yet alternative, which is a radical of 5-6 membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. The heterocyclyl also includes a ring system wherein the heterocyclyl described above is fused with one or more cycloalkyl groups, wherein the point of attachment is on the cycloalkyl ring, or the heterocyclyl described above is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring; and in such cases, the number of ring members continues to represent the number of ring members in the heterocyclyl ring system. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, but are not limited to, aziridinyl, oxiranyl and

thiorenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, but are not limited to, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothienyl, pyrrolidinyl, dihydropyrrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, but are not limited to, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, but are not limited to, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, but are not limited to, piperidyl, tetrahydropyranyl, dihydropyridyl and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, but are not limited to, piperazinyl, morpholinyl, dithianyl and dioxanyl. Exemplary 6-membered heterocyclyl groups containing three heteroatoms include, but are not limited to, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, but are not limited to, azepanyl, oxepanyl and thiepanyl. Exemplary 5-membered heterocyclyl groups fused with a C_6 aryl (also referred as 5,6-bicyclic heterocyclyl herein) include, but are not limited to, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, benzoxazolinonyl, etc. Exemplary 6-membered heterocyclyl groups fused with a C_6 aryl (also referred as 6,6-bicyclic heterocyclyl herein) include, but are not limited to, tetrahydroquinolinyl, tetrahydroisoquinolinyl, etc. The heterocyclyl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0079] " C_{6-10} aryl" refers to a radical of monocyclic or polycyclic (e.g., bicyclic) $4n+2$ aromatic ring system having 6-10 ring carbon atoms and zero heteroatoms (e.g., having 6 or 10 shared π electrons in a cyclic array). In some embodiments, the aryl group has six ring carbon atoms (" C_6 aryl"; for example, phenyl). In some embodiments, the aryl group has ten ring carbon atoms (" C_{10} aryl"; for example, naphthyl, e.g., 1-naphthyl and 2-naphthyl). The aryl group also includes a ring system in which the aryl ring described above is fused with one or more cycloalkyl or heterocyclyl groups, and the point of attachment is on the aryl ring, in which case the number of carbon atoms continues to represent the number of carbon atoms in the aryl ring system. The aryl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0080] "5-14 membered heteroaryl" refers to a radical of 5-14 membered monocyclic or bicyclic $4n+2$ aromatic ring system (e.g., having 6, 10 or 14 shared π electrons in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In the heteroaryl group containing one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom as long as the valence permits. Heteroaryl bicyclic systems may include one or more heteroatoms in one or two rings. Heteroaryl also includes ring systems wherein the heteroaryl ring described above is fused with one or more cycloalkyl or heterocyclyl groups, and the point of attachment is on the heteroaryl ring. In such case, the number the carbon atoms continues to represent the number of carbon atoms in the heteroaryl ring system. In some embodiments, 5-10 membered heteroaryl

groups are alternative, which are radicals of 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring systems having ring carbon atoms and 1-4 ring heteroatoms. In other embodiments, 5-6 membered heteroaryl groups are yet alternative, which are radicals of 5-6 membered monocyclic or bicyclic 4n+2 aromatic ring systems having ring carbon atoms and 1-4 ring heteroatoms. Exemplary 5-membered heteroaryl groups containing one heteroatom include, but are not limited to, pyrrolyl, furyl and thienyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, but are not limited to, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, but are not limited to, triazolyl, oxadiazolyl (such as, 1,2,4-oxadiazolyl), and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, but are not limited to, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, but are not limited to, pyridyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, but are not limited to, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, but are not limited to, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, but are not limited to, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, but are not limited to, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzoxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, indolizinyl and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, but are not limited to, naphthyridinyl, pteridinyl, quinolyl, isoquinolyl, cinnolinyl, quinoxalinyl, phthalazinyl and quinazolinyl. The heteroaryl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0081] “Oxo” represents $=\text{O}$.

[0082] Alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl as defined herein are optionally substituted groups.

[0083] Exemplary substituents on carbon atoms include, but are not limited to, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}_{\text{bb}})_3\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(\text{=O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(\text{=O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(\text{=O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(\text{=O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(\text{=O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(\text{=NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(\text{=NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(\text{=NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(\text{=NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(\text{=NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(\text{=NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(\text{=O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(\text{=O})\text{R}^{\text{aa}}$, $-\text{OS}(\text{=O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(\text{=S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(\text{=O})\text{SR}^{\text{aa}}$, $-\text{C}(\text{=S})\text{SR}^{\text{aa}}$, $-\text{SC}(\text{=O})\text{SR}^{\text{aa}}$, $-\text{SC}(\text{=O})\text{OR}^{\text{aa}}$, $-\text{SC}(\text{=O})\text{R}^{\text{aa}}$, $-\text{P}(\text{=O})_2\text{R}^{\text{aa}}$, $-\text{OP}(\text{=O})_2\text{R}^{\text{aa}}$, $-\text{P}(\text{=O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(\text{=O})(\text{R}^{\text{aa}})_2$, $-\text{P}(\text{=O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OP}(\text{=O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{P}(\text{=O})(\text{NR}^{\text{bb}})_2$, $-\text{OP}(\text{=O})(\text{NR}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{P}(\text{=O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(\text{=O})(\text{NR}^{\text{bb}})_2$, $-\text{P}(\text{=O})(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{=O})(\text{R}^{\text{cc}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl

and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 Rad groups;

[0084] or two geminal hydrogen on a carbon atom are replaced with $=\text{O}$, $=\text{S}$, $=\text{NN}(\text{R}^{\text{bb}})_2$, $=\text{NNR}^{\text{bb}}\text{C}(\text{=O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(\text{=O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$ or $=\text{NOR}^{\text{cc}}$ groups;

[0085] each of the R^{aa} is independently selected from alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, or two of the R^{aa} groups are combined to form a heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0086] each of the R^{bb} is independently selected from hydrogen, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$, $-\text{C}(\text{=O})\text{R}^{\text{aa}}$, $-\text{C}(\text{=O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(\text{=NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(\text{=NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(\text{=S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(\text{=O})\text{SR}^{\text{cc}}$, $-\text{C}(\text{=S})\text{SR}^{\text{cc}}$, $-\text{P}(\text{=O})_2\text{R}^{\text{aa}}$, $-\text{P}(\text{=O})(\text{R}^{\text{aa}})_2$, $-\text{P}(\text{=O})_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{=O})(\text{NR}^{\text{cc}})_2$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0087] each of the R^{cc} is independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, or two R^{cc} groups are combined to form a heterocyclyl or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0088] each of the R^{dd} is independently selected from halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{ee}}$, $-\text{ON}(\text{R}^{\text{ff}})_2$, $-\text{N}(\text{R}^{\text{ff}})_2$, $-\text{N}(\text{R}^{\text{ff}})_3\text{X}^-$, $-\text{N}(\text{OR}^{\text{ee}})\text{R}^{\text{ff}}$, $-\text{SH}$, $-\text{SR}^{\text{ee}}$, $-\text{SSR}^{\text{ee}}$, $-\text{C}(\text{=O})\text{R}^{\text{ee}}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{\text{ee}}$, $-\text{OC}(\text{=O})\text{R}^{\text{ee}}$, $-\text{OCO}_2\text{R}^{\text{ee}}$, $-\text{C}(\text{=O})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{OC}(\text{=O})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{NR}^{\text{ff}}\text{C}(\text{=O})\text{R}^{\text{ee}}$, $-\text{NR}^{\text{ff}}\text{CO}_2\text{R}^{\text{ee}}$, $-\text{NR}^{\text{ff}}\text{C}(\text{=O})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{C}(\text{=NR}^{\text{ff}})\text{OR}^{\text{ee}}$, $-\text{OC}(\text{=NR}^{\text{ff}})\text{R}^{\text{ee}}$, $-\text{OC}(\text{=NR}^{\text{ff}})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{NR}^{\text{ff}}\text{C}(\text{=NR}^{\text{ff}})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{NR}^{\text{ff}}\text{C}(\text{=NR}^{\text{ff}})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{NR}^{\text{ff}}\text{SO}_2\text{R}^{\text{ee}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{ff}})_2$, $-\text{SO}_2\text{R}^{\text{ee}}$, $-\text{SO}_2\text{OR}^{\text{ee}}$, $-\text{OSO}_2\text{R}^{\text{ee}}$, $-\text{S}(\text{=O})\text{R}^{\text{ee}}$, $-\text{Si}(\text{R}^{\text{ee}})_3$, $-\text{OSi}(\text{R}^{\text{ee}})_3$, $-\text{C}(\text{=S})\text{N}(\text{R}^{\text{ff}})_2$, $-\text{C}(\text{=O})\text{SR}^{\text{ee}}$, $-\text{C}(\text{=S})\text{SR}^{\text{ee}}$, $-\text{SC}(\text{=S})\text{SR}^{\text{ee}}$, $-\text{P}(\text{=O})_2\text{R}^{\text{ee}}$, $-\text{P}(\text{=O})(\text{R}^{\text{ee}})_2$, $-\text{OP}(\text{=O})(\text{R}^{\text{ee}})_2$, $-\text{OP}(\text{=O})(\text{OR}^{\text{ee}})_2$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{gg} groups, or two geminal R^{dd} substituents can be combined to form $=\text{O}$ or $=\text{S}$;

[0089] each of the R^{ee} is independently selected from alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{gg} groups;

[0090] each of the R^{ff} is independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, or two R^{ff} groups

are combined to form a heterocyclol or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclol, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{gg} groups;

[0091] each of the R^{gg} is independently selected from halogen, —CN, —NO₂, —N₃, —SO₂H, —SO₃H, —OH, —OC₁₋₆ alkyl, —ON(C₁₋₆ alkyl)₂, —N(C₁₋₆ alkyl)₂, —N(C₁₋₆ alkyl)₃⁺X⁻, —NH(C₁₋₆ alkyl)₂⁺X⁻, —NH₂(C₁₋₆ alkyl)⁺X⁻, —NH₃⁺X⁻, —N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), —N(OH)(C₁₋₆ alkyl), —NH(OH), —SH, —SC₁₋₆ alkyl, —SS(C₁₋₆ alkyl), —C(=O)(C₁₋₆ alkyl), —CO₂H, —CO₂(C₁₋₆ alkyl), —OC(=O)(C₁₋₆ alkyl), —OCO₂(C₁₋₆ alkyl), —C(=O)NH₂, —C(=O)N(C₁₋₆ alkyl)₂, —OC(=O)NH(C₁₋₆ alkyl), —NHC(=O)(C₁₋₆ alkyl), —N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), —NHCO₂(C₁₋₆ alkyl), —NHC(=O)N(C₁₋₆ alkyl)₂, —NHC(=O)NH(C₁₋₆ alkyl), —NHC(=O)NH₂, —C(=NH)O(C₁₋₆ alkyl), —OC(=NH)(C₁₋₆ alkyl), —OC(=NH)OC₁₋₆ alkyl, —C(=NH)N(C₁₋₆ alkyl)₂, —C(=NH)NH(C₁₋₆ alkyl), —C(=NH)NH₂, —OC(=NH)N(C₁₋₆ alkyl)₂, —OC(NH)NH(C₁₋₆ alkyl), —OC(NH)NH₂, —NHC(NH)N(C₁₋₆ alkyl)₂, —NHC(=NH)NH₂, —NHSO₂(C₁₋₆ alkyl), —SO₂N(C₁₋₆ alkyl)₂, —SO₂NH(C₁₋₆ alkyl), —SO₂NH₂, —SO₂C₁₋₆ alkyl, —SO₂OC₁₋₆ alkyl, —OSO₂C₁₋₆ alkyl, —SOC₁₋₆ alkyl, —Si(C₁₋₆ alkyl)₃, —OSi(C₁₋₆ alkyl)₃, —C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, —C(=O)S(C₁₋₆ alkyl), —C(=S)SC₁₋₆ alkyl, —SC(=S)SC₁₋₆ alkyl, —P(=O)₂(C₁₋₆ alkyl), —P(=O)(C₁₋₆ alkyl)₂, —OP(=O)(C₁₋₆ alkyl)₂, —OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₆-C₁₀ aryl, C₃-C₇ heterocyclol, C₅-C₁₀ heteroaryl; or two geminal R^{gg} substituents may combine to form =O or =S; wherein X⁻ is a counterion.

[0092] Exemplary substituents on nitrogen atoms include, but are not limited to, hydrogen, —OH, —OR^{aa}, —N(R_{cc})₂, —CN, —C(=O)R^{aa}, —C(=O)N(R^{cc})₂, —CO₂R^{aa}, —SO₂R^{aa}, —C(=NR^{bb})R^{aa}, —C(=NR^{cc})OR^{aa}, —C(=NR^{cc})N(R^{cc})₂, —SO₂N(R^{cc})₂, —SO₂R^{cc}, —SO₂OR^{cc}, —SOR^{aa}, —C(=S)N(R^{cc})₂, —C(=O)SR^{ee}, —C(=S)SR^{cc}, —P(=O)₂R^{aa}, —P(=O)(R^{aa})₂, —P(=O)N(R^{cc})₂, —P(=O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclol, aryl and heteroaryl, or two R^{dd} groups attached to a nitrogen atom combine to form a heterocyclol or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclol, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as described herein.

Other Definitions

[0093] The term “cancer” includes, but is not limited to, the following cancers: breast, ovary, cervix, prostate, testis, esophagus, stomach, skin, lung, bone, colon, pancreas, thyroid, biliary tract, buccal cavity and pharynx (mouth), lips, tongue, oral cavity, pharynx, small intestine, colorectal, large intestine, rectum, cancer of brain and central nervous system, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder cancer, liver cancer, kidney cancer, bone

marrow disorder, lymphatic disorder, Hodgkin’s disease, hairy cell carcinoma and leukemia.

[0094] The term “treating” as used herein relates to reversing, alleviating or inhibiting the progression or prevention of the disorders or conditions to which the term applies, or of one or more symptoms of such disorders or conditions. The noun “treatment” as used herein relates to the action of treating, which is a verb, and the latter is as just defined.

[0095] The term “pharmaceutically acceptable salt” as used herein refers to those carboxylate and amino acid addition salts of the compounds of the present disclosure, which are suitable for the contact with patients’ tissues within a reliable medical judgment, and do not produce inappropriate toxicity, irritation, allergy, etc. They are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The term includes, if possible, the zwitterionic form of the compounds of the disclosure.

[0096] The pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali metal and alkaline earth metal hydroxides or organic amines. Examples of the metals used as cations include sodium, potassium, magnesium, calcium, etc. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine.

[0097] The base addition salt of the acidic compound can be prepared by contacting the free acid form with a sufficient amount of the required base to form a salt in a conventional manner. The free acid can be regenerated by contacting the salt form with an acid in a conventional manner and then isolating the free acid. The free acid forms are somewhat different from their respective salt forms in their physical properties, such as solubility in polar solvents. But for the purposes of the present disclosure, the salts are still equivalent to their respective free acids.

[0098] The salts can be prepared from the inorganic acids, which include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogen phosphates, dihydrogen phosphates, metaphosphates, pyrophosphates, chlorides, bromides and iodides. Examples of the acids include hydrochloric acid, nitric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, etc. The representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthalate, methanesulfonate, glucoheptanate, lactobionate, lauryl sulfonate, isethionate, etc. The salts can also be prepared from the organic acids, which include aliphatic monocarboxylic and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxyalkanoic acids, alkanedioic acid, aromatic acids, aliphatic and aromatic sulfonic acids, etc. The representative salts include acetate, propionate, octanoate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methyl benzoate, dinitrobenzoate, naphthoate, besylate, tosylate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, etc. The pharmaceutically acceptable salts can include cations based on alkali metals and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, etc., as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tet-

raethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, etc. Salts of amino acids are also included, such as arginine salts, gluconates, galacturonates, etc. (for example, see Berge S. M. et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977; 66: 1-19 for reference).

[0099] "Subjects" to which administration is contemplated include, but are not limited to, humans (e.g., males or females of any age group, e.g., paediatric subjects (e.g., infants, children, adolescents) or adult subjects (e.g., young adults, middle-aged adults or older adults) and/or non-human animals, such as mammals, e.g., primates (e.g., cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats and/or dogs. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human animal. The terms "human", "patient" and "subject" can be used interchangeably herein.

[0100] "Disease," "disorder," and "condition" can be used interchangeably herein.

[0101] Unless indicated, otherwise the term "treatment" as used herein includes the effect on a subject who is suffering from a particular disease, disorder, or condition, which reduces the severity of the disease, disorder, or condition, or delays or slows the progression of the disease, disorder or condition ("therapeutic treatment"). The term also includes the effect that occurs before the subject begins to suffer from a specific disease, disorder or condition ("prophylactic treatment").

[0102] Generally, the "effective amount" of a compound refers to an amount sufficient to elicit a target biological response. As understood by those skilled in the art, the effective amount of the compound of the disclosure can vary depending on the following factors, such as the desired biological endpoint, the pharmacokinetics of the compound, the diseases being treated, the mode of administration, and the age, health status and symptoms of the subjects. The effective amount includes therapeutically effective amount and prophylactically effective amount.

[0103] Unless indicated, otherwise the "therapeutically effective amount" of the compound as used herein is an amount sufficient to provide therapeutic benefits in the course of treating a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. The therapeutically effective amount of a compound refers to the amount of the therapeutic agent that, when used alone or in combination with other therapies, provides a therapeutic benefit in the treatment of a disease, disorder or condition. The term "therapeutically effective amount" can include an amount that improves the overall treatment, reduces or avoids the symptoms or causes of the disease or condition, or enhances the therapeutic effect of other therapeutic agents.

[0104] Unless indicated, otherwise the "prophylactically effective amount" of the compound as used herein is an amount sufficient to prevent a disease, disorder or condition, or an amount sufficient to prevent one or more symptoms

associated with a disease, disorder or condition, or an amount sufficient to prevent the recurrence of a disease, disorder or condition. The prophylactically effective amount of a compound refers to the amount of a therapeutic agent that, when used alone or in combination with other agents, provides a prophylactic benefit in the prevention of a disease, disorder or condition. The term "prophylactically effective amount" can include an amount that improves the overall prevention, or an amount that enhances the prophylactic effect of other preventive agents.

[0105] "Combination" and related terms refer to the simultaneous or sequential administration of the compounds of the present disclosure and other therapeutic agents. For example, the compounds of the present disclosure can be administered simultaneously or sequentially in separate unit dosage with other therapeutic agents, or simultaneously in a single unit dosage with other therapeutic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0106] FIG. 1 is a graph showing the effects of compounds D078, Osimertinib and Brigatinib on the protein levels of EGFR^{L858R/T790M/C797S} proteins.

[0107] FIG. 2 is a graph showing the effects of compound D552 and comparative compound L527 on the protein levels of EGFR^{L858R/T790M/C797S} proteins.

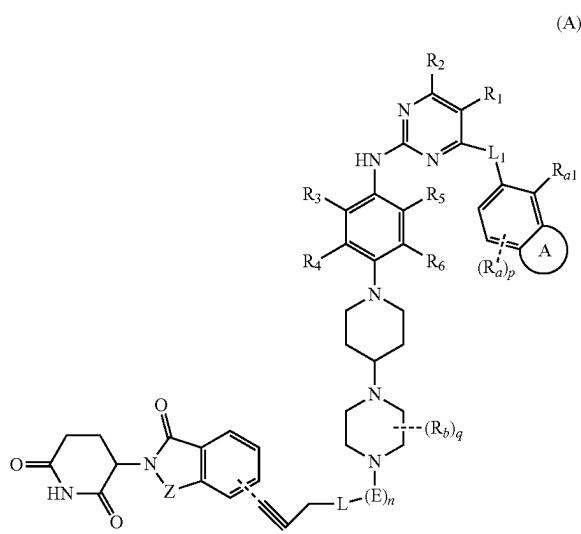
[0108] FIG. 3 is a graph showing the effects of compounds D058, D552 and Osimertinib on the protein levels of EGFR^{Del19/T790M/C797S} proteins.

DETAILED DESCRIPTION OF THE INVENTION

[0109] As used herein, the term "compound disclosed herein" refers to the following compounds of formula (A) or (X) (including sub general formulas, such as formula (I), (II), (III) etc), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug, or isotopic variant thereof, or a mixture thereof.

[0110] In the present disclosure, compounds are named using standard nomenclature. For compounds having an asymmetric center, it should be understood, unless otherwise stated, that all optical isomers and mixtures thereof are included. Furthermore, unless otherwise specified, all isomer compounds and carbon-carbon double bonds included in the present disclosure may occur in the form of Z and E. Compounds which exist in different tautomeric forms, one of which is not limited to any particular tautomer, but is intended to cover all tautomeric forms.

[0111] In one embodiment, the present disclosure relates to a compound of general formula (A) or (X), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug, or isotopic variant thereof, or a mixture thereof:



[0112] wherein

[0113] represents that the point of attachment to the rest of the molecule can be located at an available point of a ring where it is located;

[0114] Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocycl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;

[0115] R₁ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0116] R₂ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0117] R₃ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OC₁₋₆ alkyl, —OC₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

[0118] R₄ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0119] R₅ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

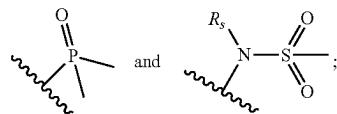
[0120] R₆ is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0121] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocycl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocycl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;

[0122] R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocycl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0123] Z is CH₂, C=O, C=S or C≡NH;

[0124] R_{a1} is selected from



[0125] R_s is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0126] R_a is selected from H, halogen, —OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;

[0127] alternatively, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C₄₋₁₀ cycloalkyl, a 5-8 membered heterocycl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;

[0128] R_b is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

[0129] alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C₃₋₁₀ cycloalkyl, a 3-10 membered heterocycl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;

[0130] R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocycl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0131] R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocycl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0132] alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocycl;

[0133] L is selected from a chemical bond, —O—, —NR #, —CR #R #-, —S—, —SO— and —S(O)₂—;

[0134] L₁ is selected from a chemical bond, —O—, —NR #, —CR #R #-, —S—, —SO— and —S(O)₂—;

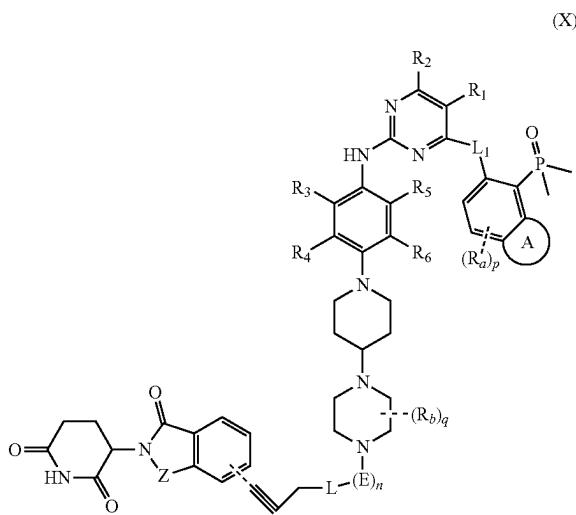
[0135] E is selected from a chemical bond and —CR #R #-,

[0136] wherein R # and R # are independently selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0137] p is 0, 1, 2, 3, or 4;

[0138] q is 0, 1, 2, 3, or 4;

[0139] n is 0, 1, 2, 3, 4, or 5.



[0140] wherein

[0141] _____ represents that the point of attachment to the rest of the molecule can be located at an available point of a ring where it is located;

[0142] Ring A is absent, or is selected from C_{4-10} cycloalkyl, 5-8 membered heterocyclyl, C_{6-10} aryl and 5-14 membered heteroaryl;

[0143] R_1 is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0144] R_2 is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0145] R_3 is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl, C_{1-6} haloalkyl, —OC C_{1-6} alkyl, —OC C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

[0146] R_4 is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0147] R_5 is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0148] R_6 is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";

[0149] wherein R, R' and R" are each independently selected from H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;

[0150] R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

[0151] Z is CH₂, C=O, C=S or C≡NH;

[0152] R_a is selected from H, halogen, —OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;

[0153] alternatively, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C_{4-10} cycloalkyl, a 5-8 membered heterocyclyl, a C_{6-10} aryl, or a 5-10 membered heteroaryl

[0154] R_b is selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

[0155] alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C_{3-10} cycloalkyl, a 3-10 membered heterocyclyl, a C_{6-10} aryl, or a 5-10 membered heteroaryl;

[0156] R_c is selected from H, —OH, —NH₂, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

[0157] R_d is selected from H, —OH, —NH₂, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

[0158] alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocyclyl;

[0159] L is selected from a chemical bond, —O—, —NR#, —CR#R#, —S—, —SO— and —S(O)₂—;

[0160] L₁ is selected from a chemical bond, —O—, —NR#, —CR#R#, —S—, —SO— and —S(O)₂—;

[0161] E is selected from a chemical bond and —CR#R#—;

[0162] wherein R# and R# are independently selected from H, halogen, —OH, —NH₂, —CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

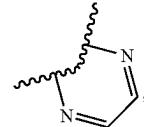
[0163] p is 0, 1, 2, 3, or 4;

[0164] q is 0, 1, 2, 3, or 4;

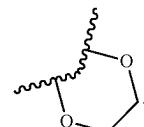
[0165] n is 0, 1, 2, 3, 4, or 5.

Ring A

[0166] In one embodiment, ring A is absent; in another embodiment, ring A is C_{4-10} cycloalkyl; in another embodiment, ring A is a 5-8 membered heterocyclyl; in another embodiment, ring A is C_{6-10} aryl; in another embodiment, ring A is a 5-14 membered heteroaryl; in another embodiment, ring A is a 5-10 membered heteroaryl; in another embodiment, ring A is a 5-6 membered heteroaryl; in another embodiment, ring A is a 5-6 membered heterocyclyl; in another embodiment, ring A is



in another embodiment, ring A is



R₁

[0167] In one embodiment, R₁ is H; in another embodiment, R₁ is halogen; in another embodiment, R₁ is —OH; in another embodiment, R₁ is —NH₂; in another embodiment,

R_1 is $-\text{CN}$; in another embodiment, R_1 is C_{1-6} alkyl; in another embodiment, R_1 is C_{1-4} alkyl; in another embodiment, R_1 is C_{1-6} haloalkyl; in another embodiment, R_1 is C_{1-4} haloalkyl; in another embodiment, R_1 is C_1 ; in another embodiment, R_1 is Br ; in another embodiment, R_1 is $-\text{CF}_3$.

R_2

[0168] In one embodiment, R_2 is H ; in another embodiment, R_2 is halogen; in another embodiment, R_2 is $-\text{OH}$; in another embodiment, R_2 is $-\text{NH}_2$; in another embodiment, R_2 is $-\text{CN}$; in another embodiment, R_2 is C_{1-6} alkyl; in another embodiment, R_2 is C_{1-4} alkyl; in another embodiment, R_2 is C_{1-6} haloalkyl; in another embodiment, R_2 is C_{1-4} haloalkyl.

R_3

[0169] In one embodiment, R_3 is H ; in another embodiment, R_3 is halogen; in another embodiment, R_3 is $-\text{OH}$; in another embodiment, R_3 is $-\text{NH}_2$; in another embodiment, R_3 is $-\text{CN}$; in another embodiment, R_3 is C_{1-6} alkyl; in another embodiment, R_3 is C_{1-4} alkyl; in another embodiment, R_3 is C_{1-6} haloalkyl; in another embodiment, R_3 is C_{1-4} haloalkyl; in another embodiment, R_3 is $-\text{OC}_{1-6}$ alkyl; in another embodiment, R_3 is $-\text{OC}_{1-4}$ alkyl; in another embodiment, R_3 is $-\text{OC}_{1-6}$ haloalkyl; in another embodiment, R_3 is $-\text{OC}_{1-4}$ haloalkyl; in another embodiment, R_3 is C_{2-6} alkenyl; in another embodiment, R_3 is C_{2-6} alkynyl.

[0170] In one embodiment, R_3 is F ; in another embodiment, R_3 is Cl ; in another embodiment, R_3 is $-\text{OCH}_3$; in another embodiment, R_3 is $-\text{OCF}_3$.

R_4

[0171] In one embodiment, R_4 is H ; in another embodiment, R_4 is halogen; in another embodiment, R_4 is $-\text{OH}$; in another embodiment, R_4 is $-\text{NH}_2$; in another embodiment, R_4 is $-\text{CN}$; in another embodiment, R_4 is C_{1-6} alkyl; in another embodiment, R_4 is C_{1-4} alkyl; in another embodiment, R_4 is C_{1-6} haloalkyl; in another embodiment, R_4 is C_{1-4} haloalkyl.

R_5

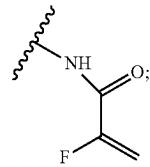
[0172] In one embodiment, R_5 is H ; in another embodiment, R_5 is halogen; in another embodiment, R_5 is $-\text{OH}$; in another embodiment, R_5 is $-\text{NH}_2$; in another embodiment, R_5 is $-\text{CN}$; in another embodiment, R_5 is C_{1-6} alkyl; in another embodiment, R_5 is C_{1-4} alkyl; in another embodiment, R_5 is C_{1-6} haloalkyl; in another embodiment, R_5 is C_{1-4} haloalkyl.

R_6

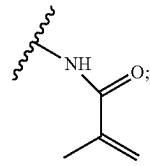
[0173] In one embodiment, R_6 is C_{1-6} alkyl; in another embodiment, R_6 is C_{1-6} haloalkyl; in another embodiment, R_6 is $-\text{NH}-\text{C}(\text{O})-\text{CR}=\text{CR}'\text{R}''$; in another embodiment, R_6 is $-\text{NH}-\text{C}(\text{O})-\text{C}\equiv\text{CR}'$.

[0174] In one embodiment, R_6 is

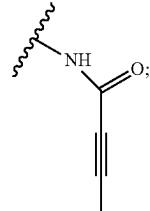
in another embodiment, R_6 is



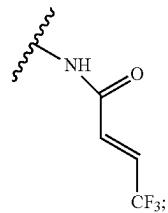
in another embodiment, R_6 is



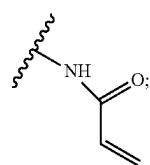
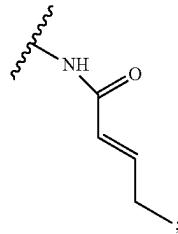
in another embodiment, R_6 is



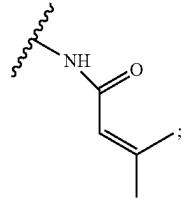
in another embodiment, R_6 is



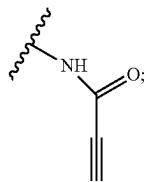
in another embodiment, R_6 is



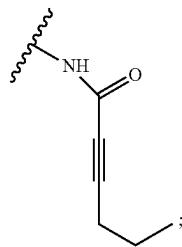
in another embodiment, R₆ is



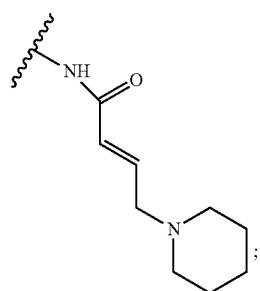
in another embodiment, R₆ is



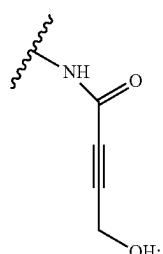
in another embodiment, R₆ is



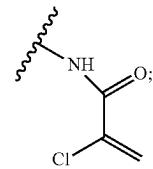
in another embodiment, R₆ is



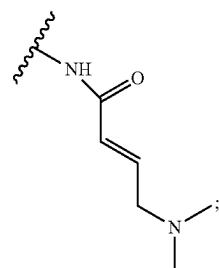
in another embodiment, R₆ is



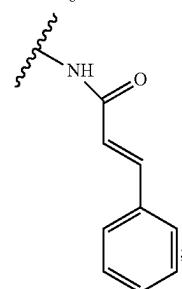
in another embodiment, R₆ is



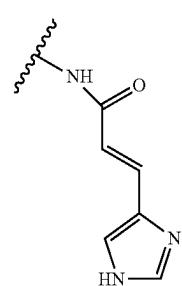
in another embodiment, R₆ is



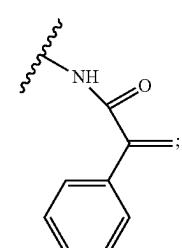
in another embodiment, R₆ is



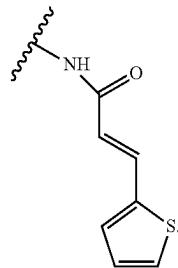
in another embodiment, R₆ is



in another embodiment, R₆ is



in another embodiment, R₆ is



R

[0175] In one embodiment, R is H; in another embodiment, R is halogen; in another embodiment, R is F; in another embodiment, R is optionally substituted C₁₋₆ alkyl; in another embodiment, R is optionally substituted C₁₋₄ alkyl; in another embodiment, R is optionally substituted C₁₋₆ haloalkyl; in another embodiment, R is optionally substituted C₁₋₄ haloalkyl; in another embodiment, R is optionally substituted C₂₋₆ alkenyl; in another embodiment, R is optionally substituted C₂₋₆ alkynyl; in another embodiment, R is optionally substituted C₃₋₁₀ cycloalkyl; in another embodiment, R is optionally substituted C₃₋₇ cycloalkyl; in another embodiment, R is optionally substituted 3-10 membered heterocyclyl; in another embodiment, R is optionally substituted 3-7 membered heterocyclyl; in another embodiment, R is optionally substituted 5-6 membered heterocyclyl; in another embodiment, R is optionally substituted C₆₋₁₀ aryl; in another embodiment, R is an optionally substituted 5-10 membered heteroaryl; in another embodiment, R is an optionally substituted 5-6 membered heteroaryl.

[0176] In one embodiment, R is unsubstituted; in another embodiment, R is substituted with 1 R*; in another embodiment, R is substituted with 2 R*; in another embodiment, R is substituted with 3 R*; in another embodiment, R is substituted with 4 R*; in another embodiment, R is substituted with 5 R*; as long as the valence permits.

R'

[0177] In one embodiment, R' is H; in another embodiment, R' is halogen; in another embodiment, R' is F; in another embodiment, R' is optionally substituted C₁₋₆ alkyl; in another embodiment, R' is optionally substituted C₁₋₄ alkyl; in another embodiment, R' is optionally substituted C₁₋₆ haloalkyl; in another embodiment, R' is optionally substituted C₁₋₄ haloalkyl; in another embodiment, R' is optionally substituted C₂₋₆ alkenyl; in another embodiment, R' is optionally substituted C₂₋₆ alkynyl; in another embodiment, R' is optionally substituted C₃₋₁₀ cycloalkyl; in another embodiment, R' is optionally substituted C₃₋₇ cycloalkyl; in another embodiment, R' is an optionally substituted 3-10 membered heterocyclyl; in another embodiment, R' is an optionally substituted 3-7 membered heterocyclyl; in another embodiment, R' is an optionally substituted 5-6 membered heterocyclyl; in another embodiment, R' is an optionally substituted C₆₋₁₀ aryl; In another specific

tuted 5-6 membered heterocyclyl; in another embodiment, R' is an optionally substituted C₆₋₁₀ aryl; in another embodiment, R' is an optionally substituted 5-10 membered heteroaryl; in another embodiment, R' is an optionally substituted 5-6 membered heteroaryl.

[0178] In one embodiment, R' is unsubstituted; in another embodiment, R' is substituted with 1 R*; in another embodiment, R' is substituted with 2 R*; in another embodiment, R' is substituted with 3 R*; in another embodiment, R' is substituted with 4 R*; in another embodiment, R' is substituted with 5 R*; as long as the valence permits.

R"

[0179] In one embodiment, R" is H; in another embodiment, R" is halogen; in another embodiment, R" is F; in another embodiment, R" is optionally substituted C₁₋₆ alkyl; in another embodiment, R" is optionally substituted C₁₋₄ alkyl; in another embodiment, R" is optionally substituted C₁₋₆ haloalkyl; in another embodiment, R" is optionally substituted C₁₋₄ haloalkyl; in another embodiment, R" is optionally substituted C₂₋₆ alkenyl; in another embodiment, R" is optionally substituted C₂₋₆ alkynyl; in another embodiment, R" is optionally substituted C₃₋₁₀ cycloalkyl; in another embodiment, R" is optionally substituted C₃₋₇ cycloalkyl; in another embodiment, R" is an optionally substituted 3-10 membered heterocyclyl; in another embodiment, R" is an optionally substituted 3-7 membered heterocyclyl; in another embodiment, R" is an optionally substituted 5-6 membered heterocyclyl; in another embodiment, R" is an optionally substituted C₆₋₁₀ aryl; in another embodiment, R" is an optionally substituted 5-10 membered heteroaryl; in another embodiment, R" is an optionally substituted 5-6 membered heteroaryl.

[0180] In one embodiment, R" is unsubstituted; in another embodiment, R" is substituted with 1 R*; in another embodiment, R" is substituted with 2 R*; in another embodiment, R" is substituted with 3 R*; in another embodiment, R" is substituted with 4 R*; in another embodiment, R" is substituted with 5 R*; as long as the valence permits.

R*

[0181] In one embodiment, R* is H; in another embodiment, R* is halogen; in another embodiment, R* is —OR_c; in another embodiment, R* is —OH; in another embodiment, R* is —NH₂; in another embodiment, R* is —CN; in another embodiment, R* is C₁₋₆ alkyl; in another embodiment, R* is C₁₋₄ alkyl; in another embodiment, R* is C₁₋₆ haloalkyl; in another embodiment, R* is C₁₋₄ haloalkyl; in another embodiment, R* is C₂₋₆ alkenyl; in another embodiment, R* is C₃₋₁₀ cycloalkyl; in another embodiment, R* is C₂₋₆ alkynyl; in another embodiment, R* is C₃₋₇ cycloalkyl; in another embodiment, R* is 3-10 membered heterocyclyl; in another embodiment, R* is 5-6 membered heterocyclyl; in another embodiment, R* is C₆₋₁₀ aryl; In another specific

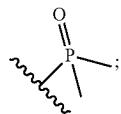
embodiment, R^* is a 5-10 membered heteroaryl; in another specific embodiment, R^* is a 5-6 membered heteroaryl.

Z

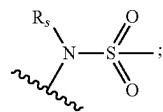
[0182] In one embodiment, Z is CH_2 ; in another embodiment, Z is $\text{C}=\text{O}$; in another embodiment, Z is $\text{C}=\text{S}$; in another embodiment, Z is $\text{C}=\text{NH}$.

R_{a1}

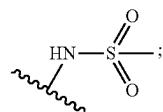
[0183] In one specific embodiment, R_{a1} is



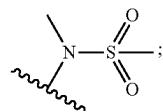
in another specific embodiment, R_{a1} is



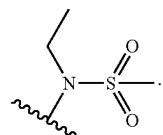
in another specific embodiment, R_{a1} is



in another specific embodiment, R_{a1} is



in another specific embodiment, R_{a1} is



R_a

[0184] In one embodiment, R_a is H; in another embodiment, R_a is halogen; in another embodiment, R_a is $-\text{OH}$; in another embodiment, R_a is C_{1-6} alkyl; in another embodiment, R_a is C_{1-4} alkyl; in another embodiment, R_a is C_{1-6} haloalkyl; in another embodiment, R_a is C_{1-4} haloalkyl; in another embodiment, R_a is C_{2-6} alkenyl; in another embodiment, R_a is C_{2-6} alkynyl; in another embodiment, R_a is $-\text{CN}$; in another embodiment, R_a is $-\text{NR}_c\text{R}_d$; in another embodiment, R_a is $-\text{NH}(\text{CH}_2)_{0-5}\text{R}_c$; in another embodiment, R_d is $-\text{NHC(O)(CH}_2)_{0-5}\text{R}_c$.

[0185] In one embodiment, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C_{4-10} cycloalkyl; in one embodiment, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C_{3-7} cycloalkyl; in one embodiment, two R_a on the same carbon atom or on different carbon atoms are taken together to form a 5-8 membered heterocycl; in one

embodiment, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C_{6-10} aryl; in one embodiment, two R_a on the same carbon atom or on different carbon atoms are taken together to form a 5-10 membered heteroaryl.

R_b

[0186] In one embodiment, R_b is H; in another embodiment, R_b is halogen; in another embodiment, R_b is $-\text{OH}$; in another embodiment, R_b is $-\text{NH}_2$; in another embodiment, R_b is $-\text{CN}$; in another embodiment, R_b is C_{1-6} alkyl; in another embodiment, R_b is C_{1-4} alkyl; in another embodiment, R_b is C_{1-6} haloalkyl; in another embodiment, R_b is C_{1-4} haloalkyl; in another embodiment, R_b is C_{2-6} alkenyl; in another embodiment, R_b is C_{2-6} alkynyl; in another embodiment, R_b is $-\text{CH}_3$.

[0187] In one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form C_{3-10} cycloalkyl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form C_{3-7} cycloalkyl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form 3-10 membered heterocycl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form 5-8 membered heterocycl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form 5-6 membered heterocycl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form C_{6-10} aryl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form 5-10 membered heteroaryl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form 5-6 membered heteroaryl; in one embodiment, two R_b on the same carbon atom or on different carbon atoms are taken together to form C_{1-6} alkyl; in another embodiment, R_b is C_{1-4} alkyl; in another embodiment, R_b is C_{1-6} haloalkyl; in another embodiment, R_b is C_{1-4} haloalkyl; in another embodiment, R_b is C_{3-10} cycloalkyl; in another embodiment, R_b is C_{3-7} cycloalkyl; in another embodiment, R_b is 3-10 membered heterocycl; in another embodiment, R_b is 5-6 membered heterocycl; in another embodiment, R_b is C_{6-10} aryl; in another embodiment, R_b is 5-10 membered heteroaryl; in another embodiment, R_b is 5-6 membered heteroaryl.

R_c and R_d

[0188] In one embodiment, R_c is H; in another embodiment, R_c is $-\text{OH}$; in another embodiment, R_c is $-\text{NH}_2$; in another embodiment, R_c is halogen; in another embodiment, R_c is C_{1-6} alkyl; in another embodiment, R_c is C_{1-4} alkyl; in another embodiment, R_c is C_{1-6} haloalkyl; in another embodiment, R_c is C_{1-4} haloalkyl; in another embodiment, R_c is C_{3-10} cycloalkyl; in another embodiment, R_c is C_{3-7} cycloalkyl; in another embodiment, R_c is 3-10 membered heterocycl; in another embodiment, R_c is 5-6 membered heterocycl; in another embodiment, R_c is C_{6-10} aryl; in another embodiment, R_c is 5-10 membered heteroaryl; in another embodiment, R_c is 5-6 membered heteroaryl.

[0189] In one embodiment, R_d is H; in another embodiment, R_d is $-\text{OH}$; in another embodiment, R_d is $-\text{NH}_2$; in another embodiment, R_d is halogen; in another embodiment, R_d is C_{1-6} alkyl; in another embodiment, R_d is C_{1-4} alkyl; in another embodiment, R_d is C_{1-6} haloalkyl; in another embodiment, R_d is C_{1-4} haloalkyl; in another embodiment, R_d is C_{3-10} cycloalkyl; in another embodiment, R_d is C_{3-7} cycloalkyl; in another embodiment, R_d is 3-10 membered heterocycl; in another embodiment, R_d is 5-6 membered heterocycl; in another embodiment, R_d is C_{6-10} aryl; in another embodiment, R_d is 5-10 membered heteroaryl; in another embodiment, R_d is 5-6 membered heteroaryl.

[0190] In one embodiment, R_c and R_d are taken together with the N atom to which they are attached to form a 3-10

membered heterocycl; in another embodiment, R_c and R_d are taken together with the N atom to which they are attached to form a 3-7 membered heterocycl; in another embodiment, R_c and R_d are taken together with the N atom to which they are attached to form a 5-6 membered heterocycl.

L

[0191] In one embodiment, L is a chemical bond; in another embodiment, L is —O—; in another embodiment, L is —NR #—; in another embodiment, L is —CR #R #—; in another embodiment, L is —S—; in another embodiment, L is —SO—; in another embodiment, L is —S(O)₂—.

L₁

[0192] In one embodiment, L₁ is a chemical bond; in another embodiment, L₁ is —O—; in another embodiment, L₁ is —NR #—; in another embodiment, L₁ is —CR #R #—; in another embodiment, L₁ is —S—; in another embodiment, L₁ is —SO—; in another embodiment, L₁ is —S(O)₂—.

E

[0193] In one embodiment, E is a chemical bond; in another embodiment, E is —CR #R #—.

R # and R #'

[0194] In one embodiment, R # is H; in another embodiment, R # is halogen; in another embodiment, R # is —OH; in another embodiment, R # is —NH₂; in another embodiment, R # is —CN; in another embodiment, R # is C₁₋₆ alkyl; in another embodiment, R # is C₁₋₄ alkyl; in another embodiment, R # is C₁₋₆ haloalkyl; in another embodiment, R # is C₁₋₄ haloalkyl; in another embodiment, R # is C₂₋₆ alkenyl; in another embodiment, R # is C₂₋₆ alkynyl.

[0195] In one embodiment, R # is H; in another embodiment, R # is halogen; in another embodiment, R # is —OH; in another embodiment, R # is —NH₂; in another embodiment,

R # is —CN; in another embodiment, R # is C₁₋₆ alkyl; in another embodiment, R # is C₁₋₄ alkyl; in another embodiment, R # is C₁₋₆ haloalkyl; in another embodiment, R # is C₁₋₄ haloalkyl; in another embodiment, R # is C₂₋₆ alkenyl; in another embodiment, R # is C₂₋₆ alkynyl.

p

[0196] In one embodiment, p is 0; in another embodiment, p is 1; in another embodiment, p is 2; in another embodiment, p is 3; in another embodiment, p is 4; in another embodiment, p is 5.

q

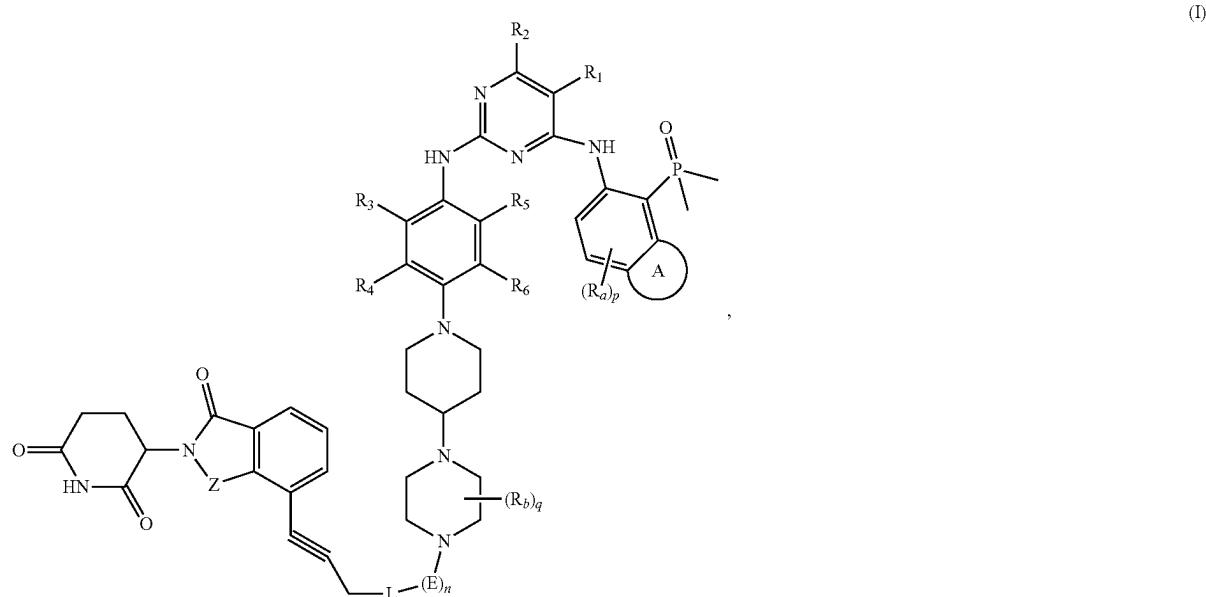
[0197] In one embodiment, q is 0; in another embodiment, q is 1; in another embodiment, q is 2; in another embodiment, q is 3; in another embodiment, q is 4; in another embodiment, q is 5.

n

[0198] In one embodiment, n is 0; in another embodiment, n is 1; in another embodiment, n is 2; in another embodiment, n is 3; in another embodiment, n is 4; in another embodiment, n is 5.

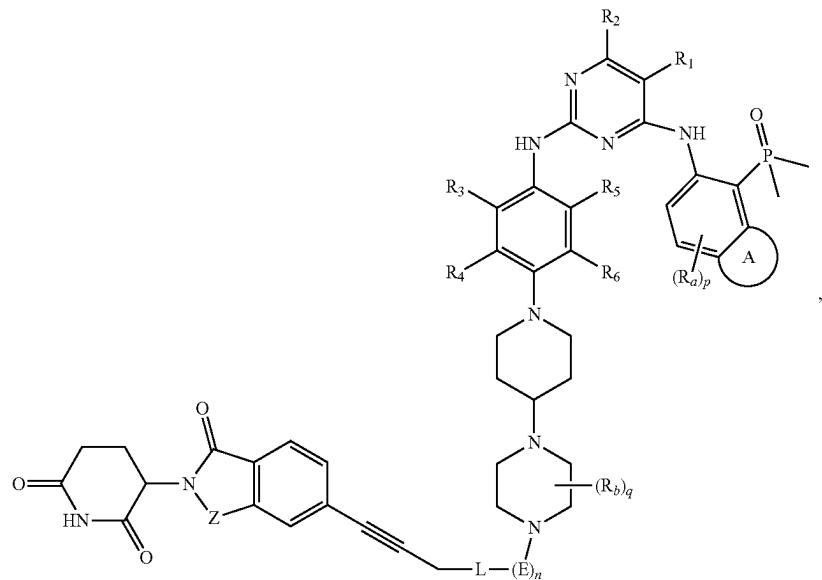
[0199] Any technical solution in any of the above specific embodiments or any combination thereof can be combined with any technical solution in other specific embodiments or any combination thereof. For example, any technical solution or any combination thereof of Ring A can be combined with any technical solution or any combination thereof of L, L₁, E, R₁-R₆, R_{a1}, R_s, R_a, R_b, p, q and n, etc. The present disclosure is intended to include all combinations of these technical solutions, which are not listed one by one due to space limitations.

[0200] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (X), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has the following general structure:

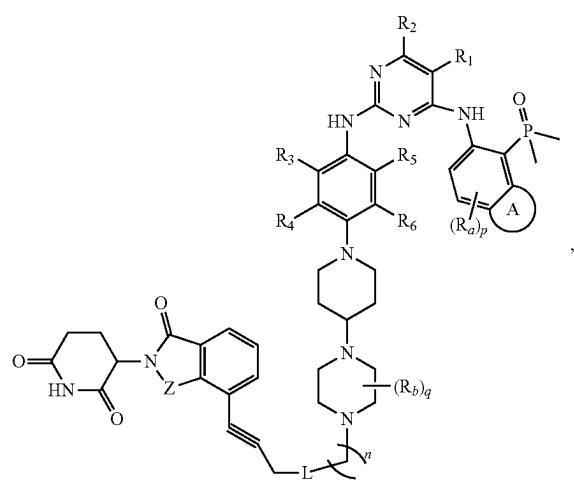


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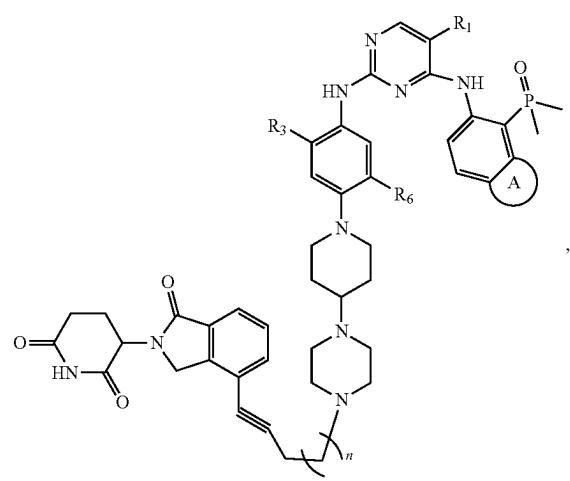
(II)



(III)

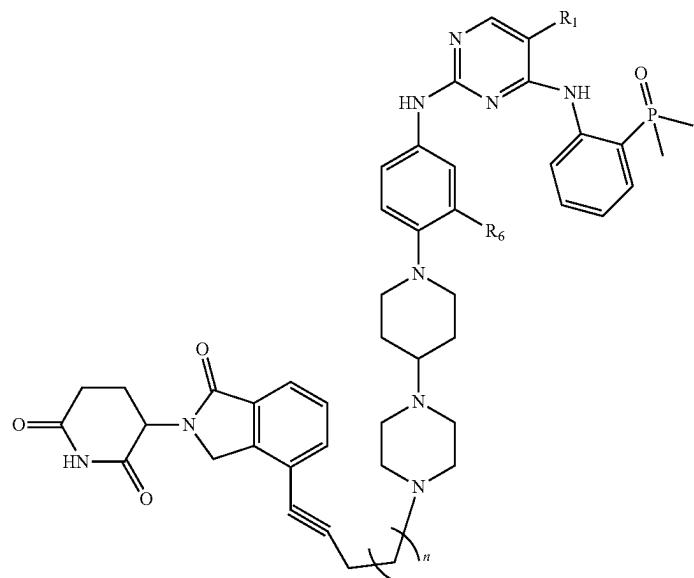


(IV)

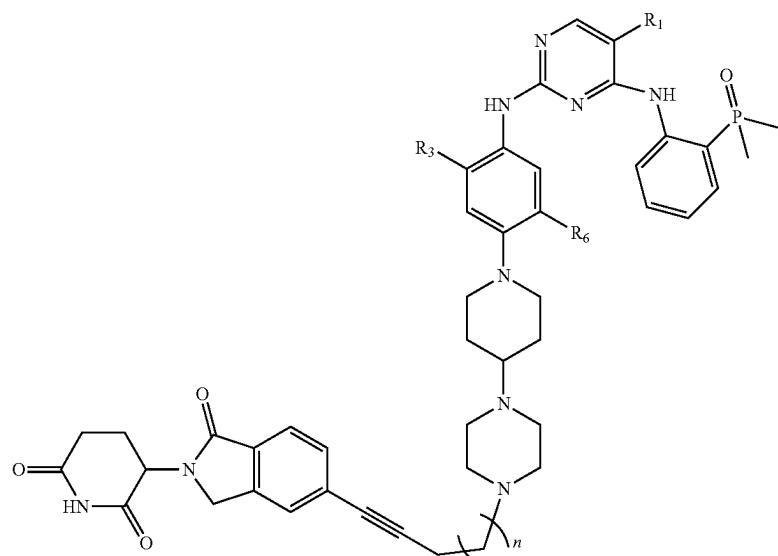


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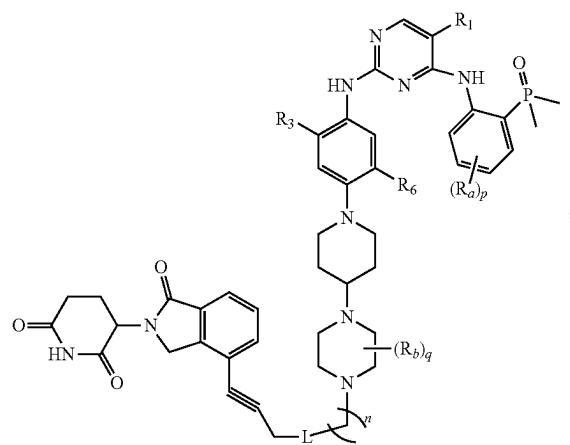


(VI)

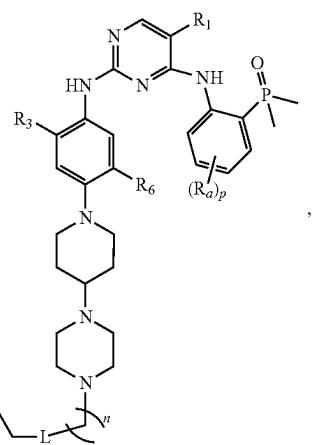


(VII)

(VIII)

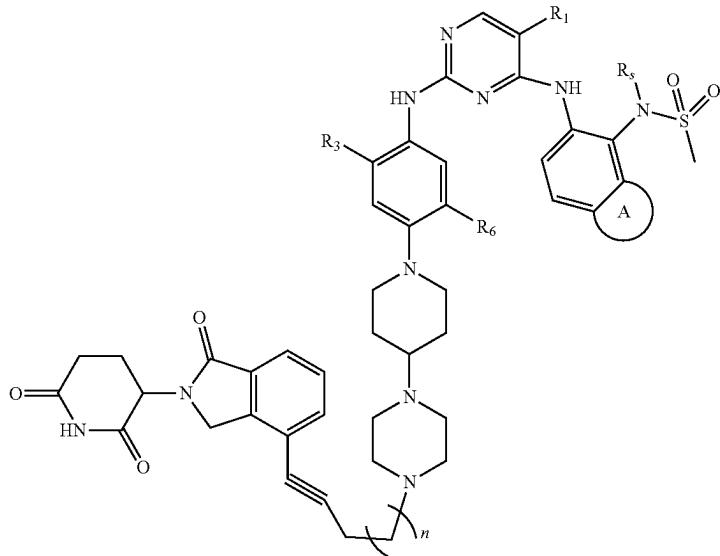


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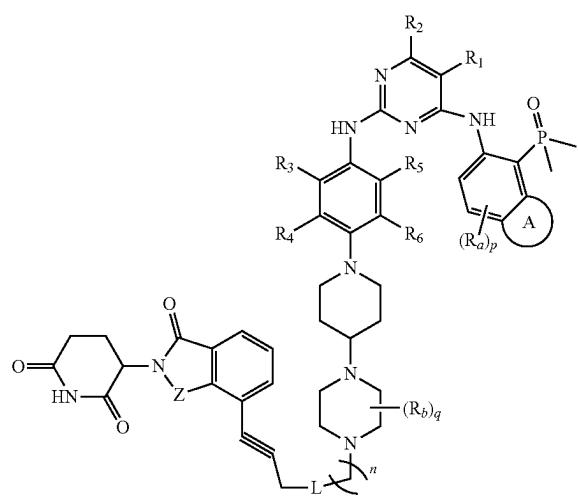
(IX)



[0201] wherein each group is as defined above.

[0202] In a more specific embodiment, the present disclosure provides a compound of formula (III), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof.

(III)



[0203] wherein

[0204] Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0205] R₁ is selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0206] R₂ is selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0207] R₃ is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OC₁₋₆ alkyl, —OC₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

[0208] R₄ is selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0209] R₅ is selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0210] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0211] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;

[0212] R* is selected from H, halogen, —OR, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0213] Z is CH₂, C=O, C=S or C=NH;

[0214] R_a is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;

[0215] R_b is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

[0216] alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C₃₋₁₀ cycloalkyl or a 3-10 membered heterocyclyl;

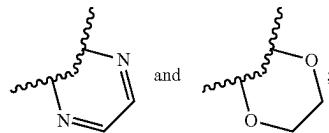
[0217] R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0218] R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

- [0219] alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocyclyl;
- [0220] L is selected from a chemical bond, —O—, —NR #, —S—, —SO— and —S(O)₂—;
- [0221] wherein R # is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;
- [0222] p is 0, 1, 2, 3, or 4;
- [0223] q is 0, 1, 2, 3, or 4;
- [0224] n is 0, 1, 2, 3, 4, or 5.
- [0225] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (III), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:
- [0226] Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0227] R₁ is selected from H, halogen and C₁₋₆ haloalkyl;
- [0228] R₂ is selected from H and halogen;
- [0229] R₃ is selected from H, halogen, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl;
- [0230] R₄ is selected from H and halogen;
- [0231] R₅ is selected from H and halogen;
- [0232] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0233] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2 or 3 R*, as long as the valence permits;
- [0234] R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl;
- [0235] Z is selected from CH₂, C=O and C=S;
- [0236] R_a is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;
- [0237] R_b is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0238] alternatively, two R_b on the same carbon atom are taken together to form a C₃₋₇ cycloalkyl or a 5-6 membered heterocyclyl;
- [0239] R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0240] R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;
- [0241] or R_c and R_d are taken together with the N atom to which they are attached to form 3-7 membered heterocyclyl;
- [0242] L is selected from a chemical bond, —O—, —S— and —NR #;
- [0243] wherein R # is selected from H, halogen, C₁₋₄ alkyl and C₁₋₄ haloalkyl;
- [0244] p is 0, 1, 2 or 3;
- [0245] q is 0, 1, 2 or 3;
- [0246] n is 1, 2, 3, 4 or 5.
- [0247] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (III), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:
- [0248] Ring A is absent, or ring A is selected from a 5-6 membered heteroaryl and a 5-6 membered heterocyclyl;
- [0249] R₁ is selected from halogen and C₁₋₄ haloalkyl;
- [0250] R₂ is H;
- [0251] R₃ is selected from H, halogen, —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl;
- [0252] R₄ is H;
- [0253] R₅ is H;
- [0254] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0255] wherein R is selected from H, halogen, C₁₋₄ alkyl and C₆₋₁₀ aryl, wherein the C₁₋₄ alkyl and C₆₋₁₀ aryl are each optionally substituted with 0, 1, or 2 R*;
- [0256] R' and R" are each independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl, wherein the C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl are each optionally substituted with 0, 1 or 2 R*, as long as the valence permits;
- [0257] R* is selected from H, halogen, —OR_c, —NR_cR_d, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl;
- [0258] Z is CH₂ or C=O;
- [0259] R_a is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c, alternatively H, halogen, —NR_cR_d and —NH(CH₂)₀₋₅R_c, still alternatively H and halogen;
- [0260] R_b is selected from H and C₁₋₄ alkyl;
- [0261] alternatively, two R_b on the same carbon atom are taken together to form a C₃₋₇ cycloalkyl group;
- [0262] R_c is selected from H, —OH, —NH₂, halogen, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, alternatively H, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl and 3-10 membered heterocyclyl, still alternatively H and C₁₋₄ alkyl;
- [0263] R_d is selected from H, —OH, —NH₂, halogen, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, alternatively H, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl and 3-10 membered heterocyclyl, still alternatively H and C₁₋₄ alkyl;
- [0264] or R_c and R_d are taken together with the N atom to which they are attached to form 5-6 membered heterocyclyl;
- [0265] L is selected from a chemical bond and —O—;
- [0266] p is 0, 1, or 2;
- [0267] q is 0, 1, or 2;
- [0268] n is 1, 2, 3, 4 or 5.

[0269] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (III), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0270] Ring A is absent, or Ring A is selected from



[0271] R₁ is selected from Cl, Br and —CF₃;

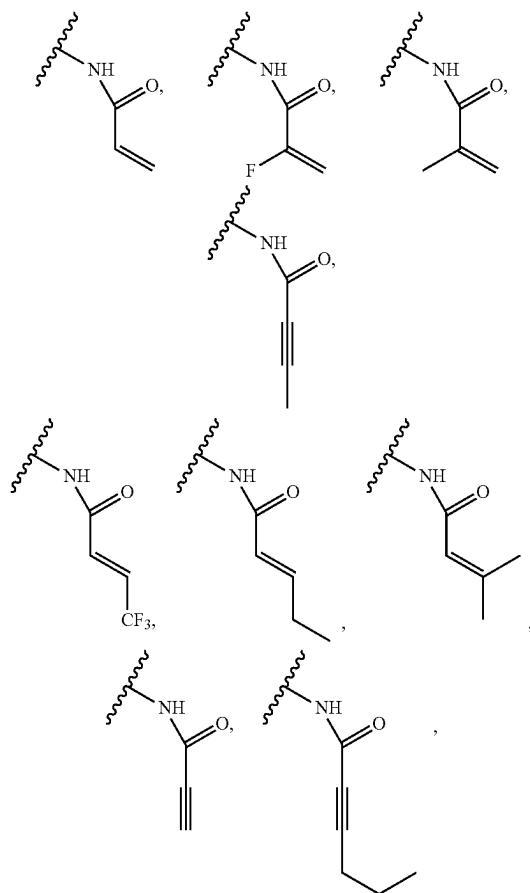
[0272] R₂ is H;

[0273] R₃ is selected from H, F, Cl, —OCH₃ and —OCF₃; alternatively, R₃ is selected from H, F, —OCH₃ and —OCF₃;

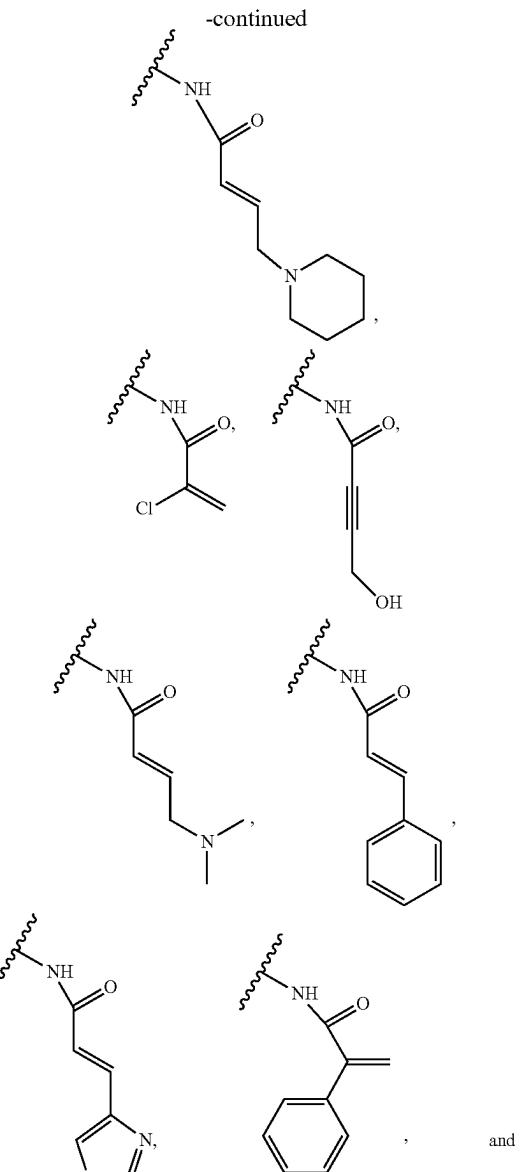
[0274] R₄ is H;

[0275] R₅ is H;

[0276] R₆ is selected from



-continued



and

[0277] Z is CH₂ or C=O;

[0278] R_a is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c, alternatively H, F, Cl, —NR_cR_d and —NH(CH₂)₀₋₅R_c, still alternatively H and F;

[0279] R_b is selected from H and —CH₃;

[0280] alternatively, two R_b on the same carbon atom are taken together to form a cyclopropyl group;

[0281] R_c is selected from H, —OH, —NH₂, halogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl, alternatively H, C₁₋₄ alkyl, C₃₋₇ cycloalkyl and 5-6 membered heterocyclyl, still alternatively H and C₁₋₄ alkyl;

[0282] R_d is selected from H, —OH, —NH₂, halogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl, alternatively H, C₁₋₄ alkyl, C₃₋₇ cycloalkyl and 5-6 membered heterocyclyl, still alternatively H and C₁₋₄ alkyl;

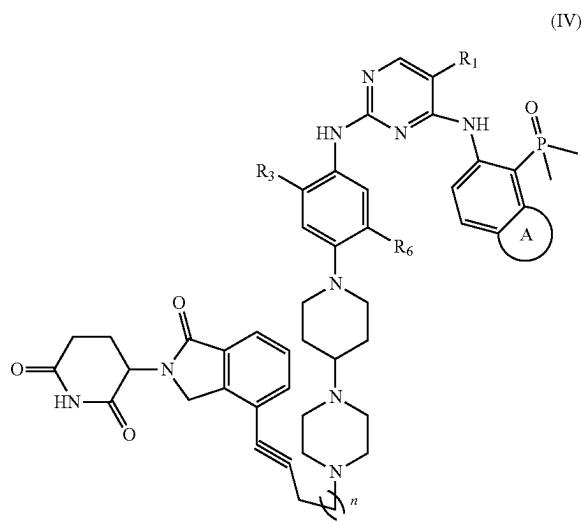
[0283] L is selected from a chemical bond and —O—;

[0284] p is 0 or 1;

[0285] q is 0, 1, or 2;

[0286] n is 2, 3 or 4.

[0287] In a more specific embodiment, the present disclosure provides a compound of formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof:



[0288] wherein

[0289] Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

[0290] R₁ is selected from H, halogen and C₁₋₄ haloalkyl, alternatively H and halogen;

[0291] R₃ is selected from H, halogen, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively H and —OC₁₋₆ alkyl;

[0292] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0293] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-10 membered heterocyclyl and C₃₋₁₀ cycloalkyl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-10 membered heterocyclyl and C₃₋₁₀ cycloalkyl are each optionally substituted with 0, 1, 2 or 3 R*;

[0294] R* is selected from H, halogen, —OH, —NH₂, —CN, 3-10 membered heterocyclyl, and C₃₋₁₀ cycloalkyl;

[0295] n is 1, 2, 3 or 4.

[0296] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0297] Ring A is absent, or Ring A is selected from 5-10 membered heteroaryl and 5-8 membered heterocyclyl;

[0298] R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen;

[0299] R₃ is selected from H, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively H and —OC₁₋₆ alkyl;

[0300] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0301] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl and C₁₋₆ haloalkyl are each optionally substituted with 0, 1 or 2 R*;

[0302] R* is selected from H, halogen, —OH and 3-10 membered heterocyclyl;

[0303] n is 1, 2, 3 or 4.

[0304] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0305] Ring A is absent, or Ring A is selected from 5-6 membered heteroaryl and 5-6 membered heterocyclyl;

[0306] R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen;

[0307] R₃ is selected from H, —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl, alternatively H and —OC₁₋₄ alkyl;

[0308] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0309] wherein R is selected from H, halogen and C₁₋₄ alkyl;

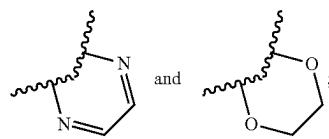
[0310] R' and R" are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl, wherein the C₁₋₄ alkyl and C₁₋₄ haloalkyl are each optionally substituted with 0, 1 or 2 R*;

[0311] R* is selected from H, halogen, —OH and 5-6 membered heterocyclyl;

[0312] n is 1, 2, 3 or 4.

[0313] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

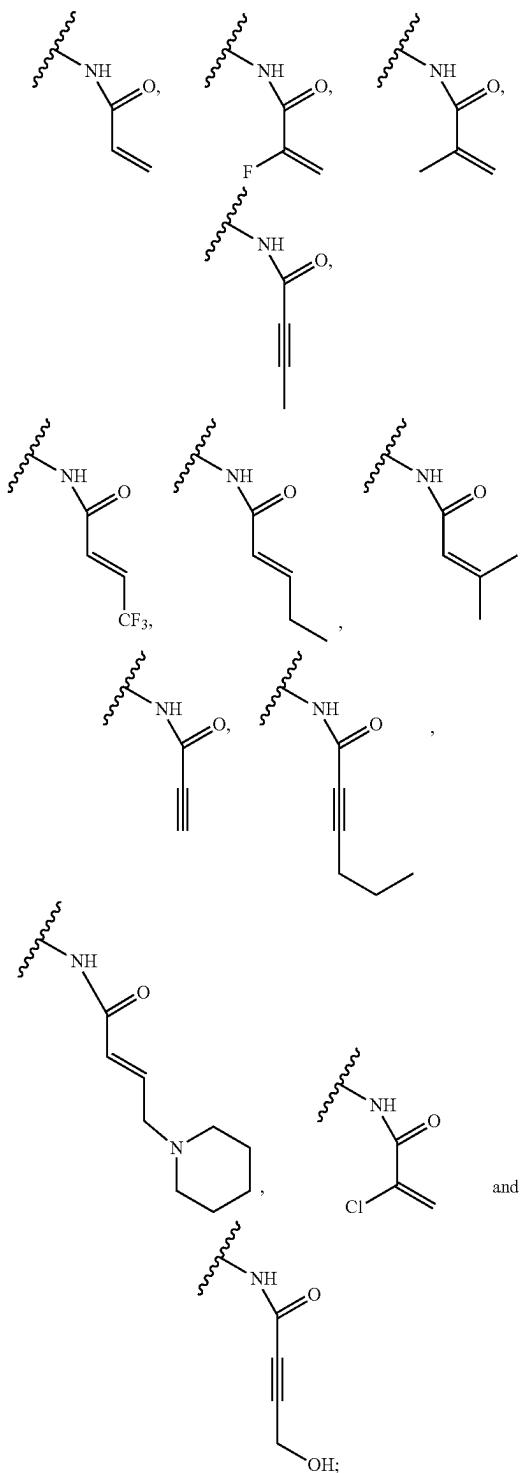
[0314] Ring A is absent, or Ring A is selected from



[0315] R_1 is selected from C_1 , Br and $-CF_3$, alternatively Cl and Br;

[0316] R_3 is selected from H and $-OCH_3$;

[0317] R_6 is selected from



[0318] n is 2, 3 or 4.

[0319] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0320] Ring A is absent, or Ring A is selected from 5-10 membered heteroaryl and 5-8 membered heterocyclyl;

[0321] R_1 is selected from halogen and C_{1-4} haloalkyl, alternatively halogen;

[0322] R_3 is selected from H, $-OC_{1-6}$ alkyl and $-OC_{1-6}$ haloalkyl, alternatively H and $-OC_{1-6}$ alkyl;

[0323] R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;

[0324] wherein R, R' and R'' are each independently selected from H, F, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0325] n is 1, 2, 3, 4 or 5.

[0326] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0327] Ring A is absent, or Ring A is selected from 5-6 membered heteroaryl and 5-6 membered heterocyclyl;

[0328] R_1 is selected from halogen and C_{1-4} haloalkyl, alternatively halogen;

[0329] R_3 is selected from H and $-OC_{1-4}$ alkyl;

[0330] R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;

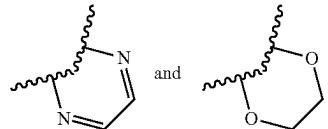
[0331] wherein R is selected from H, F and C_{1-4} alkyl;

[0332] R' and R'' are each independently selected from H, C_{1-4} alkyl and C_{1-4} haloalkyl;

[0333] n is 1, 2, 3 or 4.

[0334] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

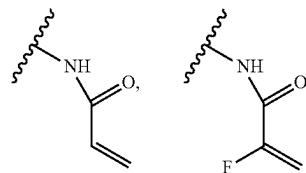
[0335] Ring A is absent, or Ring A is selected from

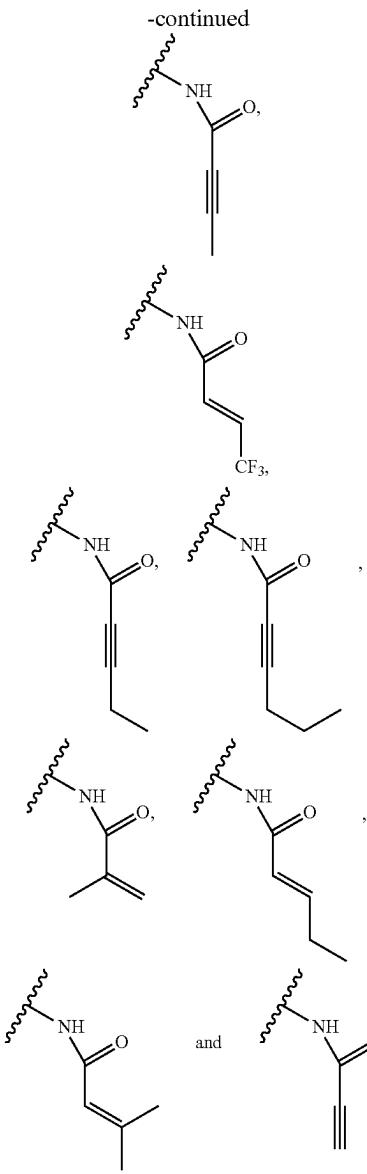


[0336] R_1 is selected from Cl, Br and $-CF_3$, alternatively Cl and Br;

[0337] R_3 is selected from H and $-OCH_3$;

[0338] R_6 is selected from





[0339] n is 1, 2 or 3.

[0340] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0341] Ring A is selected from 5-10 membered heteroaryl and 5-8 membered heterocycl;

[0342] R₁ is selected from halogen and C₁-4 haloalkyl, alternatively halogen;

[0343] R₃ is selected from —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively —OC₁₋₆ alkyl;

[0344] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";

[0345] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0346] n is 1, 2 or 3.

[0347] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0348] Ring A is selected from 5-6 membered heteroaryl and 5-6 membered heterocycl;

[0349] R₁ is selected from halogen and C₁-4 haloalkyl, alternatively halogen;

[0350] R₃ is —OC₁₋₄ alkyl;

[0351] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";

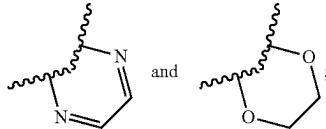
[0352] wherein R is selected from H and halogen;

[0353] R' and R" are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

[0354] n is 1, 2 or 3.

[0355] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

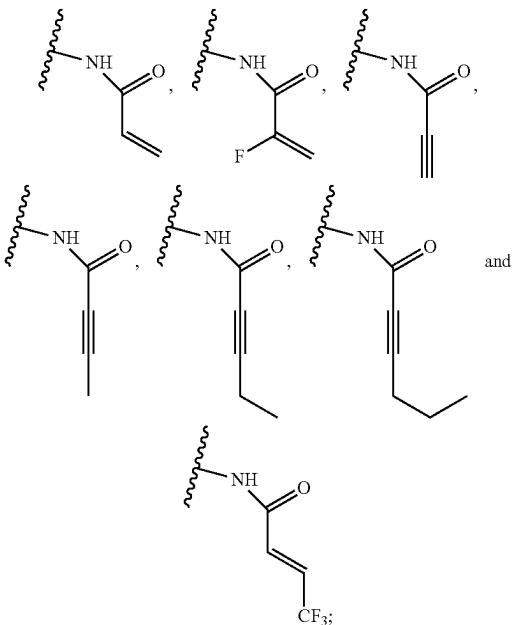
[0356] Ring A is selected from



[0357] R₁ is selected from Cl, Br and —CF₃, alternatively Cl and Br, still alternatively Cl;

[0358] R₃ is —OCH₃;

[0359] R₆ is selected from



[0360] n is 2.

[0361] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0362] Ring A is absent;
- [0363] R₁ is halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;
- [0364] R₃ is selected from —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl;
- [0365] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0366] wherein R is H, F or Me;
- [0367] R' and R" are each independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0368] n is 2.

[0369] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0370] Ring A is absent;
- [0371] R₁ is Br or C₁₋₂ haloalkyl;
- [0372] R₃ is selected from —OC₁₋₂ alkyl and —OC₁₋₂ haloalkyl;
- [0373] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0374] wherein R is H or F; R' is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R" is H;
- [0375] n is 2.

[0376] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0377] Ring A is absent;
- [0378] R₁ is Br or CF₃;
- [0379] R₃ is selected from —OMe and —OCH₂CF₃;
- [0380] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0381] wherein R is H or F; R' is H, Me, iPr or CF₃; R" is H;
- [0382] n is 2.

[0383] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0384] Ring A is absent;
- [0385] R₁ is C₁₋₄ haloalkyl;
- [0386] R₃ is selected from —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl;
- [0387] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0388] wherein R is H or halogen; R' is H, C₁₋₂ alkyl or C₁₋₂ haloalkyl; R" is H;
- [0389] n is 2.

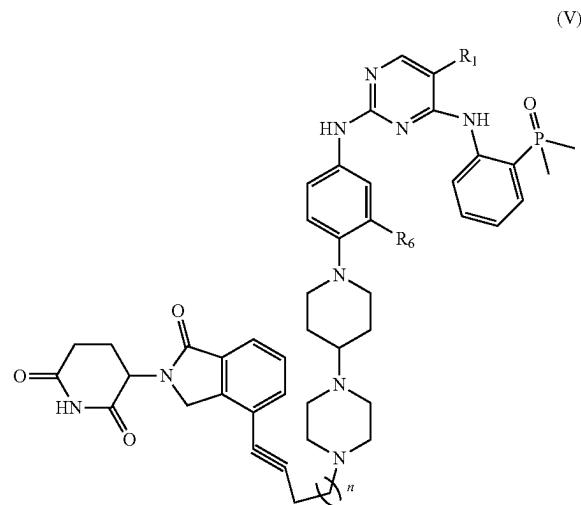
[0390] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0391] Ring A is absent;
- [0392] R₁ is C₁₋₂ haloalkyl;
- [0393] R₃ is selected from —OC₁₋₂ alkyl and —OC₁₋₂ haloalkyl;
- [0394] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0395] wherein R is H, F or Br; R' is H, C₁₋₂ alkyl or C₁₋₂ haloalkyl; R" is H;
- [0396] n is 2.

[0397] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IV), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0398] Ring A is absent;
- [0399] R₁ is CF₃;
- [0400] R₃ is selected from —OMe and —OCH₂CF₃;
- [0401] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0402] wherein R is H or F; R' is H, Me or CF₃; R" is H;
- [0403] n is 2.

[0404] In a more specific embodiment, the present disclosure provides a compound of formula (V), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof:



- [0405] wherein
- [0406] R₁ is halogen;
- [0407] R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'";
- [0408] wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;
- [0409] n is 0, 1, 2, 3, 4, or 5.

[0410] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (V), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0411] R_1 is halogen;

[0412] R_6 is selected from $-\text{NH}-\text{C}(\text{O})-\text{CR}=\text{CR}'\text{R}''$ and $-\text{NH}-\text{C}(\text{O})-\text{C}\equiv\text{CR}'$;

[0413] wherein R is selected from H and halogen;

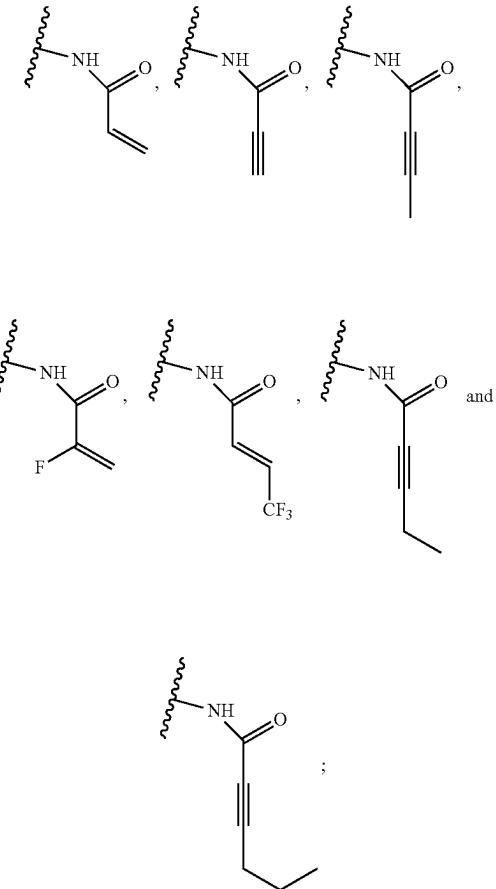
[0414] R' and R'' are each independently selected from H, C_{1-4} alkyl and C_{1-4} haloalkyl;

[0415] n is 1, 2, 3 or 4.

[0416] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (V), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

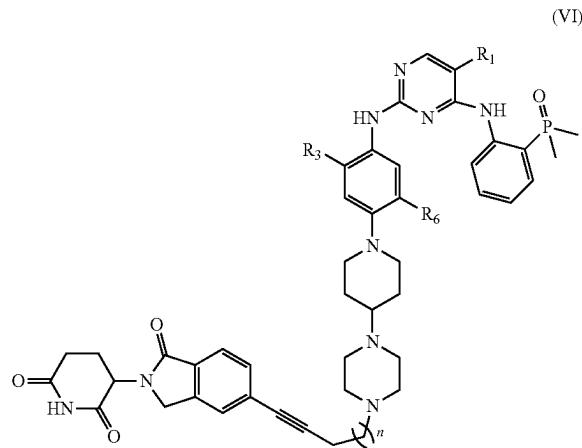
[0417] R_1 is selected from Br and Cl;

[0418] R_6 is selected from



[0419] n is 2, 3 or 4.

[0420] In a more specific embodiment, the present disclosure provides a compound of formula (VI), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof:



[0421] wherein

[0422] R_1 is halogen;

[0423] R_3 is $-\text{OC}_{1-6}$ alkyl;

[0424] R_6 is selected from $-\text{NH}-\text{C}(\text{O})-\text{CR}=\text{CR}'\text{R}''$ and $-\text{NH}-\text{C}(\text{O})-\text{C}\equiv\text{CR}'$;

[0425] wherein R, R' and R'' are independently selected from H, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0426] n is 1, 2, 3 or 4.

[0427] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (VI), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0428] R_1 is halogen;

[0429] R_3 is $-\text{OC}_{1-6}$ alkyl;

[0430] R_6 is selected from $-\text{NH}-\text{C}(\text{O})-\text{CR}=\text{CR}'\text{R}''$ and $-\text{NH}-\text{C}(\text{O})-\text{C}\equiv\text{CR}'$;

[0431] wherein R, R' and R'' are independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl;

[0432] n is 2, 3 or 4.

[0433] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (VI), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0434] R_1 is halogen;

[0435] R_3 is $-\text{OC}_{1-4}$ alkyl;

[0436] R_6 is selected from $-\text{NH}-\text{C}(\text{O})-\text{CR}=\text{CR}'\text{R}''$ and $-\text{NH}-\text{C}(\text{O})-\text{C}\equiv\text{CR}'$;

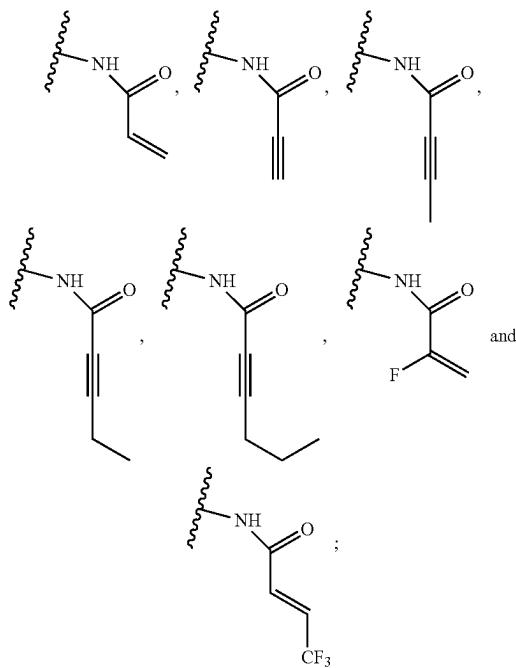
[0437] wherein R is H;

[0438] R' and R'' are independently selected from H, C_{1-4} alkyl and C_{1-4} haloalkyl;

[0439] n is 3.

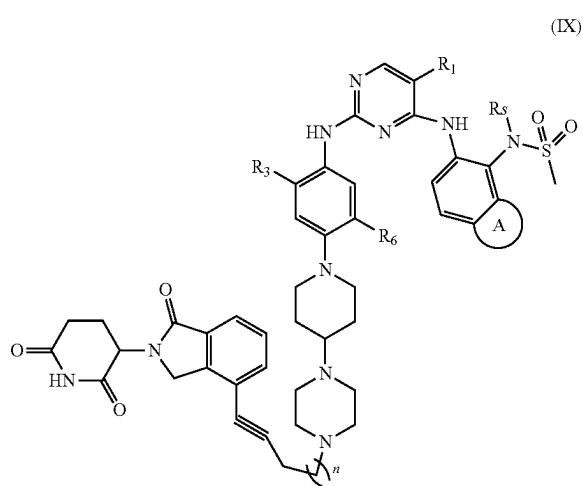
[0440] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (VI), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

- [0441] R₁ is C₁;
- [0442] R₃ is —OCH₃;
- [0443] R₆ is selected from



[0444] n is 3.

[0445] In a more specific embodiment, the present disclosure provides a compound of formula (IX), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof:



[0446] wherein

[0447] Ring A is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;

[0448] R₁ is H, halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl; alternatively, R₁ is halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

[0449] R₃ is selected from —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl;

[0450] R₆ is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0451] wherein R is H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

[0452] R' and R" are each independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0453] R_s is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

[0454] n is 2.

[0455] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IX), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0456] Ring A is selected from C₆₋₁₀ aryl and 5-6 membered heteroaryl;

[0457] R₁ is H, halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl; alternatively, R₁ is halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

[0458] R₃ is selected from —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl;

[0459] R₆ is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0460] wherein R is H or halogen; R' is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R" is H;

[0461] R_s is selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

[0462] n is 2.

[0463] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IX), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0464] Ring A is selected from phenyl and 5-6 membered heteroaryl;

[0465] R₁ is H, halogen or C₁₋₄ haloalkyl; alternatively, R₁ is halogen or C₁₋₄ haloalkyl;

[0466] R₃ is selected from —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl;

[0467] R₆ is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

[0468] wherein R is H or halogen; R' is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R" is H;

[0469] R_s is selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

[0470] n is 2.

[0471] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general formula (IX), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0472] Ring A is a 5-6 membered heteroaryl group;

[0473] R₁ is H, Cl, Br or CF₃; alternatively, R₁ is Br or CF₃;

[0474] R₃ is selected from —OC₁₋₂ alkyl and —OC₁₋₂ haloalkyl;

[0475] R₆ is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl and —NH—C(O)—CR=CR'R";

[0476] wherein R is H or halogen; R' and R" are H;

[0477] R_s is selected from H and C₁₋₄ alkyl;

[0478] n is 2.

[0479] In a more specific embodiment, the present disclosure provides a compound of the above-mentioned general

formula (IX), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein:

[0480] Ring A is pyrazinyl;

[0481] R₁ is H, Cl, Br or CF₃; alternatively, R₁ is Br or CF₃;

[0482] R₃ is selected from —OC₁₋₂ alkyl and —OC₁₋₂ haloalkyl;

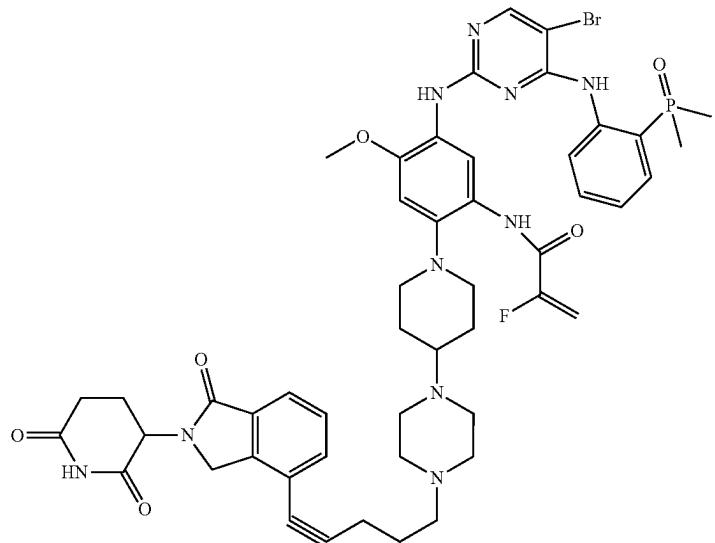
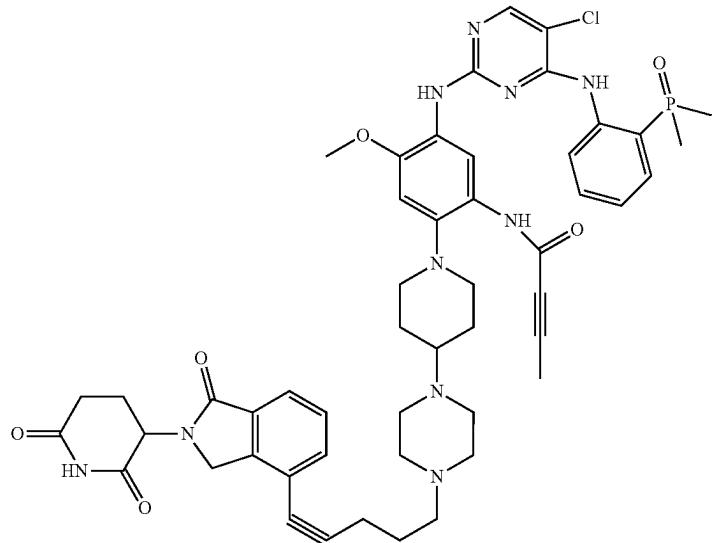
[0483] R₆ is selected from C₁₋₄ alkyl and —NH—C(O)—CR=CR'R";

[0484] wherein R is H or F; R' and R" are H;

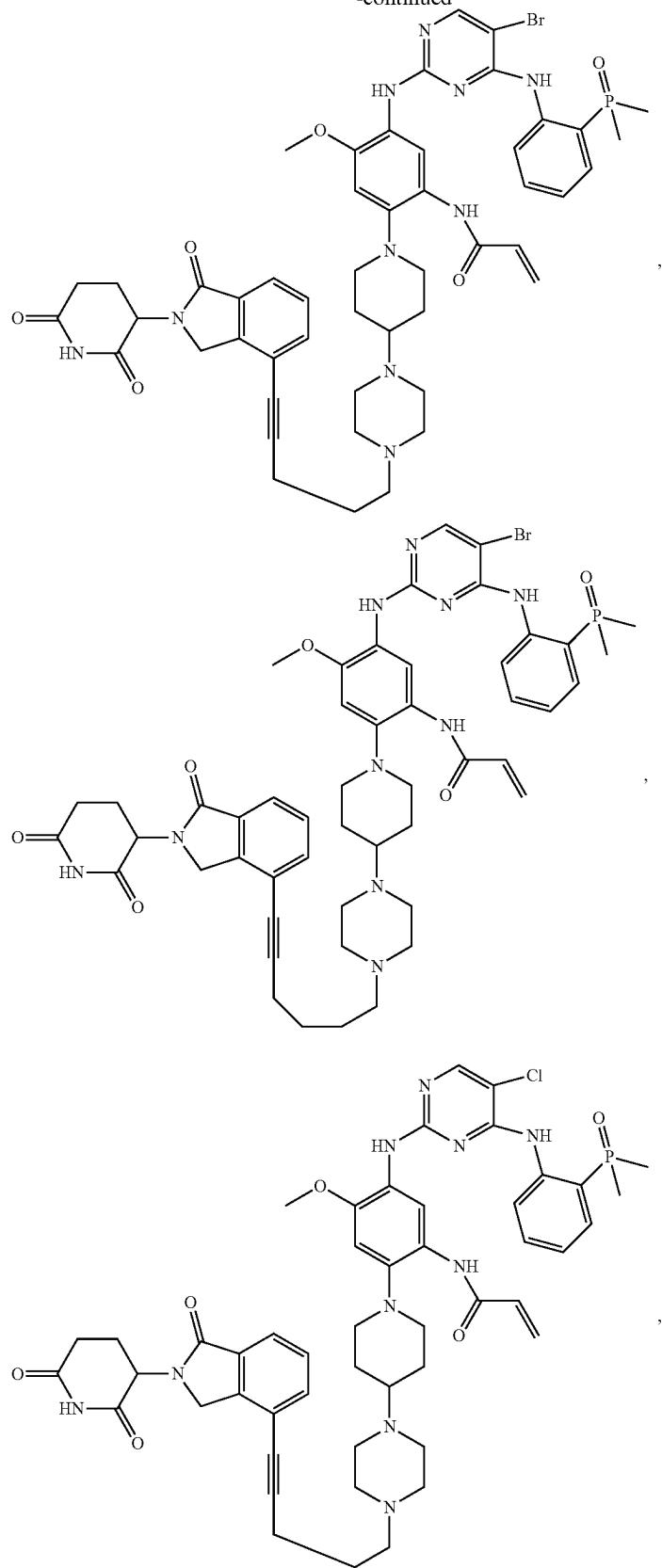
[0485] R_s is H;

[0486] n is 2.

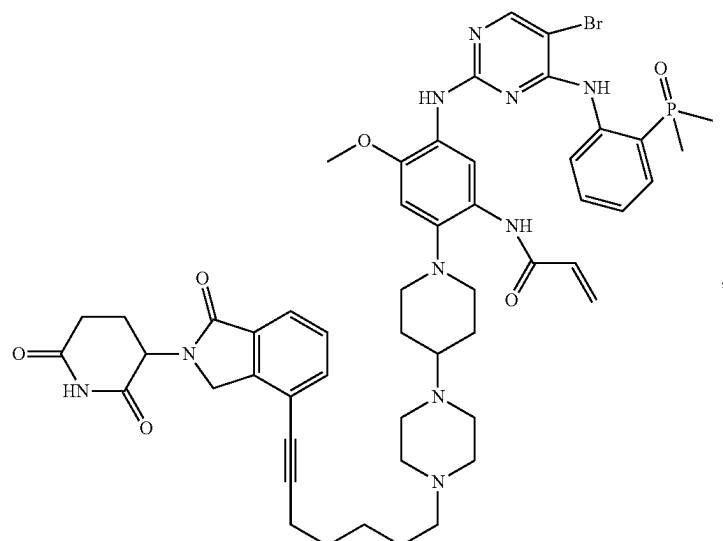
[0487] In a more specific embodiment, the present disclosure relates to a compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound is selected from:



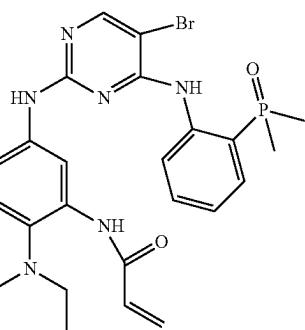
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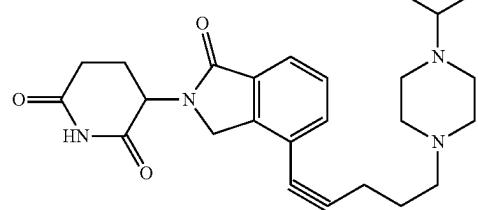
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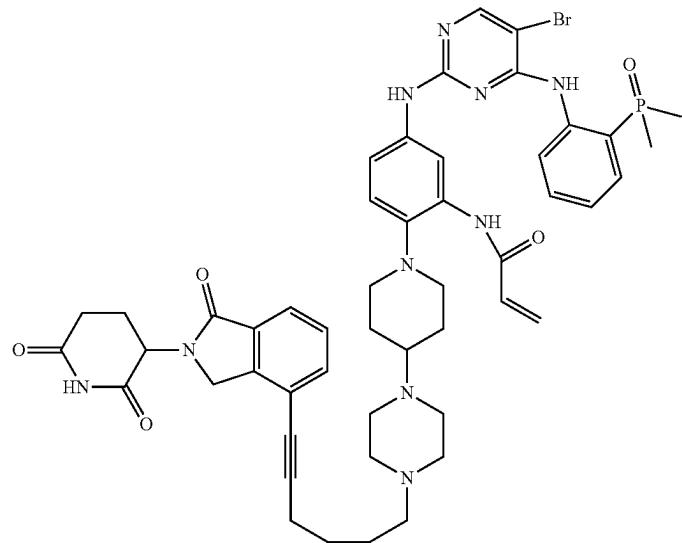
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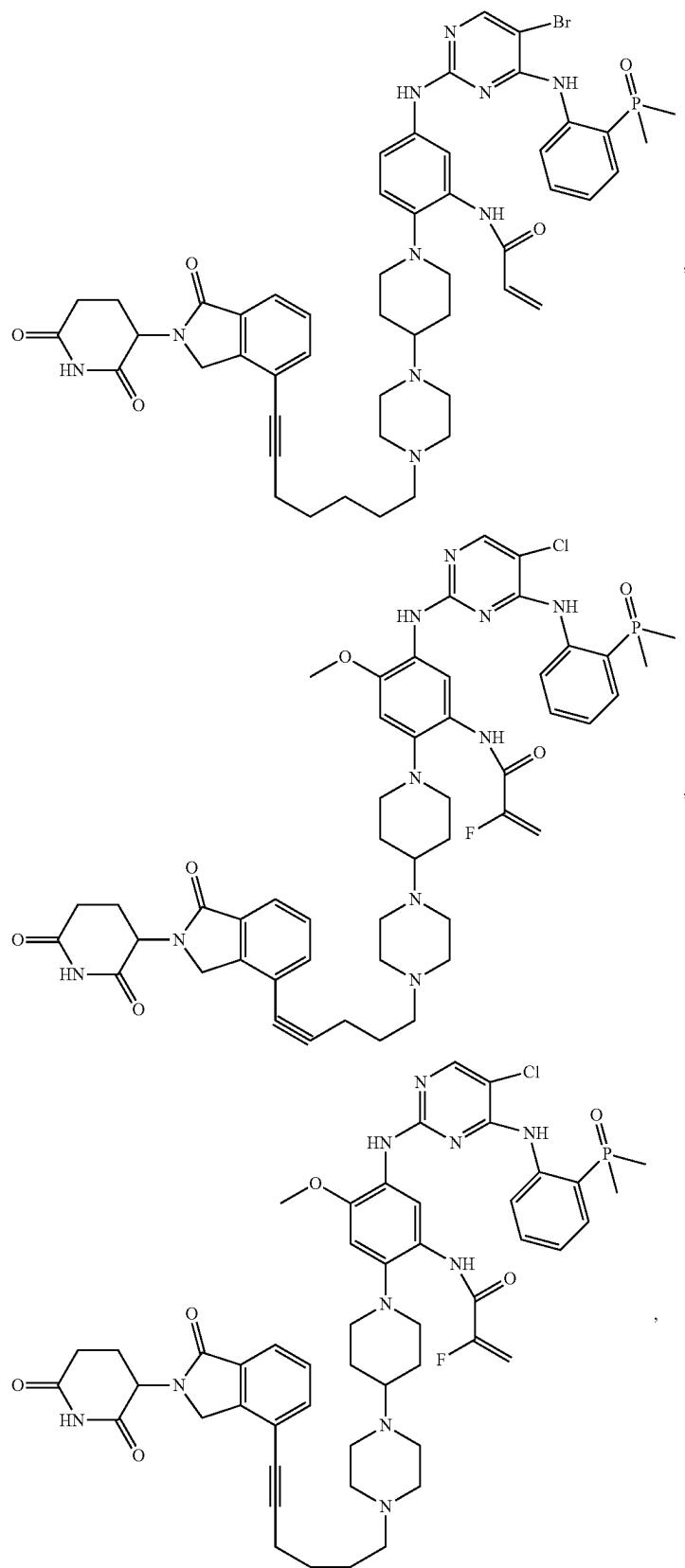


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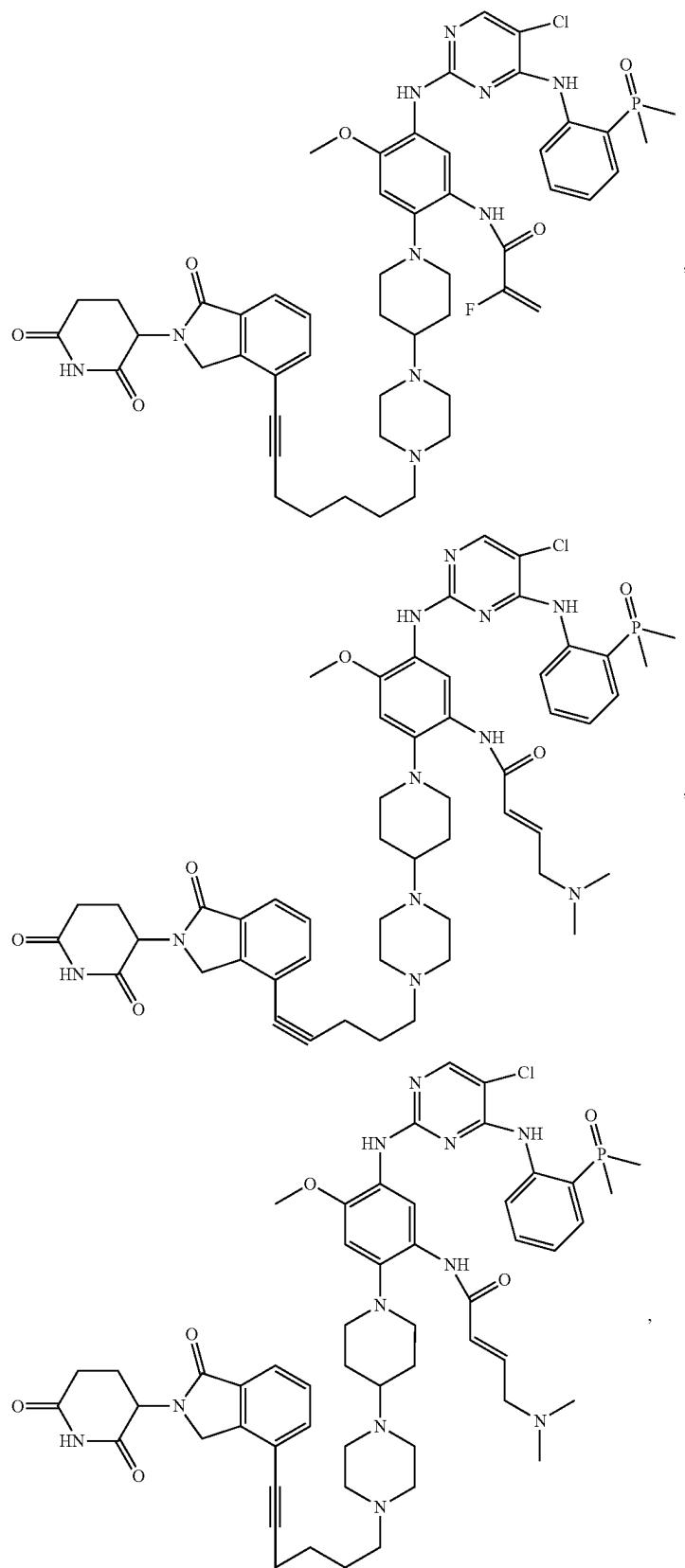


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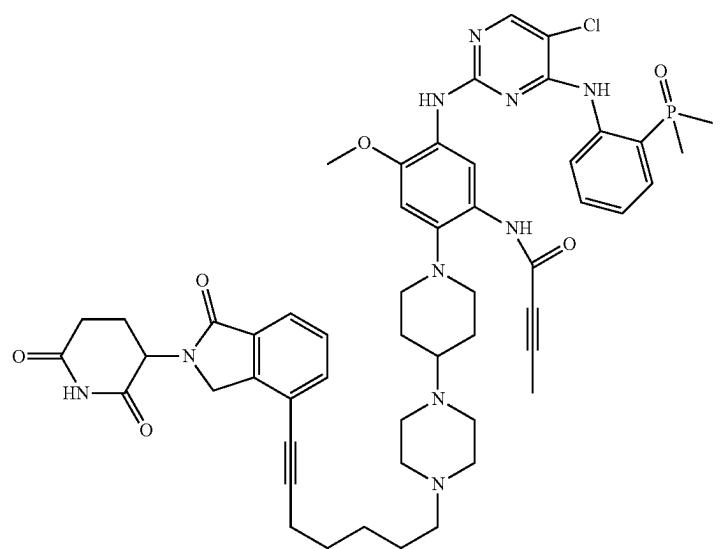
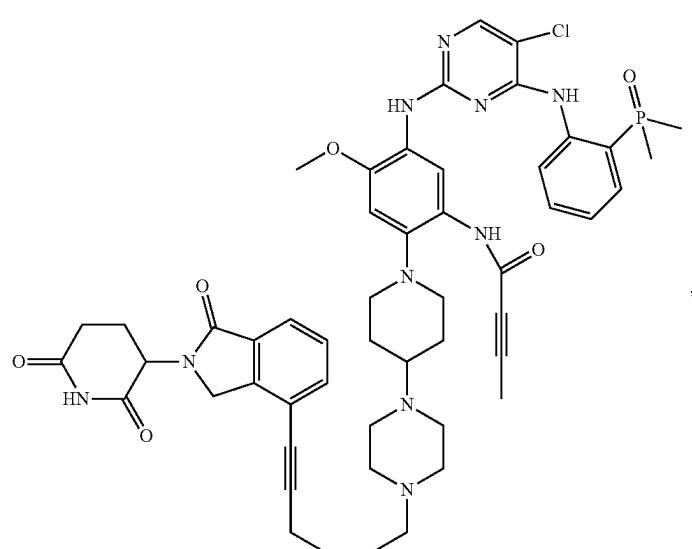
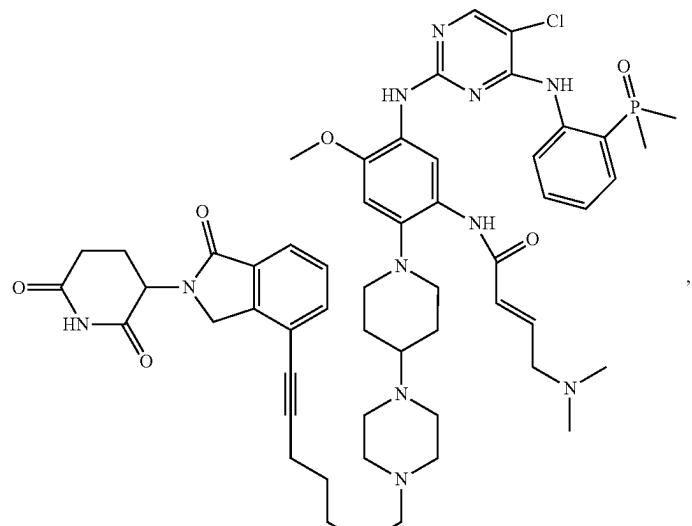
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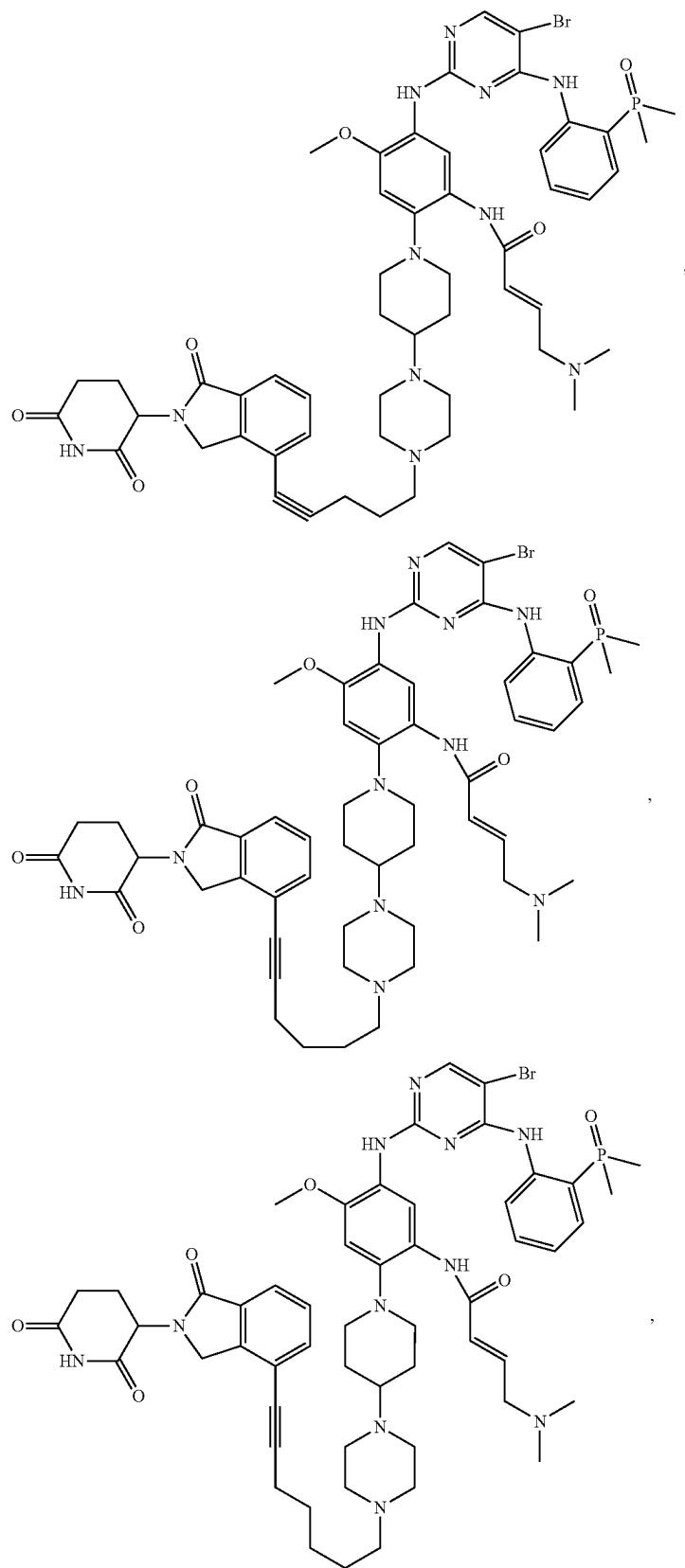
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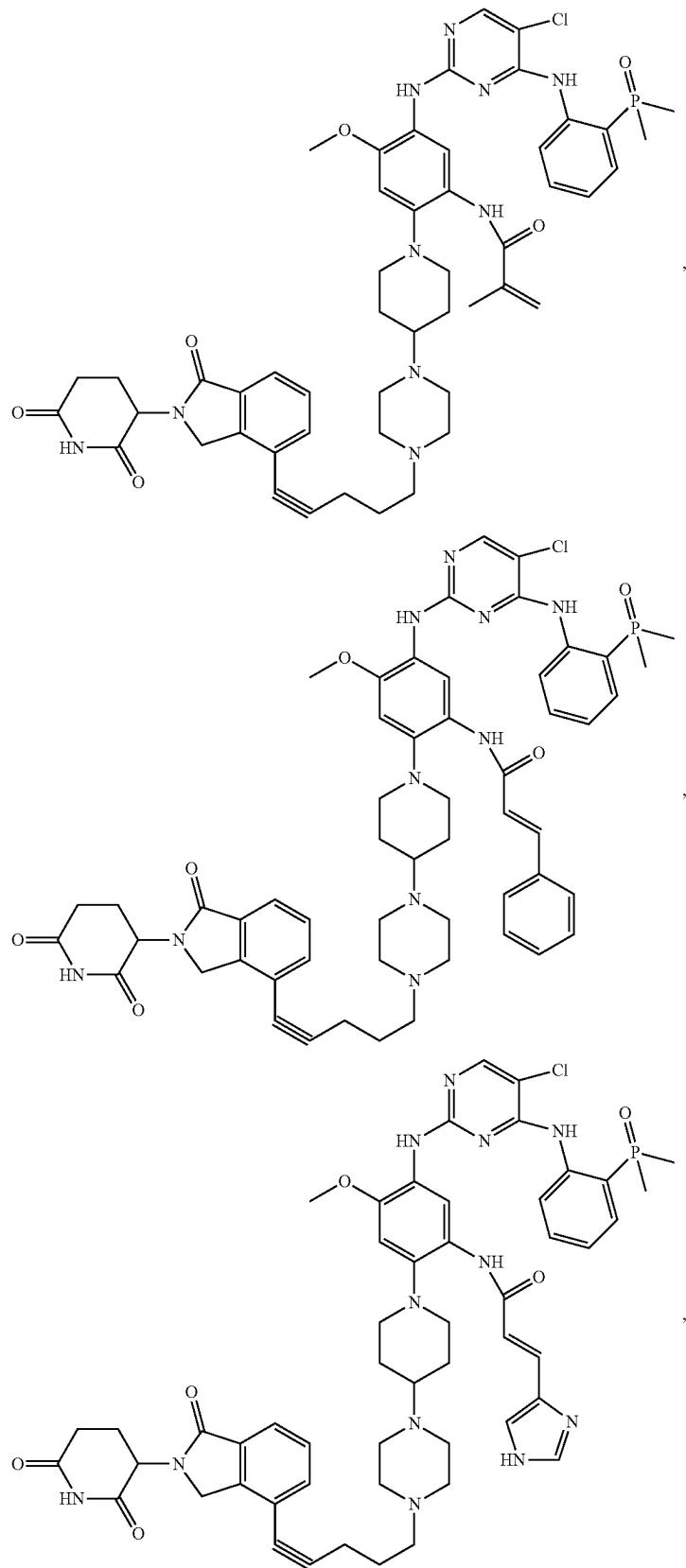
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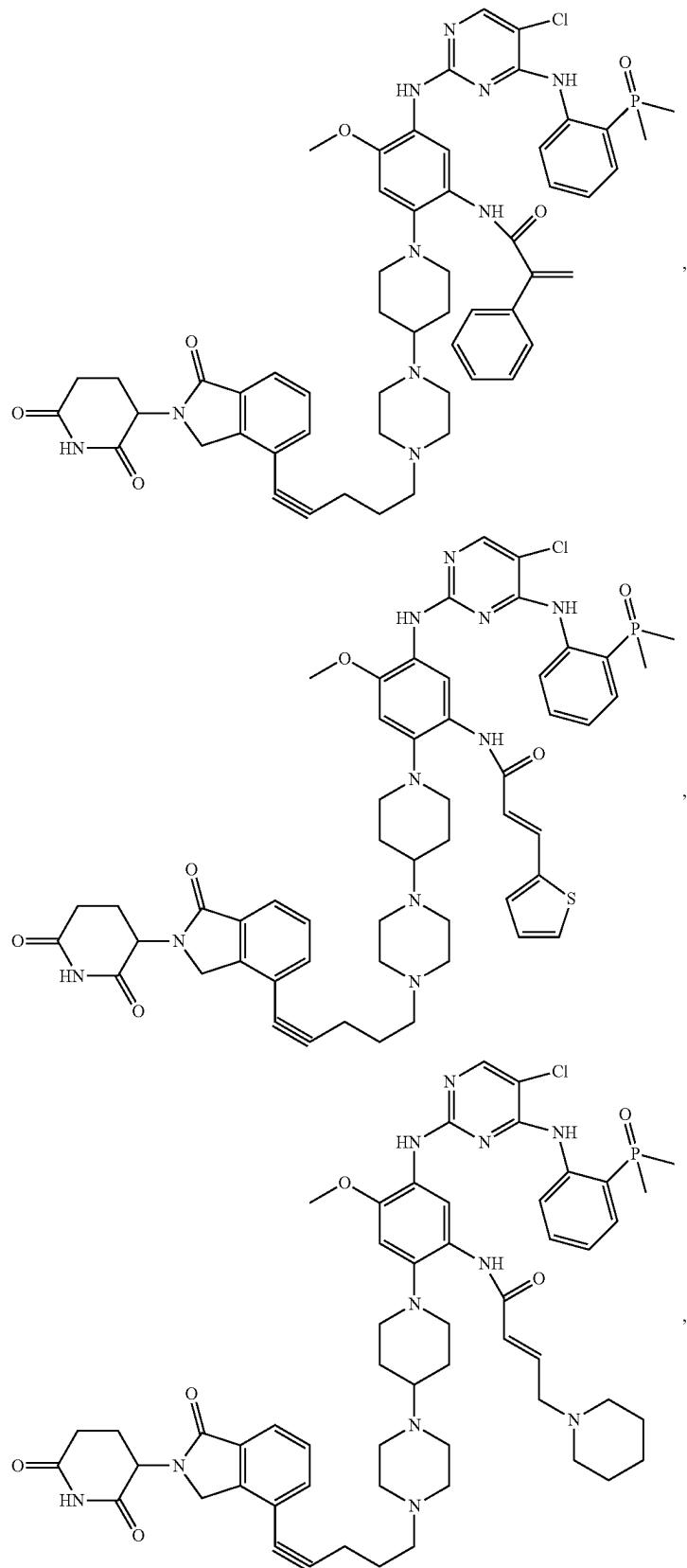
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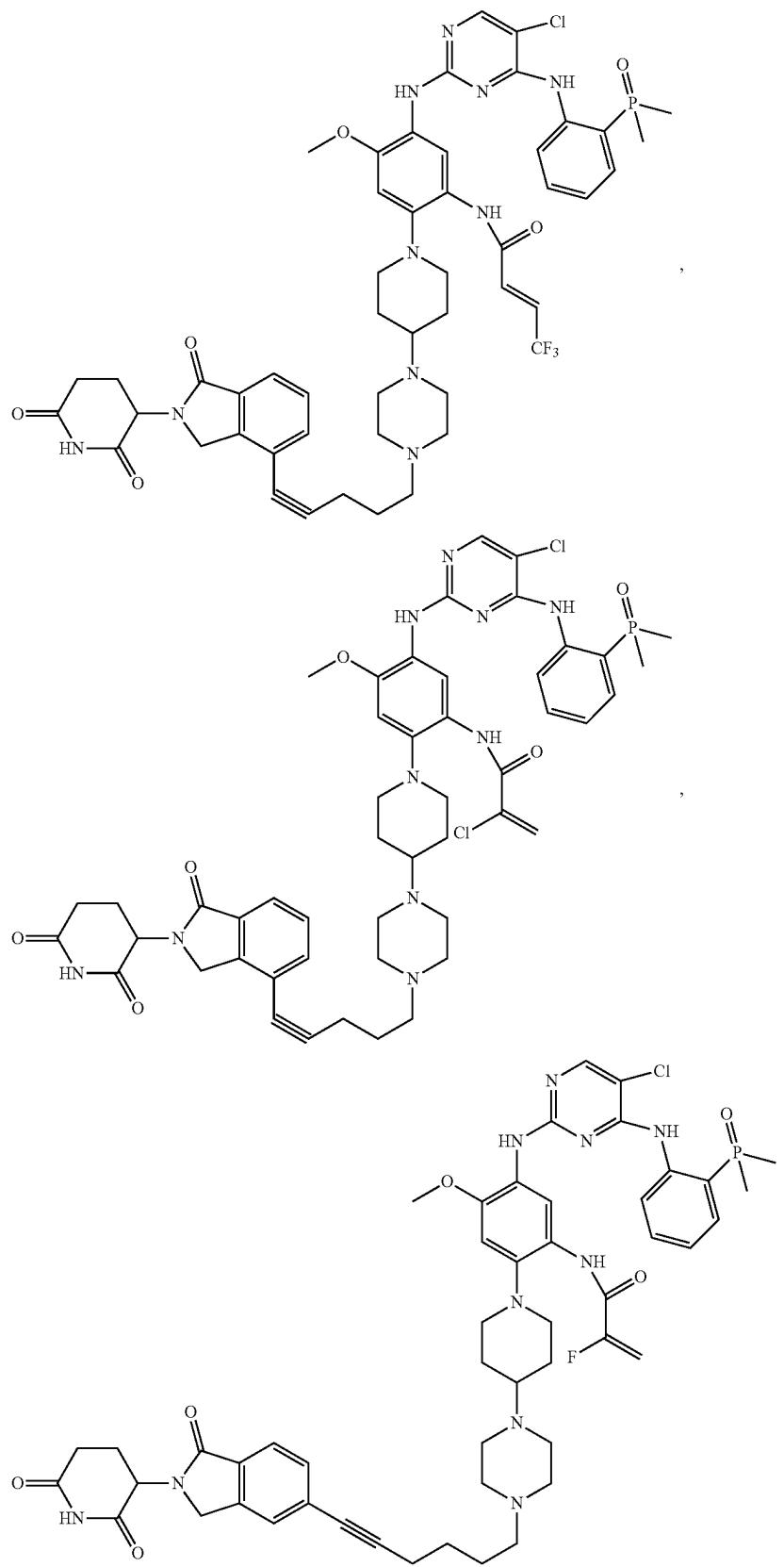
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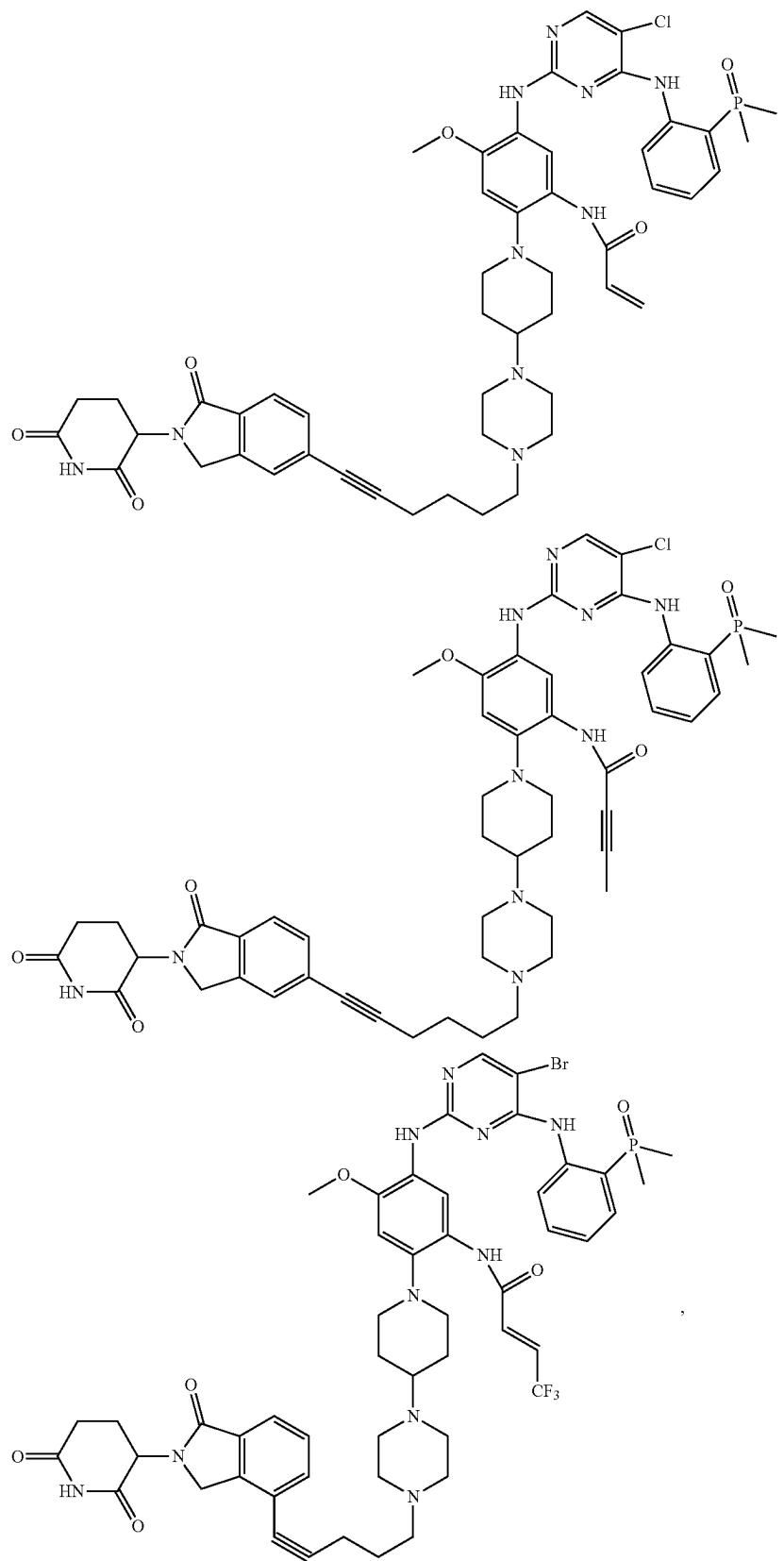
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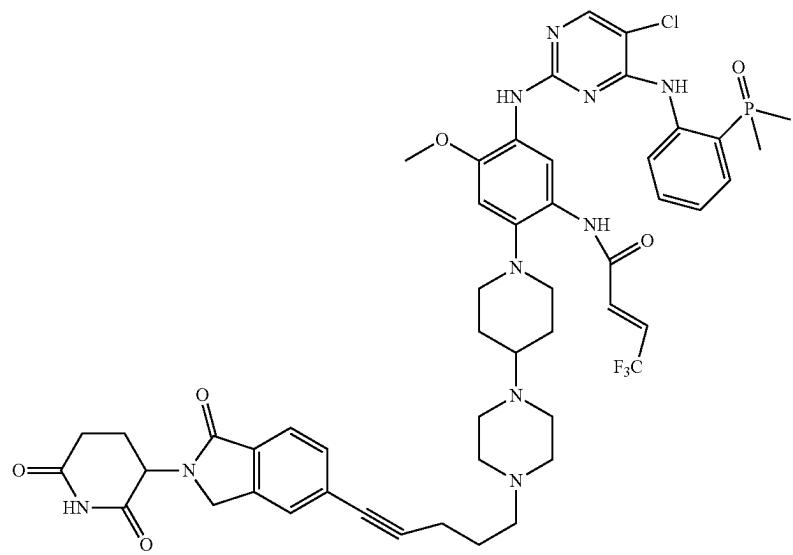
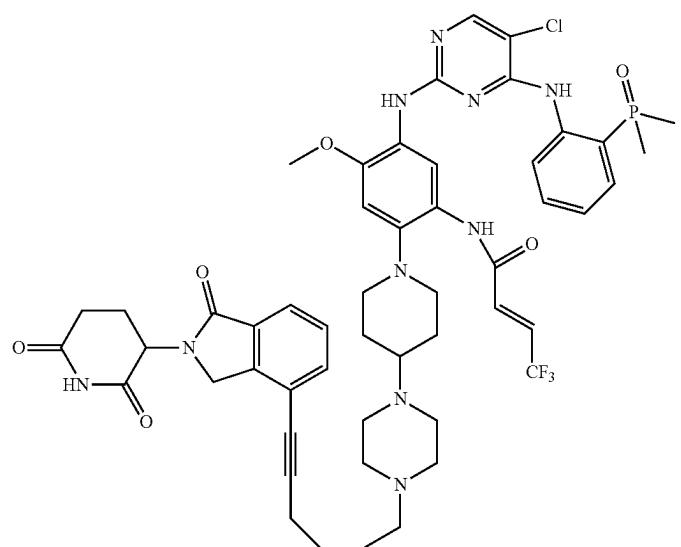
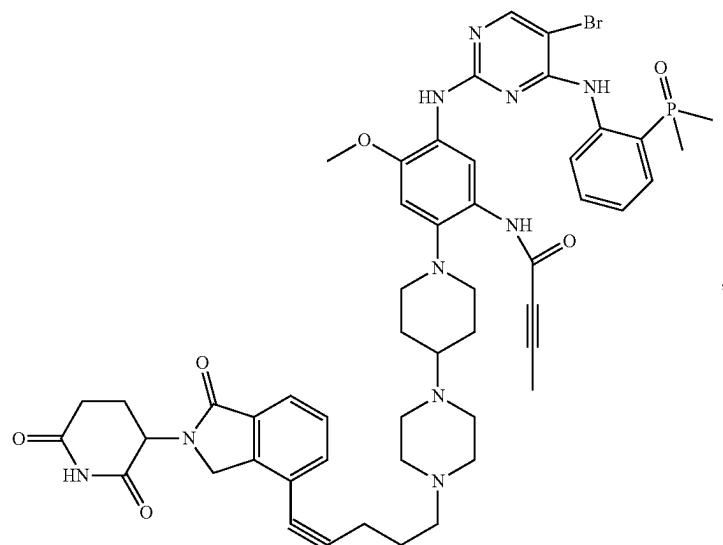
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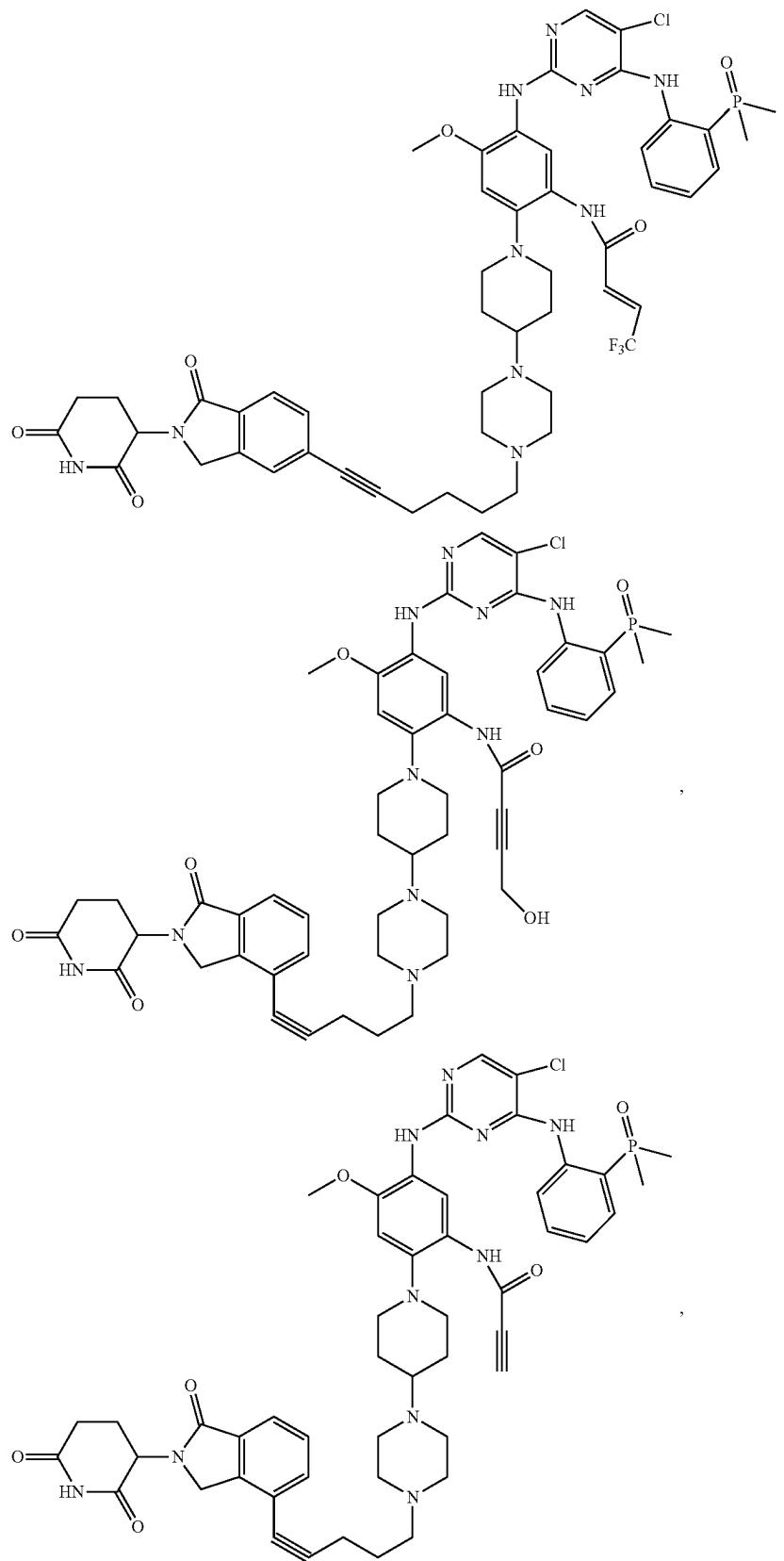
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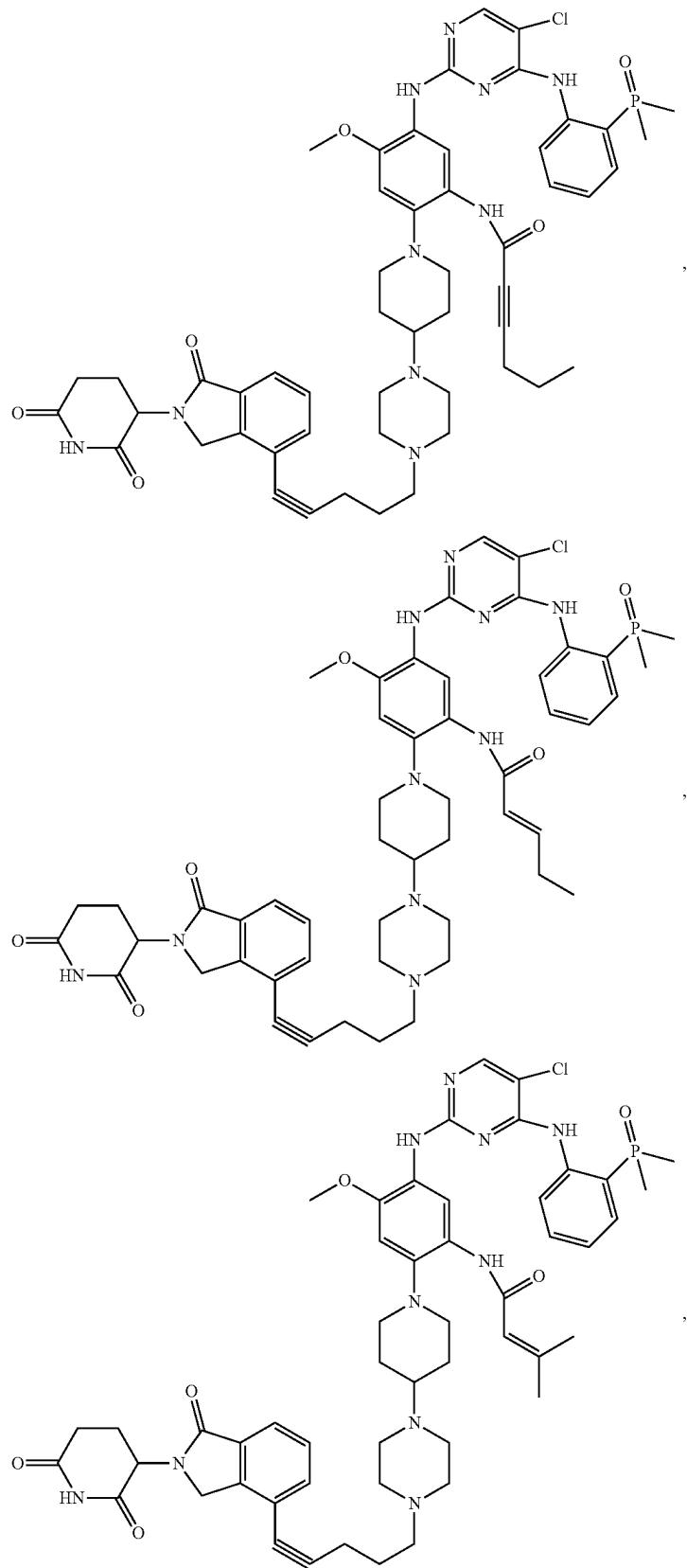
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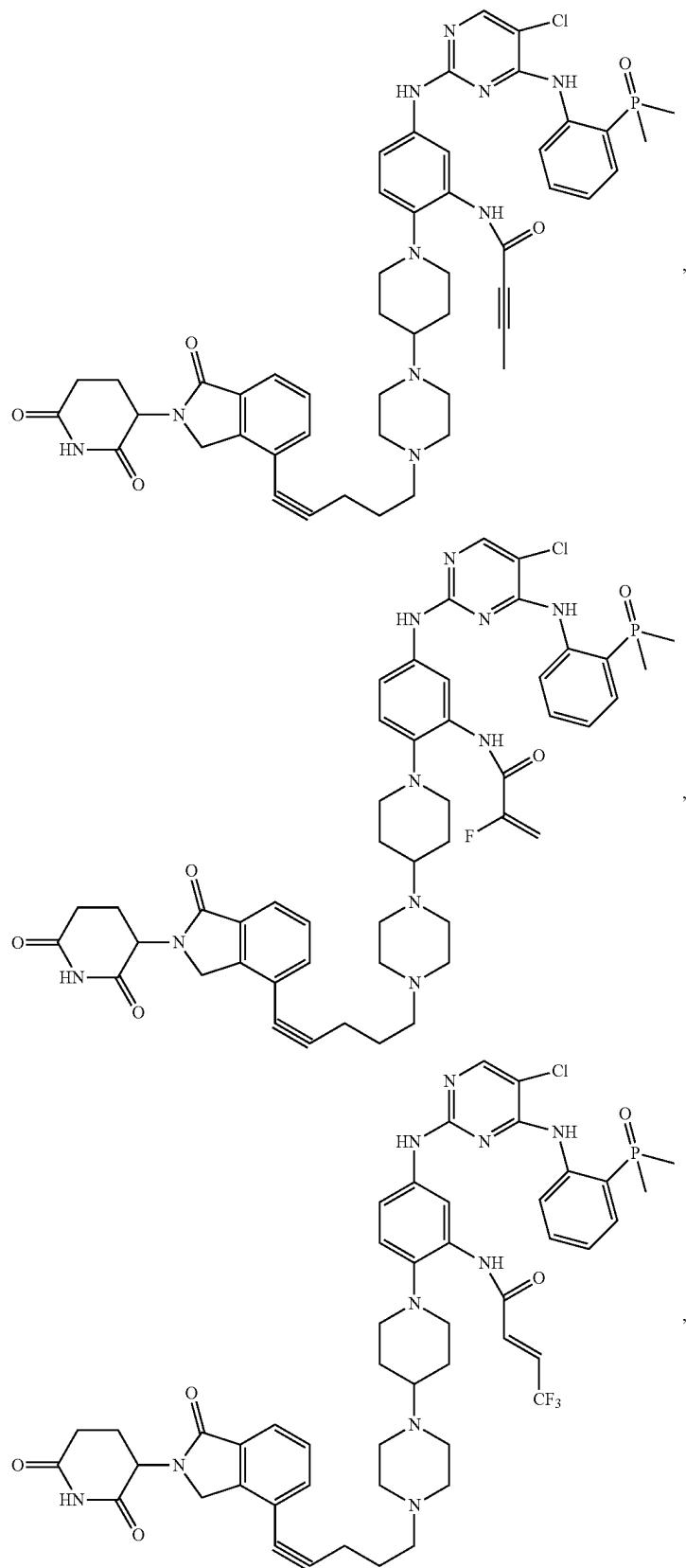
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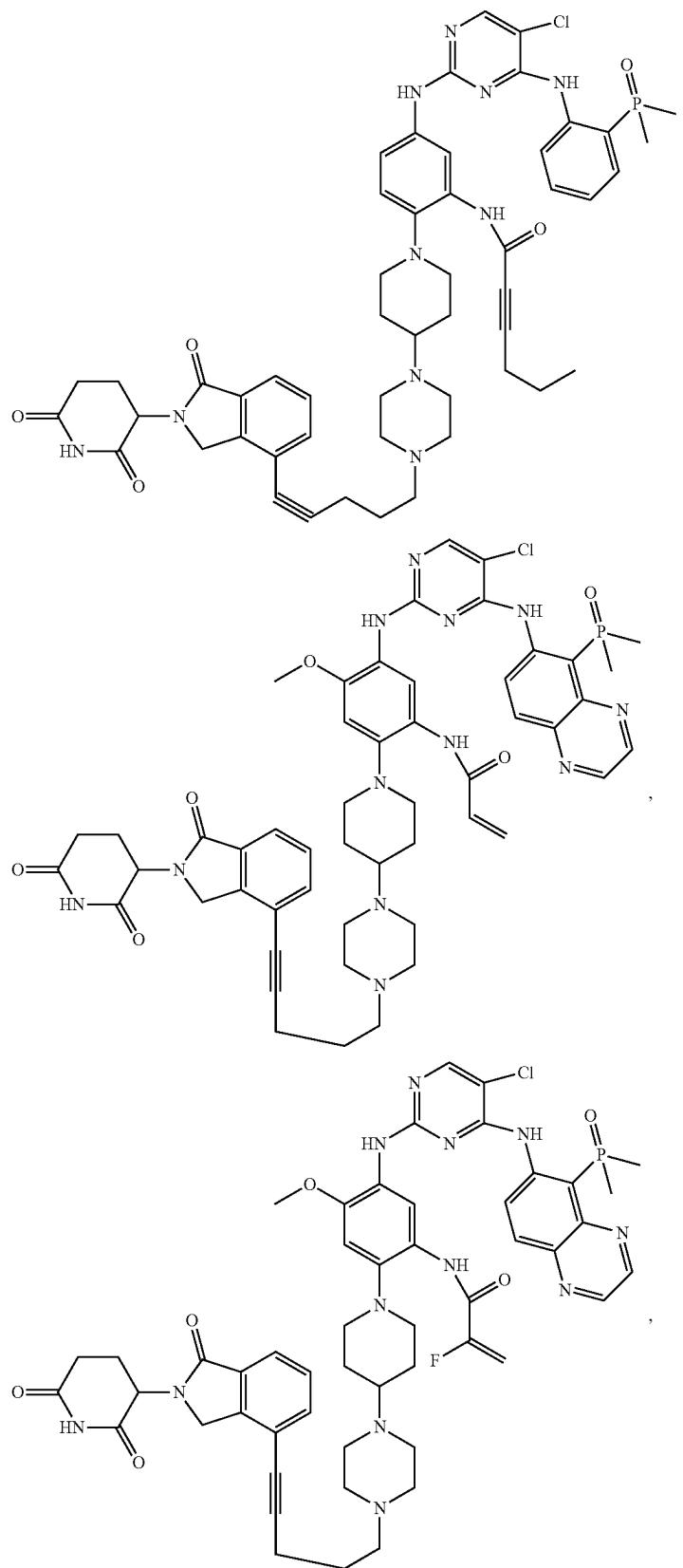
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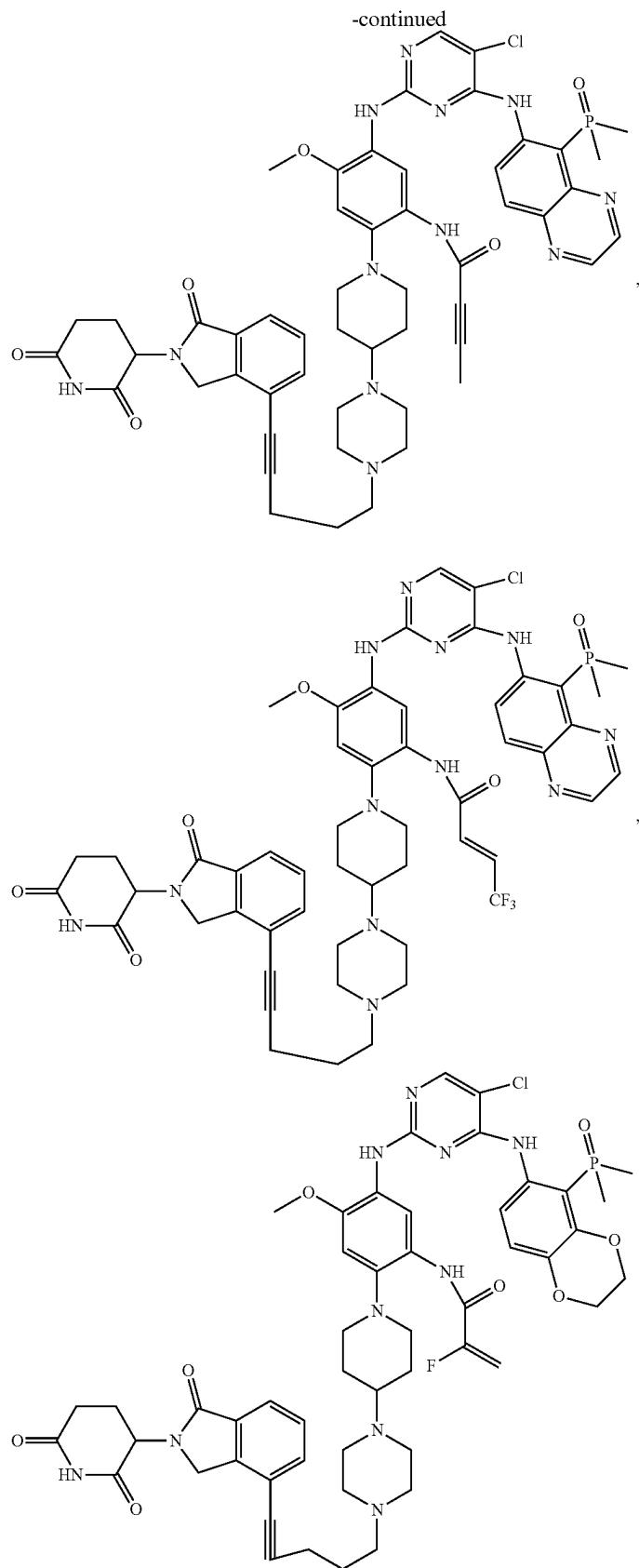


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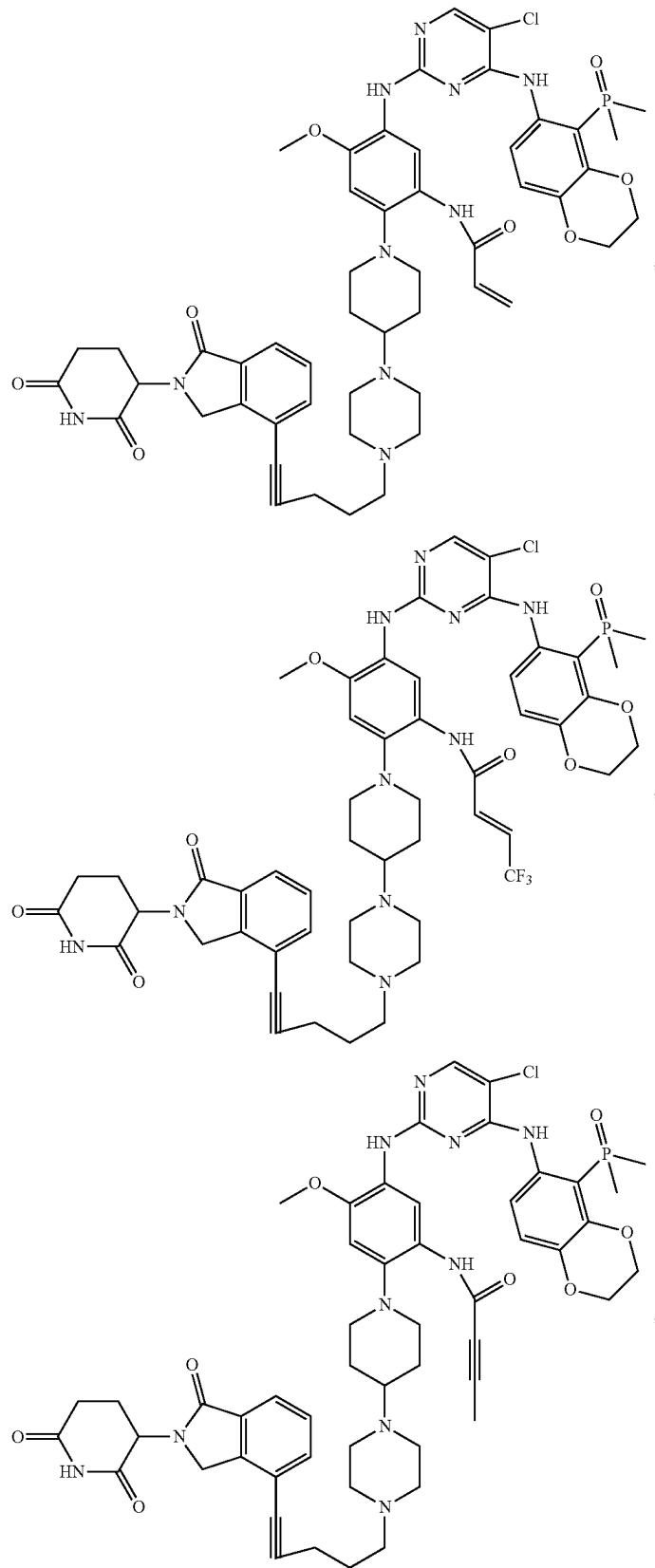


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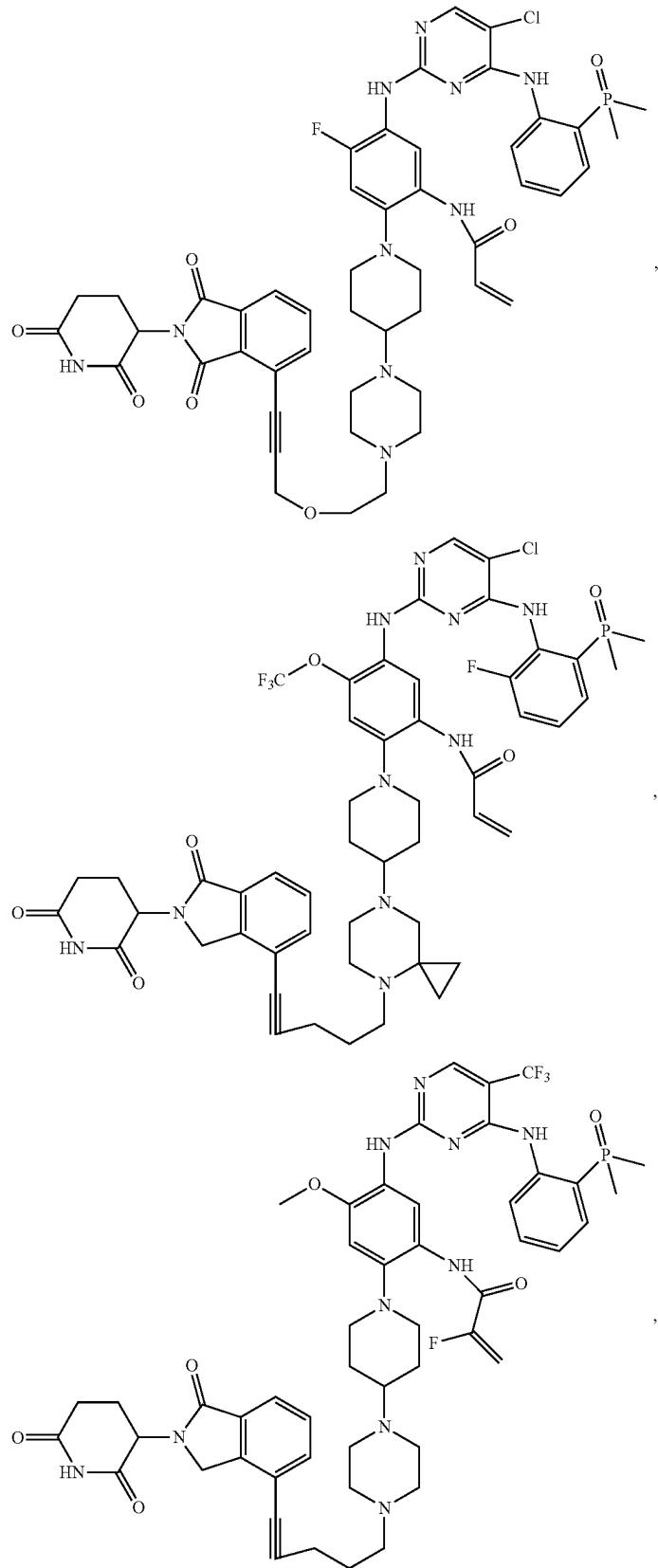




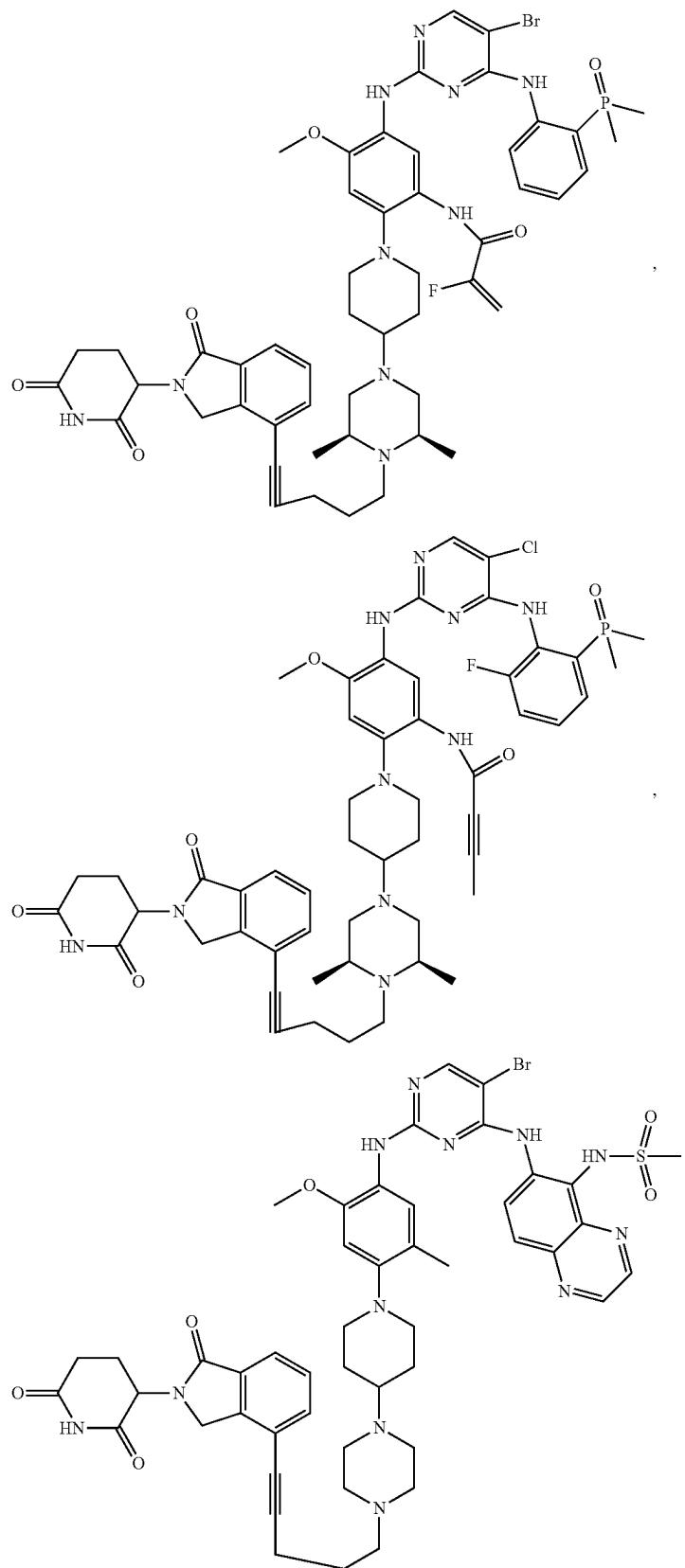
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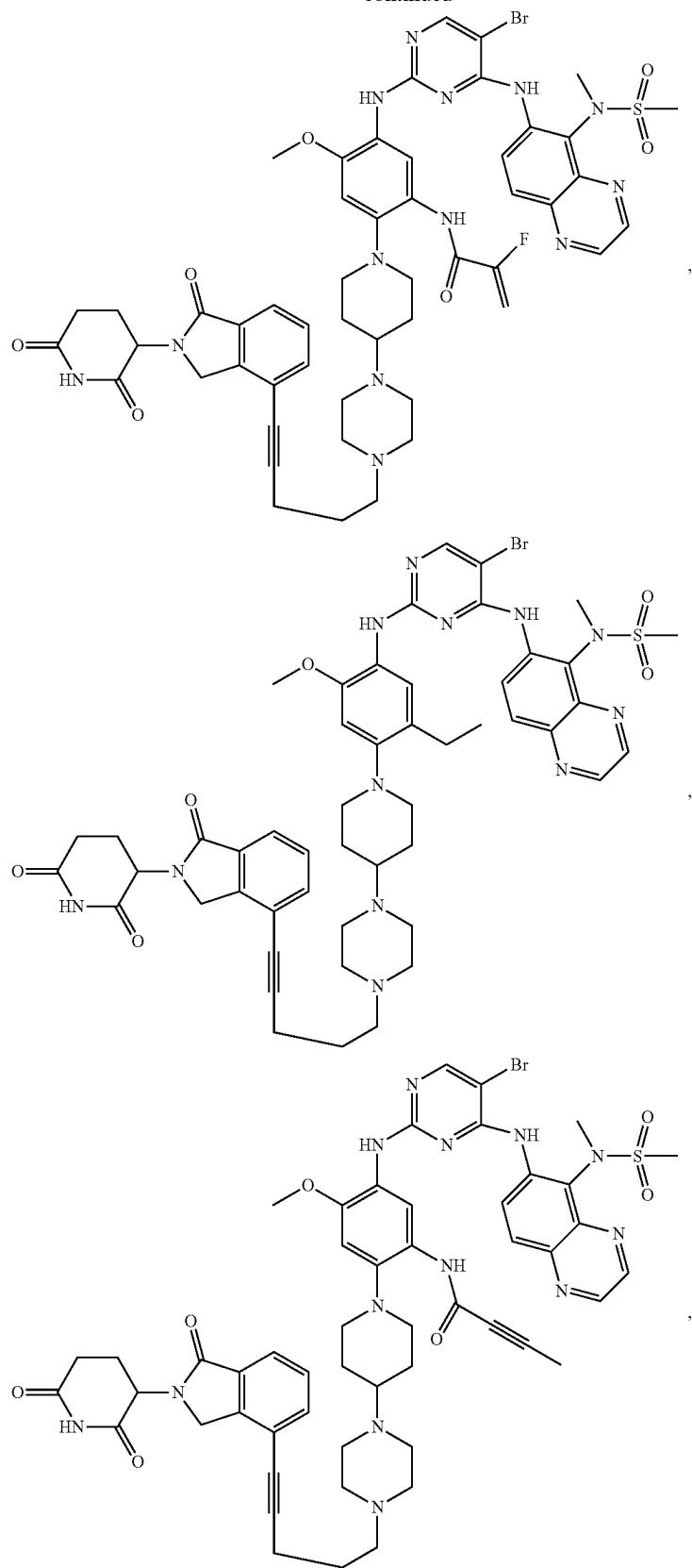
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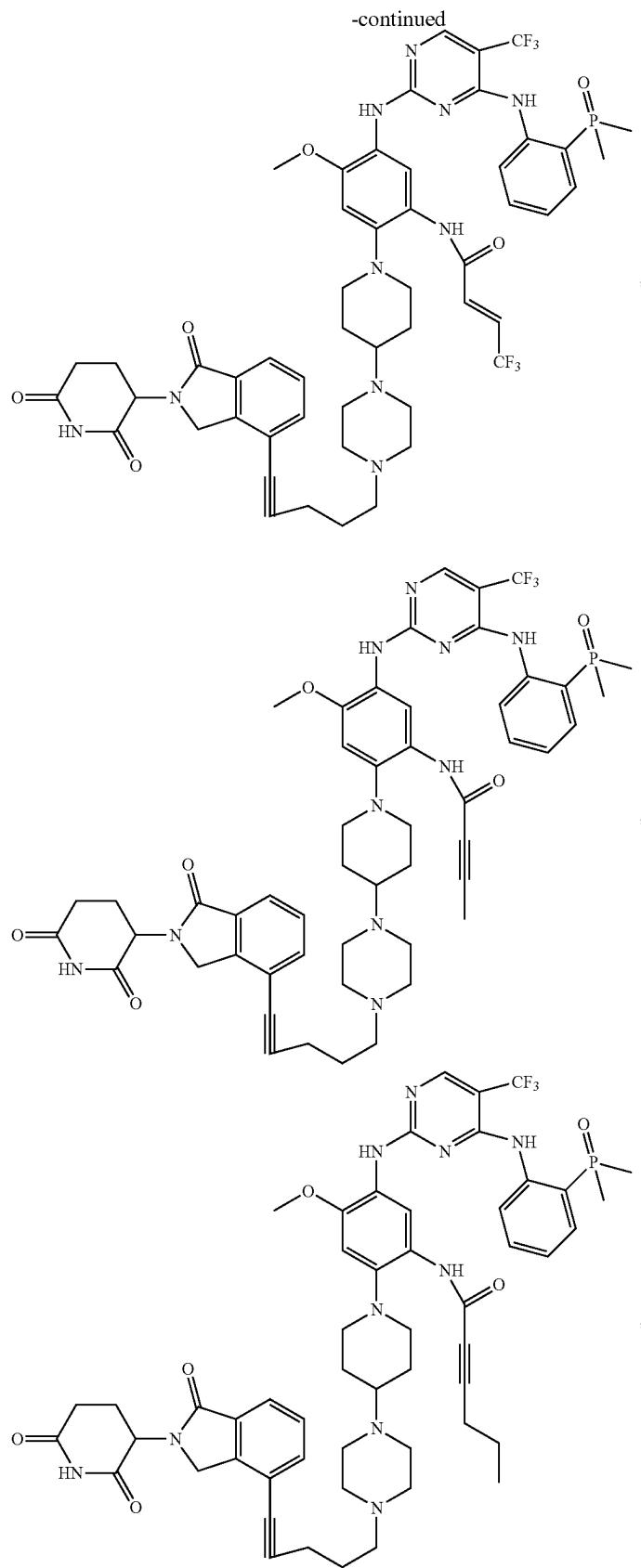


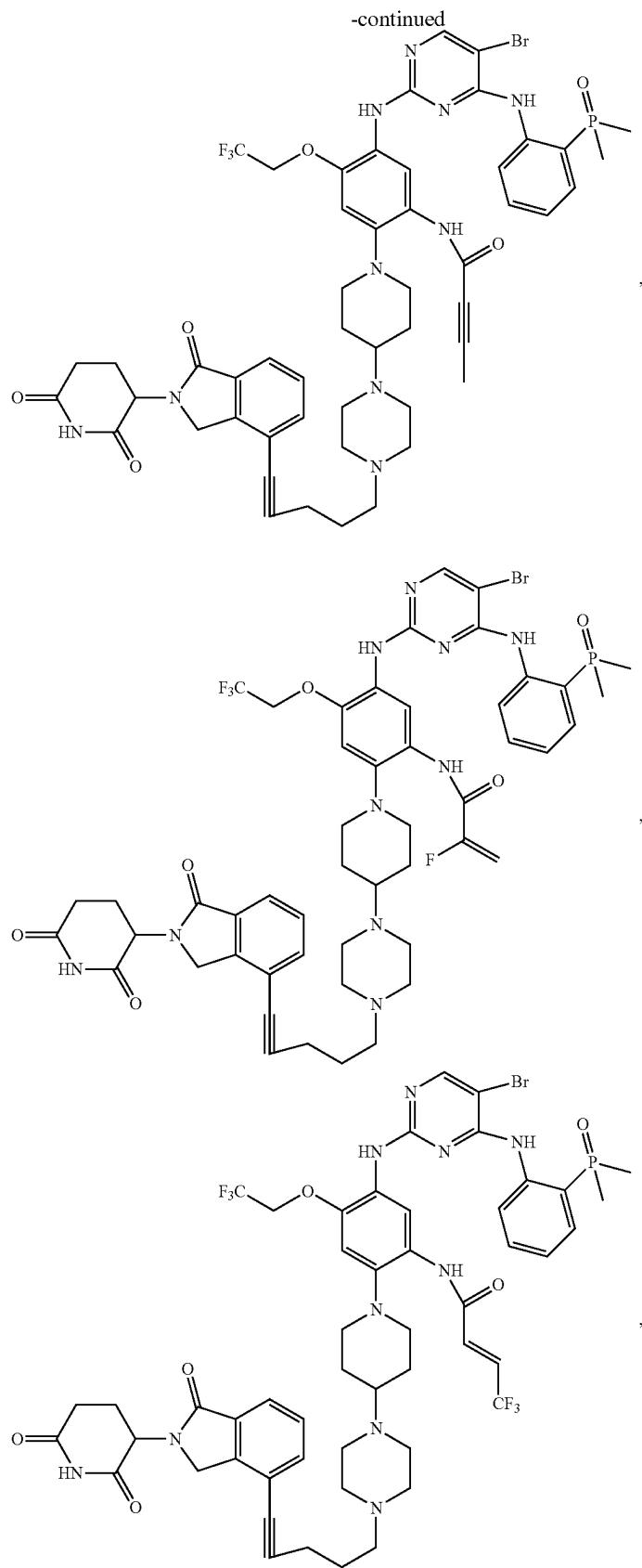
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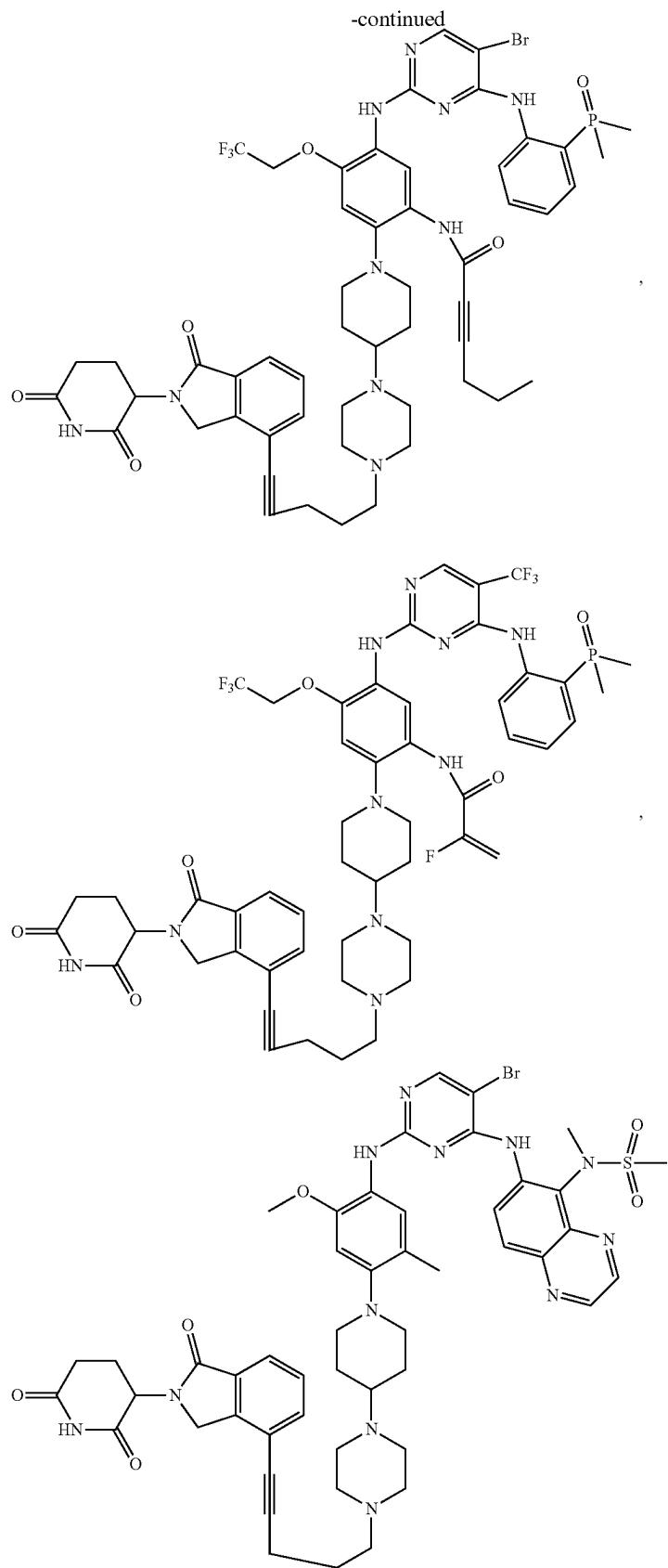


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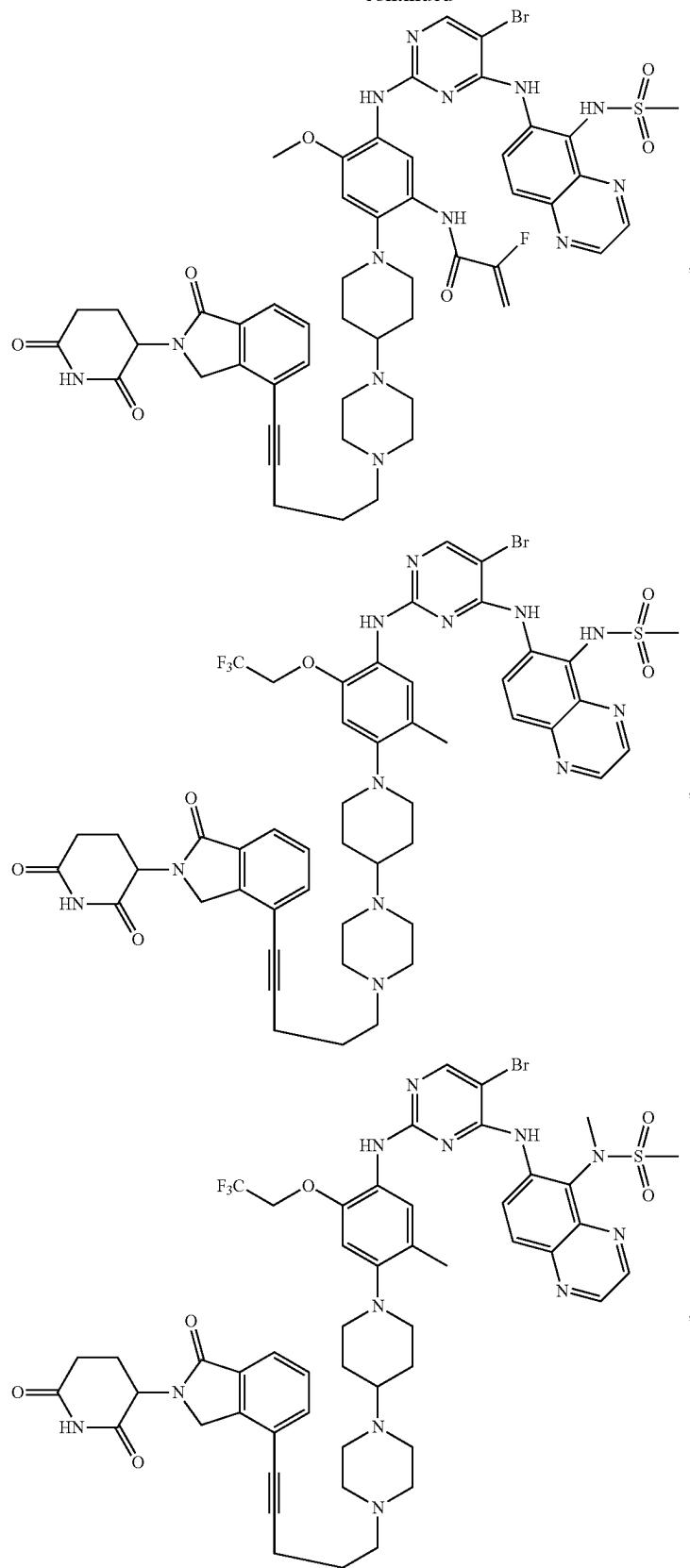




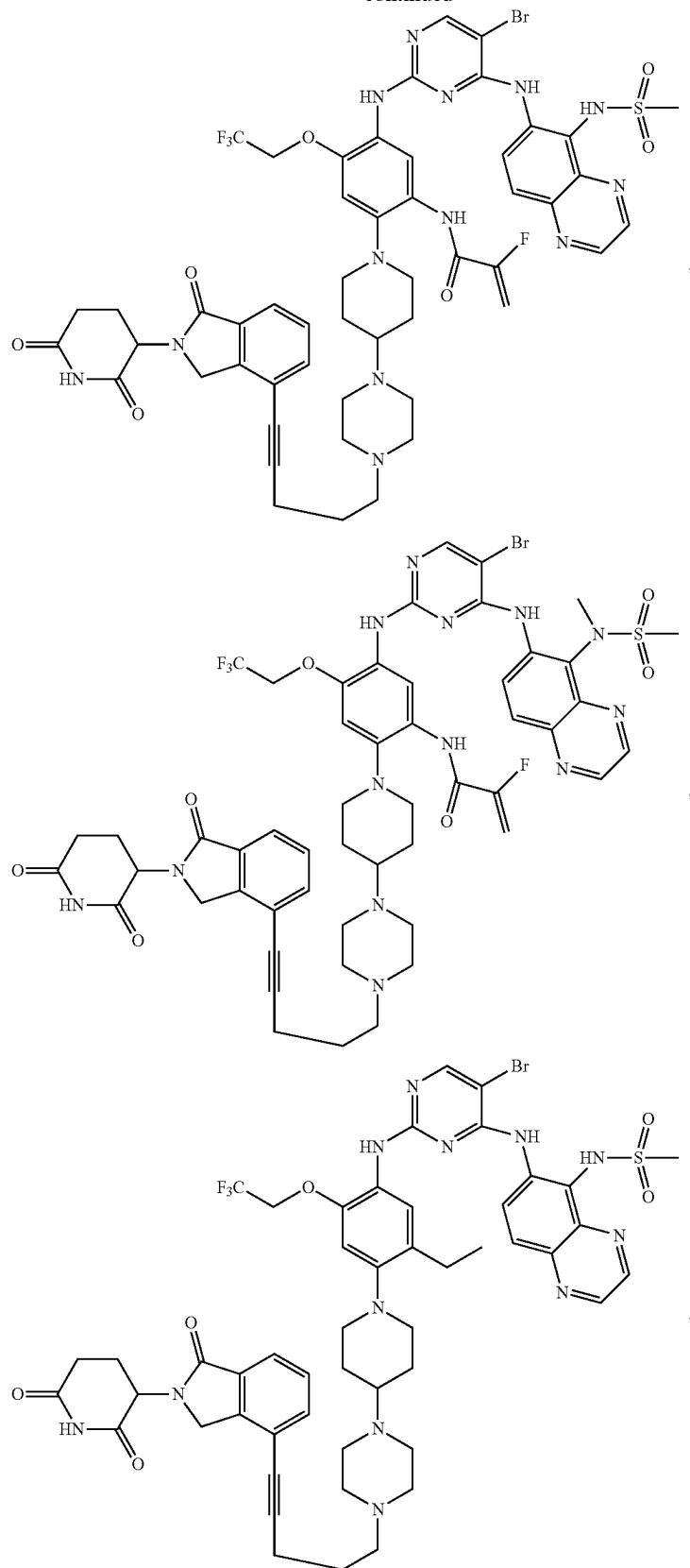




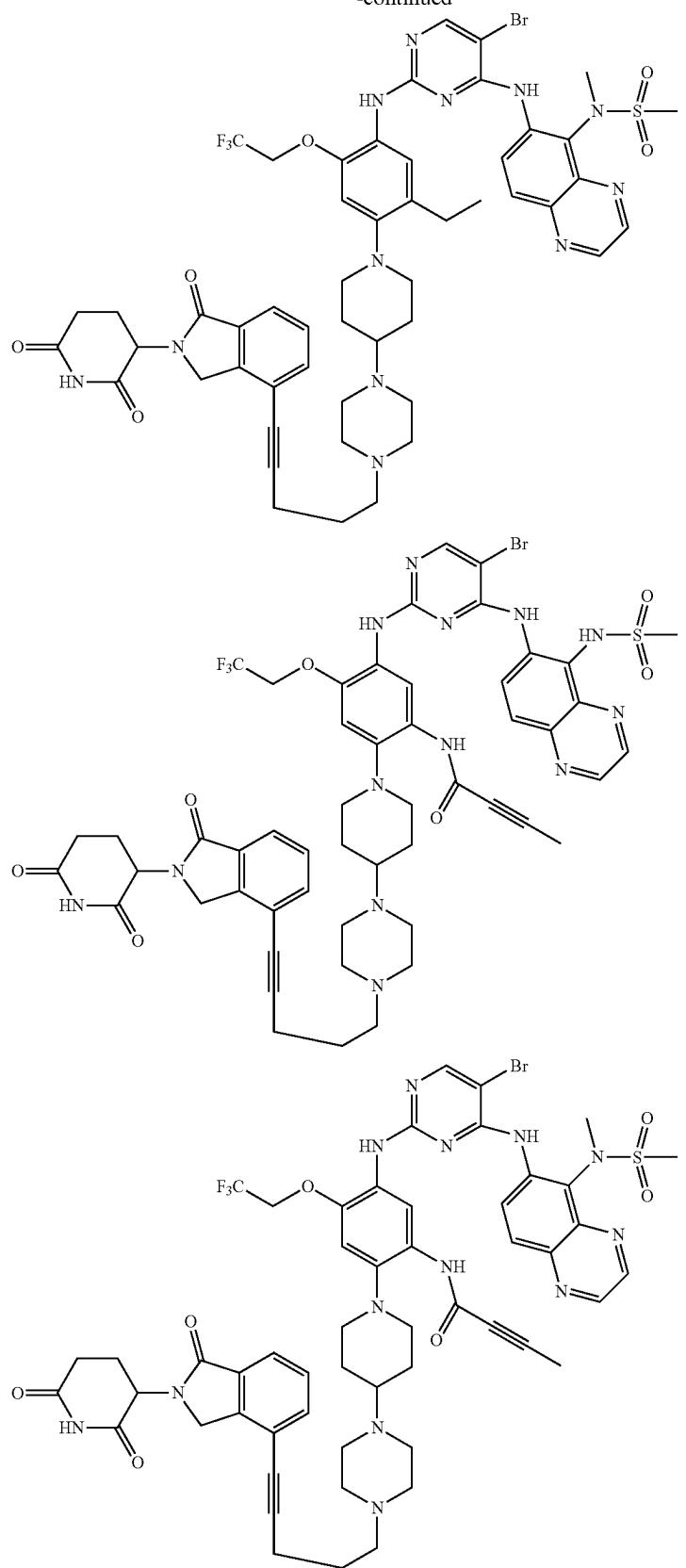
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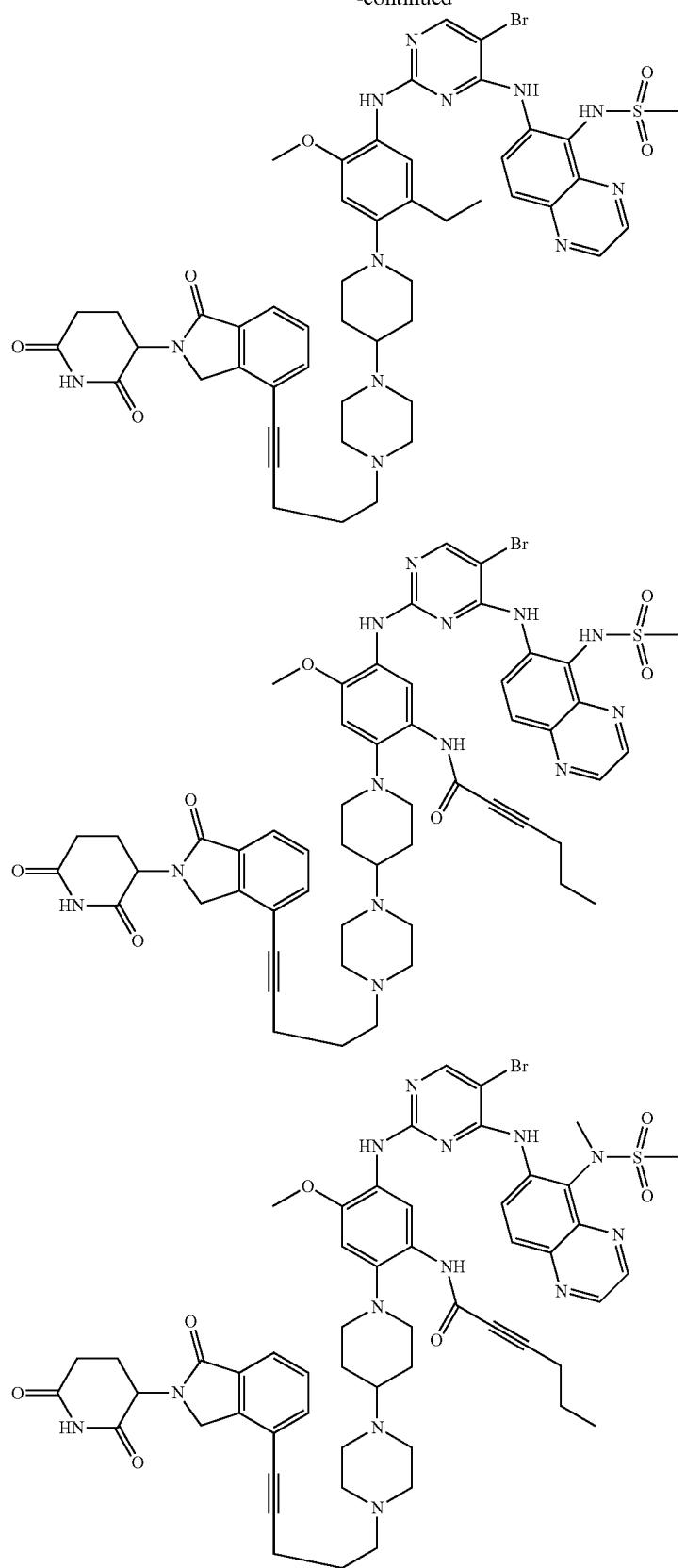
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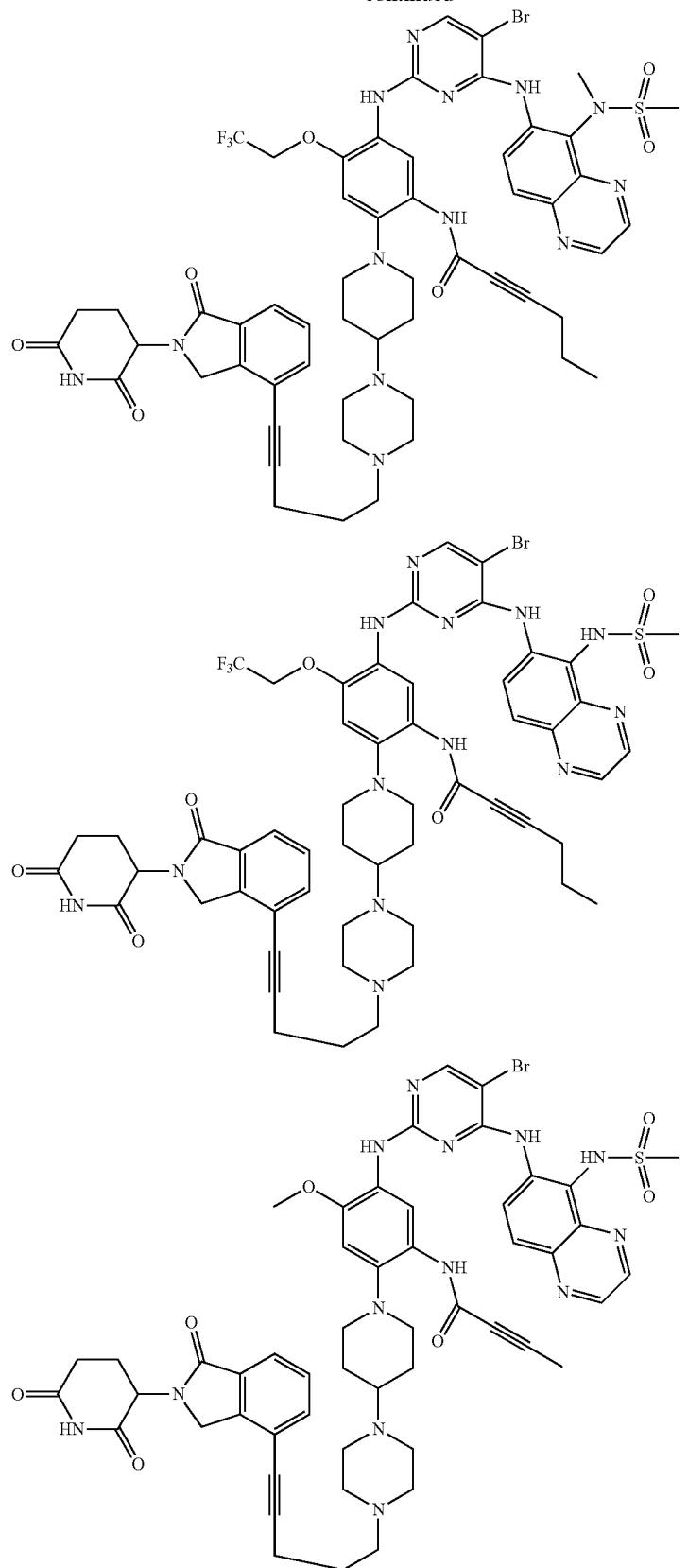
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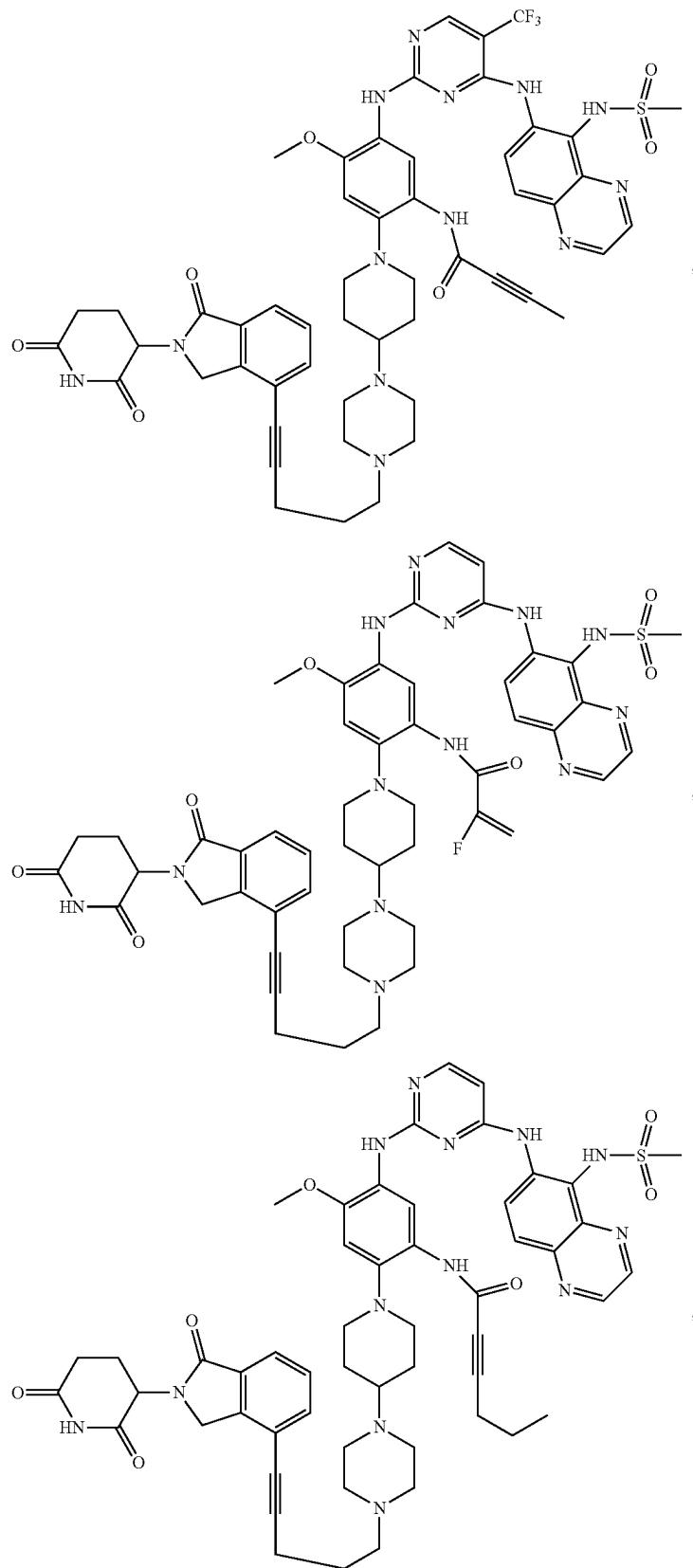
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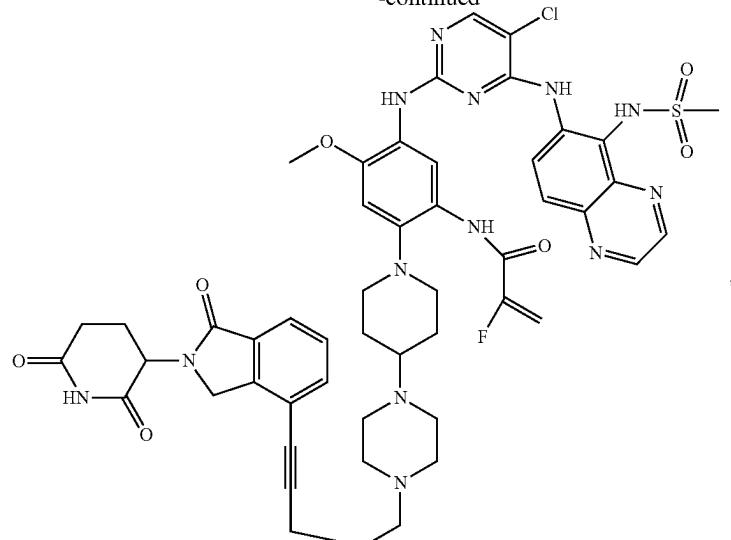
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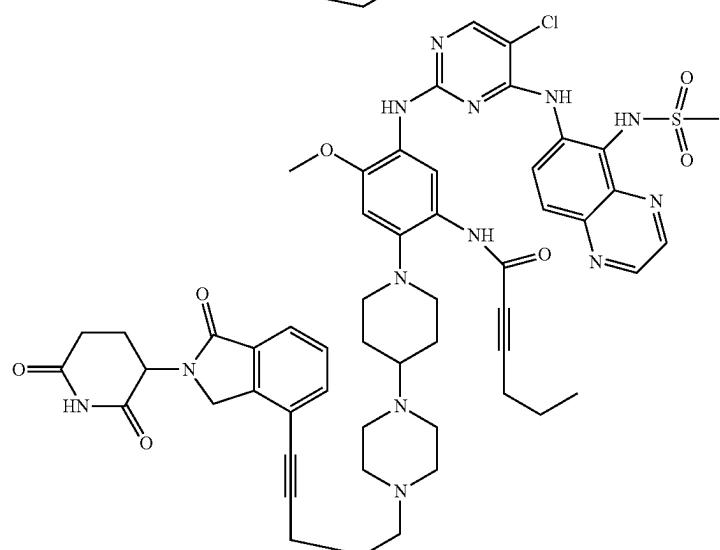
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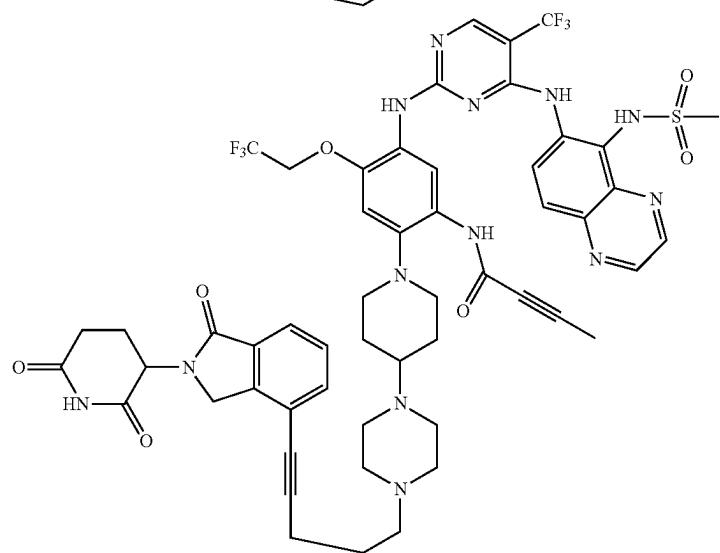
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and



[0488] The compounds of the present disclosure may include one or more asymmetric centers, and thus may exist in a variety of stereoisomeric forms, for example, enantiomers and/or diastereomers. For example, the compounds of the present disclosure may be in the form of an individual enantiomer, diastereomer or geometric isomer (e.g., cis- and trans-isomers), or may be in the form of a mixture of stereoisomers, including racemic mixture and a mixture enriched in one or more stereoisomers. The isomers can be separated from the mixture by the methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or alternative isomers can be prepared by asymmetric synthesis.

[0489] It will be understood by those skilled in the art that the organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates." Where the solvent is water, the complex is known as "hydrate." The present disclosure encompasses all solvates of the compounds of the present disclosure.

[0490] The term "solvate" refers to forms of a compound or a salt thereof, which are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, etc. The compounds described herein can be prepared, for example, in crystalline form, and can be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In some cases, the solvates will be capable of isolation, for example, when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. "Solvate" includes both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0491] The term "hydrate" refers to a compound that is associated with water. Generally, the number of water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, hydrates of a compound can be represented, for example, by a general formula $R \cdot x H_2O$, wherein R is the compound, and x is a number greater than 0. Given compounds can form more than one type of hydrates, including, for example, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, for example, hemihydrates ($R \cdot 0.5H_2O$)) and polyhydrates (x is a number greater than 1, for example, dihydrates ($R \cdot 2H_2O$) and hexahydrates ($R \cdot 6H_2O$)).

[0492] Compounds of the present disclosure may be in an amorphous or a crystalline form (polymorph). Furthermore, the compounds of the present disclosure may exist in one or more crystalline forms. Therefore, the present disclosure includes all amorphous or crystalline forms of the compounds of the present disclosure within its scope. The term "polymorph" refers to a crystalline form of a compound (or a salt, hydrate or solvate thereof) in a particular crystal packing arrangement. All polymorphs have the same elemental composition. Different crystalline forms generally have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shapes, optical and electrical properties, stability, and solubility. Recrystallization solvents, rate of crystallization, storage temperatures, and other factors may cause one crystalline form to domi-

nate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0493] The present disclosure also comprises compounds that are labeled with isotopes (isotope variants), which are equivalent to those described in formula (I), but one or more atoms are replaced by atoms having an atom mass or mass number that are different from that of atoms that are common in nature. Examples of isotopes which may be introduced into the compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as 2H , 3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds of the present disclosure that comprise the above isotopes and/or other isotopes of other atoms, prodrugs thereof and pharmaceutically acceptable salts of said compounds or prodrugs all are within the scope of the present disclosure. Certain isotope-labeled compounds of the present disclosure, such as those incorporating radioactive isotopes (e.g., 3H and ^{14}C), can be used for the measurement of the distribution of drug and/or substrate in tissue. Tritium, which is 3H and carbon-14, which is ^{14}C isotope, are yet alternative, because they are easy to prepare and detect. Furthermore, replaced by heavier isotopes, such as deuterium, which is 2H , may provide therapeutic benefits due to the higher metabolic stability, such as prolonging the half-life in vivo or decreasing the dosage requirements, and thus may be alternative in some cases. Isotope-labeled compounds of formula (I) of the present disclosure and prodrugs thereof can be prepared generally by using readily available isotope-labeled reagents to replace non-isotope-labeled reagents in the following schemes and/or the procedures disclosed in the examples and preparation examples.

[0494] In addition, prodrugs are also included within the context of the present disclosure. The term "prodrug" as used herein refers to a compound that is converted into an active form that has medical effects in vivo by, for example, hydrolysis in blood. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, A.C.S. Symposium Series, Vol. 14, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19 (2) 115-130, each of which are incorporated herein by reference.

[0495] The prodrugs are any covalently bonded compounds of the present disclosure, which release the parent compound in vivo when the prodrug is administered to a patient. Prodrugs are typically prepared by modifying functional groups in such a way that the modifications can be cleaved either by routine manipulation or decompose in vivo to yield the parent compound. Prodrugs include, for example, compounds of the present disclosure wherein the hydroxyl, amino or sulphydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxyl, amino or sulphydryl groups. Thus, representative examples of prodrugs include (but are not limited to) the acetate/acetamide, formate/formamide and benzoate/benzamide derivatives of the hydroxyl, amino or sulphydryl functional groups of the compounds of formula (I). Furthermore, in the case of carboxylic acid ($-COOH$), esters such as methyl esters and ethyl esters, etc. can be employed. The ester itself may be active in their own and/or hydrolyzable

under in vivo conditions in the human body. Suitable pharmaceutically acceptable in vivo hydrolysable ester groups include those groups that can readily break down in the human body to release the parent acids or salts thereof.

[0496] The present disclosure also provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salts thereof, and pharmaceutically acceptable carriers, diluents or excipients thereof. All of these forms belong to the present disclosure.

Pharmaceutical Compositions and Kits

[0497] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure (also referred to as the "active ingredient") and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition comprises an effective amount of the compound of the present disclosure. In certain embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound of the present disclosure. In certain embodiments, the pharmaceutical composition comprises a prophylactically effective amount of the compound of the present disclosure.

[0498] A pharmaceutically acceptable excipient for use in the present disclosure refers to a non-toxic carrier, adjuvant or vehicle which does not destroy the pharmacological activity of the compound formulated together. Pharmaceutically acceptable carriers, adjuvants, or vehicles that may be used in the compositions of the present disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (e.g., human serum albumin), buffer substances (such as phosphate), glycine, sorbic acid, potassium sorbate, a mixture of partial glycerides of saturated plant fatty acids, water, salt or electrolyte (such as protamine sulfate), disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salt, silica gel, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based materials, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylate, wax, polyethylene-polyoxypropylene block polymers, polyethylene glycol and lanolin.

[0499] The present disclosure also includes kits (e.g., pharmaceutical packs). Kits provided may include a compound disclosed herein, other therapeutic agents, and a first and a second containers (e.g., vials, ampoules, bottles, syringes, and/or dispersible packages or other materials) containing the compound disclosed herein or other therapeutic agents. In some embodiments, kits provided can also optionally include a third container containing a pharmaceutically acceptable excipient for diluting or suspending the compound disclosed herein and/or other therapeutic agent. In some embodiments, the compound disclosed herein provided in the first container and the other therapeutic agents provided in the second container is combined to form a unit dosage form.

Administration

[0500] The pharmaceutical composition provided by the present disclosure can be administered by a variety of routes including, but not limited to, oral administration, parenteral administration, inhalation administration, topical administration, rectal administration, nasal administration, oral administration, vaginal administration, administration by implant or other means of administration. For example,

parenteral administration as used herein includes subcutaneous administration, intradermal administration, intravenous administration, intramuscular administration, intra-articular administration, intraarterial administration, intrasynovial administration, intrasternal administration, intracerebroventricular administration, intralesional administration, and intracranial injection or infusion techniques.

[0501] Generally, the compounds provided herein are administered in an effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0502] When used to prevent the disorder disclosed herein, the compounds provided herein will be administered to a subject at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Subjects at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0503] The pharmaceutical compositions provided herein can also be administered chronically ("chronic administration"). Chronic administration refers to administration of a compound or pharmaceutical composition thereof over an extended period of time, e.g., for example, over 3 months, 6 months, 1 year, 2 years, 3 years, 5 years, etc, or may be continued indefinitely, for example, for the rest of the subject's life. In certain embodiments, the chronic administration is intended to provide a constant level of the compound in the blood, e.g., within the therapeutic window over the extended period of time.

[0504] The pharmaceutical compositions of the present disclosure may be further delivered using a variety of dosing methods. For example, in certain embodiments, the pharmaceutical composition may be given as a bolus, e.g., in order to raise the concentration of the compound in the blood to an effective level. The placement of the bolus dose depends on the systemic levels of the active ingredient desired throughout the body, e.g., an intramuscular or subcutaneous bolus dose allows a slow release of the active ingredient, while a bolus delivered directly to the veins (e.g., through an IV drip) allows a much faster delivery which quickly raises the concentration of the active ingredient in the blood to an effective level. In other embodiments, the pharmaceutical composition may be administered as a continuous infusion, e.g., by IV drip, to provide maintenance of a steady-state concentration of the active ingredient in the subject's body. Furthermore, in still yet other embodiments, the pharmaceutical composition may be administered as first as a bolus dose, followed by continuous infusion.

[0505] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled,

premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or alternatively from about 1 to about 40% by weight) with the remainder being various vehicles or excipients and processing aids helpful for forming the desired dosing form.

[0506] With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of the compound provided herein, with alternative doses each providing from about 0.1 to about 10 mg/kg, and especially about 1 to about 5 mg/kg.

[0507] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses, generally in an amount ranging from about 0.01 to about 20% by weight, alternatively from about 0.1 to about 20% by weight, alternatively from about 0.1 to about 10% by weight, and still alternatively from about 0.5 to about 15% by weight.

[0508] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[0509] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0510] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable excipients known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable excipient and the like.

[0511] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s). When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or Formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[0512] The compounds provided herein can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[0513] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of *Remington's Pharmaceutical Sciences*, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[0514] The compounds of the present disclosure can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in *Remington's Pharmaceutical Sciences*.

[0515] The present disclosure also relates to the pharmaceutically acceptable formulations of a compound of the present disclosure. In one embodiment, the formulation comprises water. In another embodiment, the formulation comprises a cyclodextrin derivative. The most common cyclodextrins are α -, β - and γ -cyclodextrins consisting of 6, 7 and 8 α -1,4-linked glucose units, respectively, optionally comprising one or more substituents on the linked sugar moieties, which include, but are not limited to, methylated, hydroxyalkylated, acylated, and sulfoalkylether substitution. In certain embodiments, the cyclodextrin is a sulfoalkyl ether β -cyclodextrin, e.g., for example, sulfobutyl ether β -cyclodextrin, also known as Captisol. See, e.g., U.S. Pat. No. 5,376,645. In certain embodiments, the formulation comprises hexapropyl- β -cyclodextrin (e.g., 10-50% in water).

Treatment

[0516] As stated herein, it is known that EGFR kinase have roles in tumourigenesis as well as numerous other diseases. We have found that the compounds of the present disclosure possess potent anti-tumour activity which it is believed is afforded by way of inhibition of EGFR kinase.

[0517] The compounds of the present disclosure are of value as anti-tumour agents. Particularly, the compounds of the present disclosure are of value as anti-proliferative, apoptotic and/or anti-invasive agents in the containment and/or treatment of solid and/or liquid tumour disease. Particularly, the compounds of the present disclosure are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of EGFR. Further, the compounds of the present disclosure are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by EGFR. The compounds may thus be used to produce an EGFR enzyme inhibitory effect in a warm-blooded animal in need of such treatment.

[0518] As stated herein, inhibitors of EGFR kinase should be of therapeutic value for the treatment of cancer, such as ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukemia, lymphoma, non-Hodgkin's lymphoma, gastric cancer, lung cancer, hepatocellular cancer, stomach cancer, gastrointestinal stromal tumor (GIST), thyroid cancer, cancer of bile duct, endometrial cancer, kidney cancer, anaplastic large cell lymphoma, acute myeloid leukemia (AML), multiple myeloma, melanoma, and mesothelioma.

[0519] Anti-cancer effects which are accordingly useful in the treatment of cancer in a patient include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present disclosure

include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

[0520] A EGFR kinase inhibitor, or a pharmaceutically acceptable salt thereof, may also be useful for the treatment patients with cancers, including, but not limited to, haematologic malignancies such as leukaemia, multiple myeloma, lymphomas such as Hodgkin's disease, non-Hodgkin's lymphomas (including mantle cell lymphoma), and myelodysplastic syndromes, and also solid tumours and their metastases such as breast cancer, lung cancer (non-small cell lung cancer (NSCL), small cell lung cancer (SCLC), squamous cell carcinoma), endometrial cancer, tumours of the central nervous system such as gliomas, dysembryoplastic neuroepithelial tumour, glioblastoma multiforme, mixed gliomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma and teratoma, cancers of the gastrointestinal tract such as gastric cancer, oesophageal cancer, hepatocellular (liver) carcinoma, cholangiocarcinomas, colon and rectal carcinomas, cancers of the small intestine, pancreatic cancers, cancers of the skin such as melanomas (in particular metastatic melanoma), thyroid cancers, cancers of the head and neck and cancers of the salivary glands, prostate, testis, ovary, cervix, uterus, vulva, bladder, kidney (including renal cell carcinoma, clear cell and renal oncocyroma), squamous cell carcinomas, sarcomas such as osteosarcoma, chondrosarcoma, leiomyosarcoma, soft tissue sarcoma, Ewing's sarcoma, gastrointestinal stromal tumour (GIST), Kaposi's sarcoma, and paediatric cancers such as rhabdomyosarcomas and neuroblastomas.

[0521] The effective dose of the compound of the present disclosure is usually at an average daily dose of 0.01 mg to 50 mg compound/kg of patient weight, alternatively 0.1 mg to 25 mg compound/kg of patient weight, in single or multiple administrations. Generally, the compound of the present disclosure can be administered to the patient who needs this treatment in the daily dose range of about 1 mg to about 3500 mg per patient, alternatively 10 mg to 1000 mg. For example, the daily dose per patient can be 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 500, 600, 700, 800, 900 or 1000 mg. It can be administered once or several times a day, weekly (or several days apart) or on an intermittent schedule. For example, on a weekly basis (e.g. every Monday), the compound can be administered one or more times a day, variably for several weeks, for example 4-10 weeks. Or, the compound may be administered daily for several days (e.g. 2-10 days), and then a few days (e.g. 1-30 days) without administering the compound, repeating the cycle arbitrarily or repeating a given number of times, e.g. 4-10 cycles. For example, the compound of the present disclosure can be administered daily for 5 days, and then interrupted for 9 days, and then administered daily for 5 days, then interrupted for 9 days, and so on, repeating the cycle arbitrarily or repeating 4-10 times in total.

Combination Therapy

[0522] The treatment defined herein may be applied as a sole therapy or may involve, in addition to the compounds of the present disclosure, conventional surgery or radiotherapy or chemotherapy. Accordingly, the compounds of

the present disclosure can also be used in combination with existing therapeutic agents for the treatment of cancer.

[0523] In addition to the compound disclosed herein, conventional surgery, radiotherapy, chemotherapy, or immunotherapy can be used for the treatment. Such chemotherapy can be administered simultaneously, sequentially or separately with the compound disclosed herein and may include one or more of the following categories of anti-tumour agents:

[0524] (i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antimicrobials (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example *vinca* alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

[0525] (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and ciproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5a-reductase such as finasteride;

[0526] (iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylendioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline [AZD0530 (saracatinib)], N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825) and bosutinib (SKI-606), and metalloprotease inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to heparanase]; (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin], the anti-EGFR antibody panitumumab and the anti-erbB1 antibody cetuximab [Erbitux, C225]); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)-quinazolin-4-amine (gefitinib, ZD 1839), N-(3-ethylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepato-

cyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (RI 15777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, PI3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulinlike growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 and AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

[0527] (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-human vascular endothelial cell growth factor antibody bevacizumab (Avastin) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SUI 1248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin)];

[0528] (vi) vascular damaging agents such as combretastatin A4;

[0529] (vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

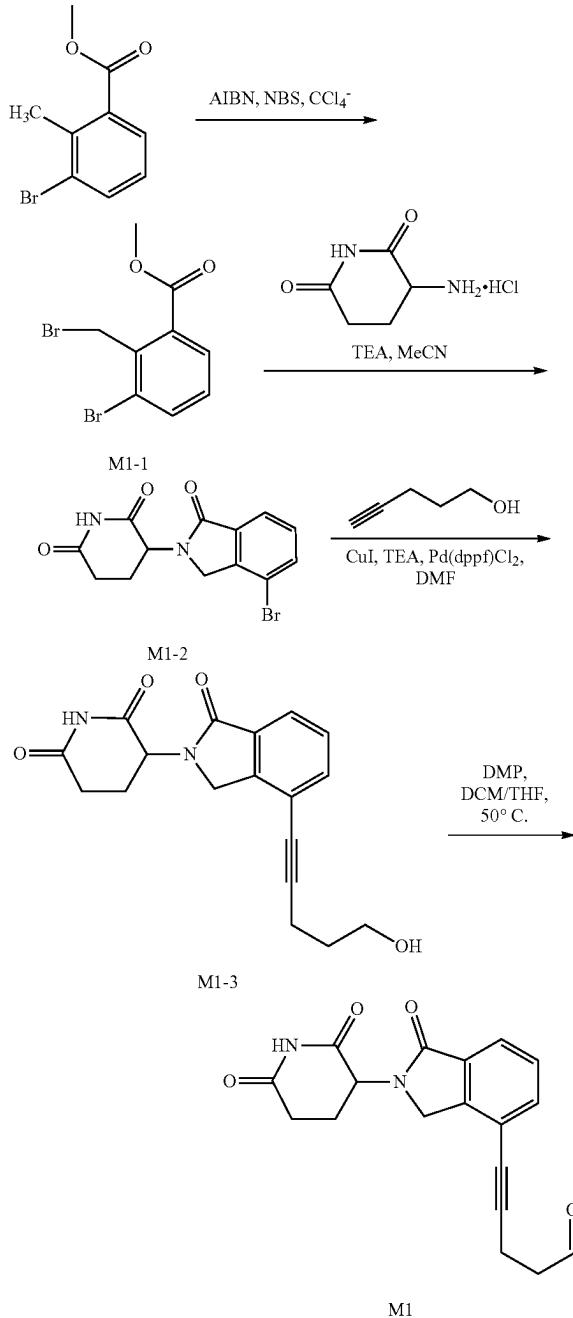
[0530] (viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

[0531] (ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

[0532] (x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines, approaches using anti-idiotype antibodies, approaches to decrease the function of immune suppressive cells such as regulatory T cells, myeloid-derived suppressor cells or IDO (indoleamine 2,3,-dehydrogenase)-expressing dendritic cells, and approaches using cancer vaccines consisting of proteins or peptides derived from tumour-associated antigens such as NY-ESO-1, MAGE-3, WT1 or Her2/neu.

EXAMPLES

Preparation of 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-ynal (M1)



Step 1

[0533] Methyl 3-bromo-2-methylbenzoate (1.14 g, 5.0 mmol) was dissolved in 20.0 mL of CCl_4 . Under nitrogen protection, NBS (1.34 g, 7.5 mmol) and AIBN (164 mg, 1.0 mmol) were added. The temperature was raised to 85°C , and the reaction was refluxed for 20 h. TLC showed that

there was no raw material remaining. The reaction solution was cooled to room temperature, and filtered with suction. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by Flash to give 1.35 g of product M1-1 as light-yellow oil. LCMS: $[M+H]^+=307$, 309.

Step 2

[0534] M1-1 (1.35 g, 4.41 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (941 mg, 5.74 mmol) were dispersed in 25.0 mL of anhydrous MeCN, and TEA (580 mg, 5.74 mmol) was added. The temperature was raised to 80° C., and the reaction was refluxed for 16 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and filtered with suction. The filter cake was rinsed three times with MeCN, and the solid was dried to give compound M1-2 (1.31 g, yield 92.3%). LCMS: $[M+H]^+=323$, 325.

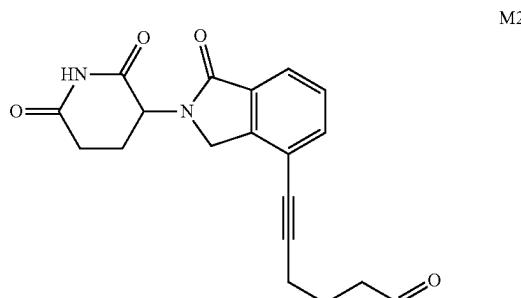
Step 3

[0535] M1-2 (322 mg, 1.0 mmol), CuI (19 mg, 0.1 mmol) and Pd(dppf)Cl₂ (73.1 mg, 0.1 mmol) were dispersed in 10.0 mL of anhydrous DMF. Under N₂ protection, 4-alkynyl-1-pentanol (210 mg, 2.5 mmol) and TEA (303 mg, 3.0 mmol) were added in sequence. The reaction was heated to 70° C. for 20 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature and purified by RP-Flash to give a crude product M1-3 as white solid (410 mg, yield 94.1%). LCMS: $[M+H]^+=327$.

Step 4

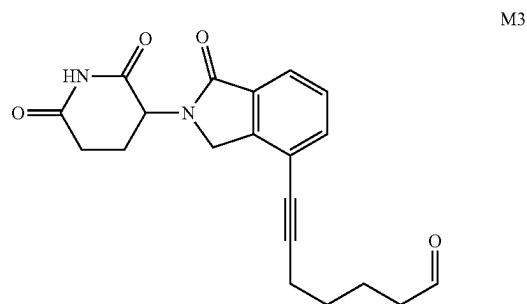
[0536] M1-3 (400 mg, 0.920 mmol) was dissolved in a mixed solvent of 150 mL of anhydrous dichloromethane and 10 mL of anhydrous tetrahydrofuran. Under N₂ protection, Dess-Martin reagent (1.04 g, 2.454 mmol) was added, the temperature was raised to 50° C., and the reaction was refluxed for 2.0 h. The reaction was completed as determined by thin layer chromatography. The reaction solution was cooled to room temperature. 20 mL of saturated NaHCO₃ solution and 20 mL of saturated Na₂S₂O₃ solution were added to the reaction solution. The mixture was stirred vigorously at room temperature for 5 min. The organic layer was separated, dried with anhydrous sodium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by Flash to give product M1 as a light yellow solid (280 mg, 93.3%). LCMS: $[M+H]^+=325$.

Preparation of 6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)hex-5-yneal (M2)



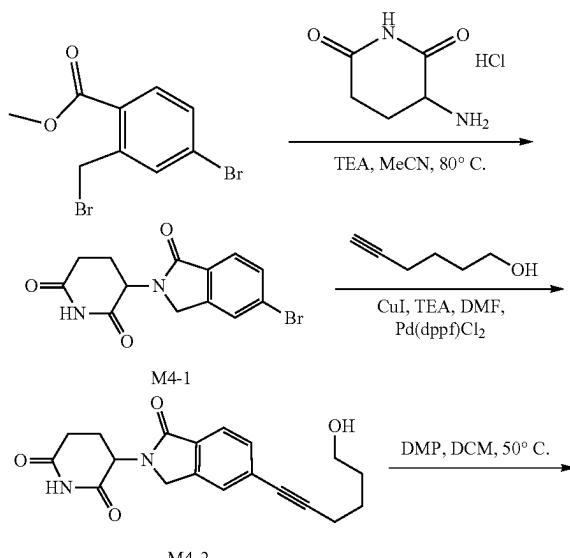
[0537] It was prepared by the same method as for the preparation of M1, except that 4-alkynyl-1-pentanol in step 3 was replaced by 5-alkynyl-1-hexanol to finally give compound M2. LCMS: $[M+H]^+=339$.

Preparation of 7-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)hept-6-yneal (M3)



[0538] It was prepared by the same method as for the preparation of M1, except that 4-alkynyl-1-pentanol in step 3 was replaced by 6-alkynyl-1-heptanol to finally give compound M3. LCMS: $[M+H]^+=353$.

Preparation of 6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)hex-5-yneal (M4)



Step 1

[0539] Methyl 4-bromo-2-(bromomethyl)benzoate (300 mg, 0.974 mmol), 3-aminopiperidine-2,6-dione hydrochloride

ride (208 mg, 1.266 mmol), and TEA (128 mg, 1.266 mmol) were dissolved in 5 mL of acetonitrile. Under nitrogen protection, the reaction was stirred at 80° C. overnight. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure to give a crude product, which was purified by Flash to give a white solid compound M4-1 (180 mg). LCMS: [M+H]⁺=323, 325.

Step 2

[0540] Compound M4-1 (100 mg, 0.31 mmol), hexyl-5-yn-1-ol (76 mg, 0.78 mmol), cuprous iodide (12 mg, 0.06 mmol), Pd(dppf)Cl₂ (87 mg, 0.12 mmol) and TEA (94 mg, 0.93 mmol) were dissolved in 4 mL of anhydrous DMF. Under nitrogen protection, the mixture was stirred at 70° C. for 5 hours. The solvent was removed under reduced pressure to give a crude product, which was purified by thin layer chromatography to give an off-white solid compound M4-2 (78 mg, yield 72.2%), LCMS: [M+H]⁺=341.

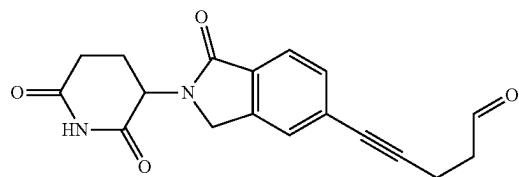
Step 3

[0541] Compound M4-2 (39 mg, 0.115 mmol) and Dess-Martin reagent (73 mg, 0.172 mmol) were dissolved in 15 mL of dichloromethane. The mixture was stirred at 50° C. for 2 hours. The mixture was cooled to room temperature

and quenched with saturated sodium bicarbonate aqueous solution. The organic phase was separated. The aqueous phase was extracted three times with dichloromethane. The organic phases were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product. The crude product was purified by thin layer chromatography to give a white solid compound M4 (30 mg, yield 77.5%), LCMS: [M+H]⁺=339.

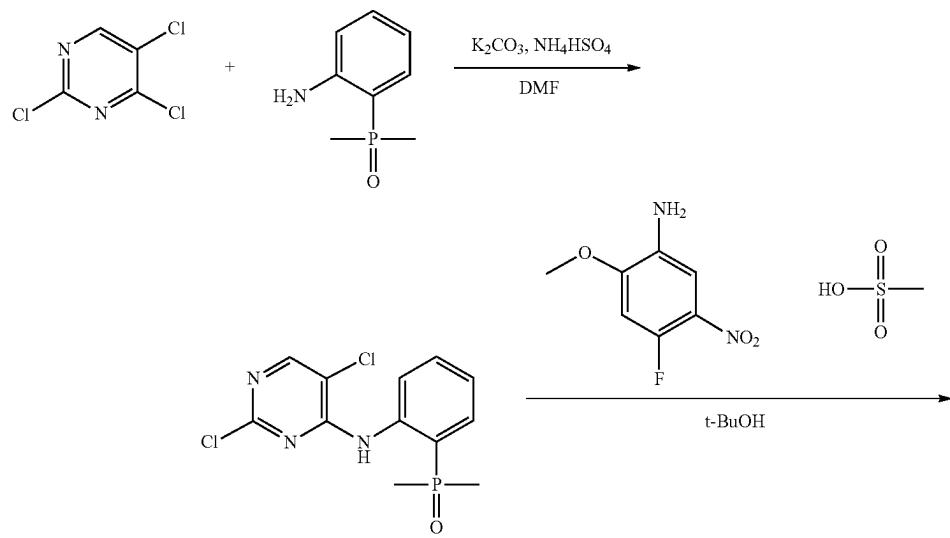
Preparation of 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)pent-4-ynal (M5)

M5

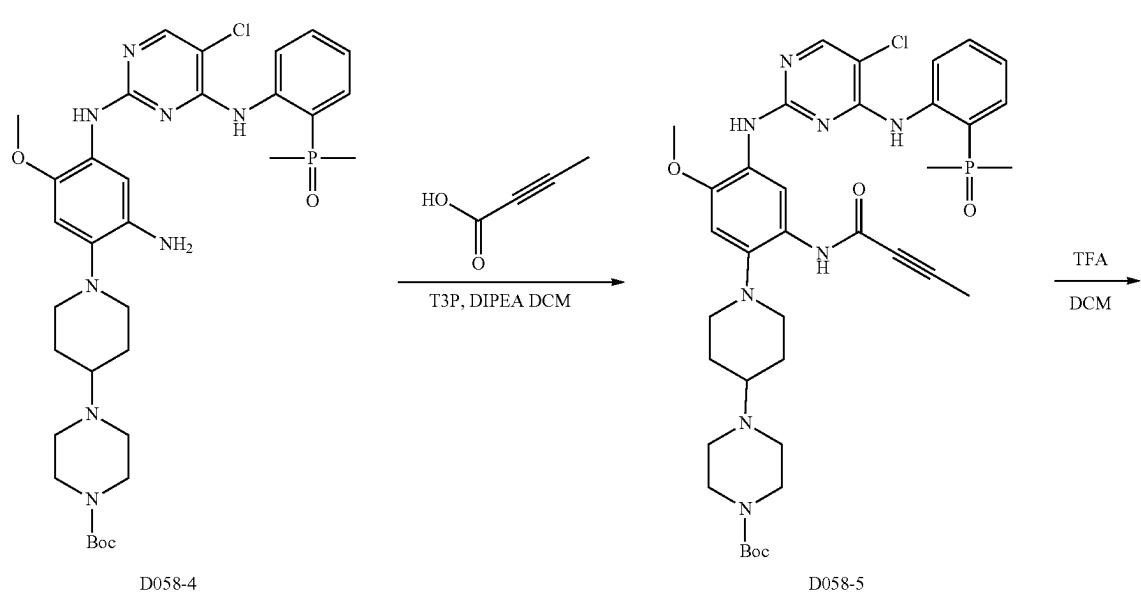
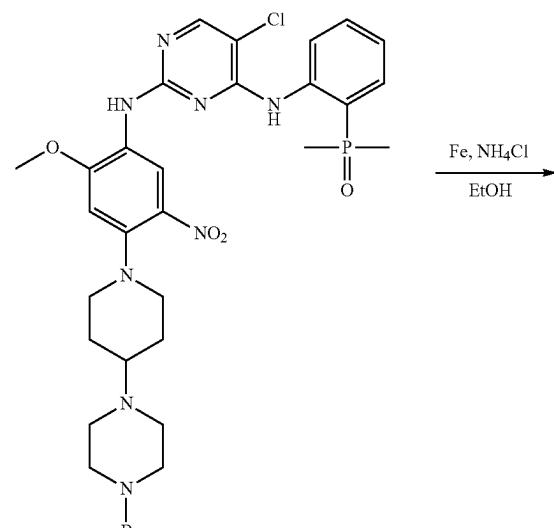
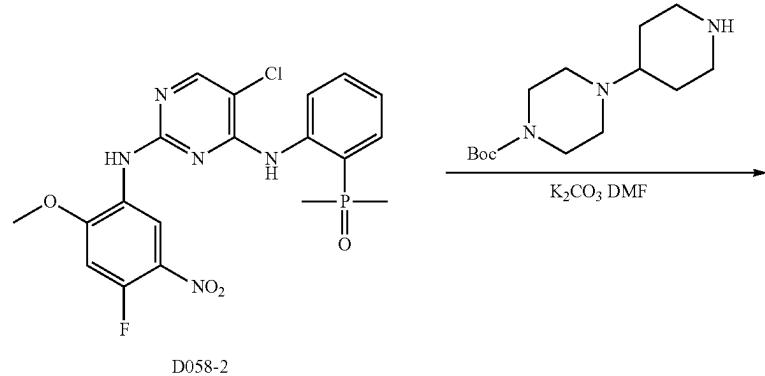


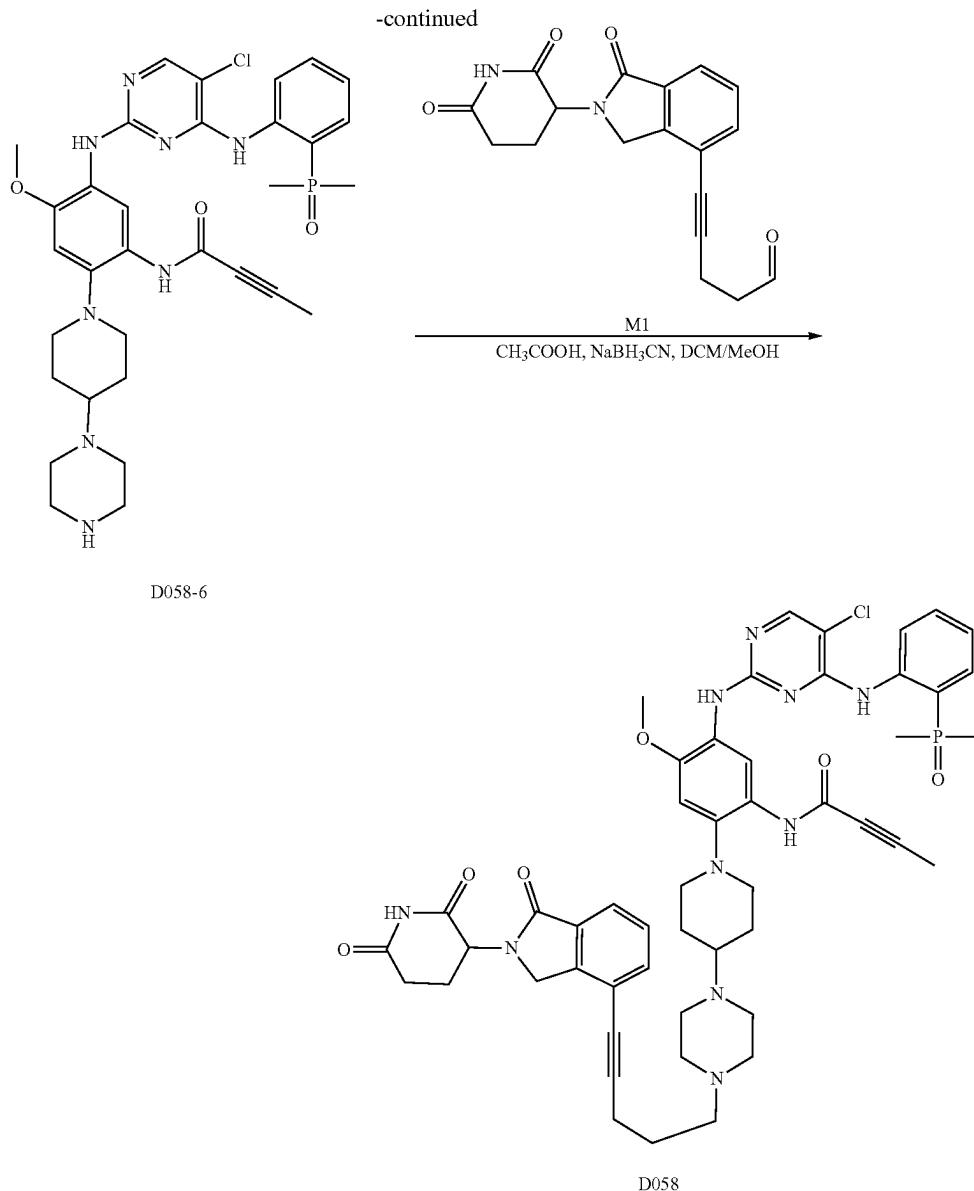
[0542] It was prepared by the same method as for the preparation of M4, except that hexyl-5-yn-1-ol in step 2 was replaced by pentyl-4-yn-1-ol to finally give compound M5. LCMS: [M+H]⁺=325.

Preparation of N-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide (D058)



-continued





Step 1

[0543] 2,4,5-Trichloropyrimidine (9.1 g, 50 mmol), (2-aminophenyl)dimethylphosphine oxide (8.45 g, 50 mmol), NH₄HSO₄ (1.7 g, 5 mmol) and K₂CO₃ (17.25 g, 125 mmol) were dispersed in 120 mL of anhydrous DMF. The reaction was heated to 65° C. for 16 h. The reaction was completed as detected by TLC. The reaction solution was cooled to room temperature, and then filtered with suction. The solid residue was washed with DMF. The filtrate was concentrated under reduced pressure to give a crude product, which was flash purified to give a light yellow solid product D058-1 (10.8 g, 34.3 mmol, 68.6%). LCMS: [M+H]⁺=316.

Step 2

[0544] D058-1 (10.8 g, 34.3 mmol) and 4-fluoro-2-methoxy-5-nitroaniline (6.38 g, 34.3 mmol) were dispersed

in 200 mL of tert butanol. Methanesulfonic acid (13.18 g, 137.2 mmol) was added to the reaction solution. The reaction was heated to 90° C. and refluxed for 16 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and then concentrated under reduced pressure to remove the solvent to give a crude product, which was flash purified to give a light yellow solid product D058-2 (11.6 g, yield 72.7%). LCMS: [M+H]⁺=466.

Step 3

[0545] D058-2 (11.6 g, 24.9 mmol), tert-butyl 4-(piperidin-4-yl)piperazine-1-carboxylate (6.7 g, 24.9 mmol) and K₂CO₃ (10.31 g, 74.7 mmol) were dispersed in 150 mL of anhydrous DMF. The reaction was heated to 60° C. for 12 h. The reaction was completed as detected by LCMS. The

reaction solution was cooled to room temperature, and then filtered with suction. The solid residue was washed with DMF. The filtrate was concentrated under reduced pressure to give a crude product, which was flash purified to give a yellow solid product D058-3 (13.5 g, yield 75.9%). LCMS: $[M+H]^+=715$.

Step 4

[0546] D058-3 (13.5 g, 18.9 mmol), iron powder (6.35 g, 113.4 mmol) and NH_4Cl (50.6 g, 945 mmol) were dispersed in a mixed solvent of 180 mL of ethanol and 60 mL of water. The reaction was heated to 90° C. and refluxed for 2 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and filtered with diatomaceous earth. The solid residue was washed with a mixed solvent of methanol and dichloromethane (150 mL). The filtrate was collected and concentrated under reduced pressure to remove ethanol. The residue was extracted twice with a mixed solvent of methanol and dichloromethane (150 mL). The organic layers were combined and washed sequentially with water (2×80 mL) and saturated brine (1×80 mL). The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D058-4 (11.5 g, 89.0%). LCMS: $[M+H]^+=685$.

Step 5

[0547] D058-4 (11.5 g, 16.8 mmol), 2-alkynylbutyric acid (1.41 g, 16.8 mmol) and T3P (21.37 g, 33.6 mmol) were dispersed in 115 mL of anhydrous dichloromethane. Under N_2 protection, diisopropylethylamine (10.8 g, 84.0 mmol) was added to the reaction solution. The mixture was reacted at room temperature for 2.0 h. The reaction was completed as detected by LCMS. The reaction solution was diluted with 115 mL of dichloromethane and silica gel was directly

added to the sample. The mixture was purified by Flash to give a yellow solid product D058-5 (11.0 g, 87.3%). LCMS: $[M+H]^+=751$.

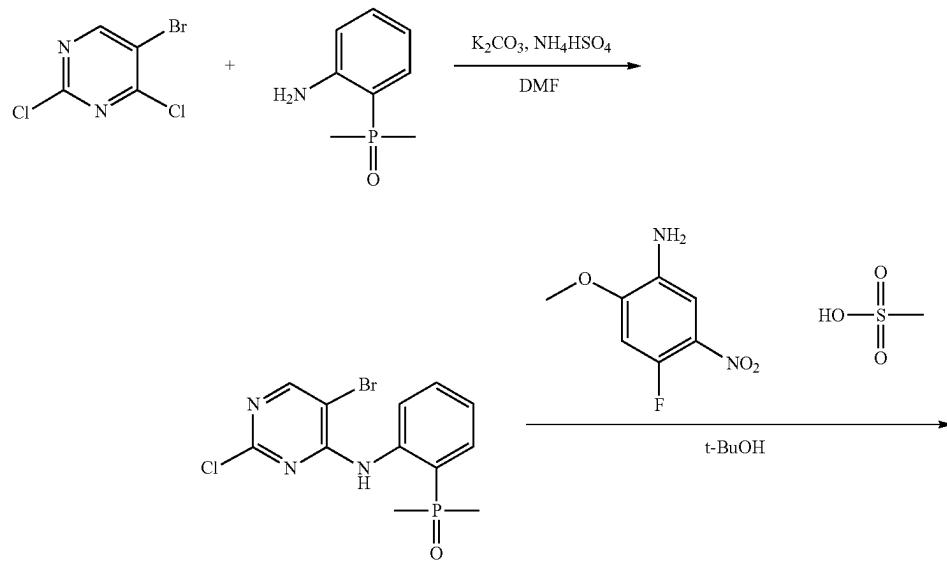
Step 6

[0548] D058-5 (11.0 g, 14.67 mmol) was dissolved in 110 mL of anhydrous dichloromethane. Under N_2 protection, 27.5 mL of trifluoroacetic acid was added to the reaction solution. The mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (200 mL), and then washed with saturated NaHCO_3 solution (2×80 mL) and saturated brine (1×80 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D058-6 (9.4 g). LCMS: $[M+H]^+=651$.

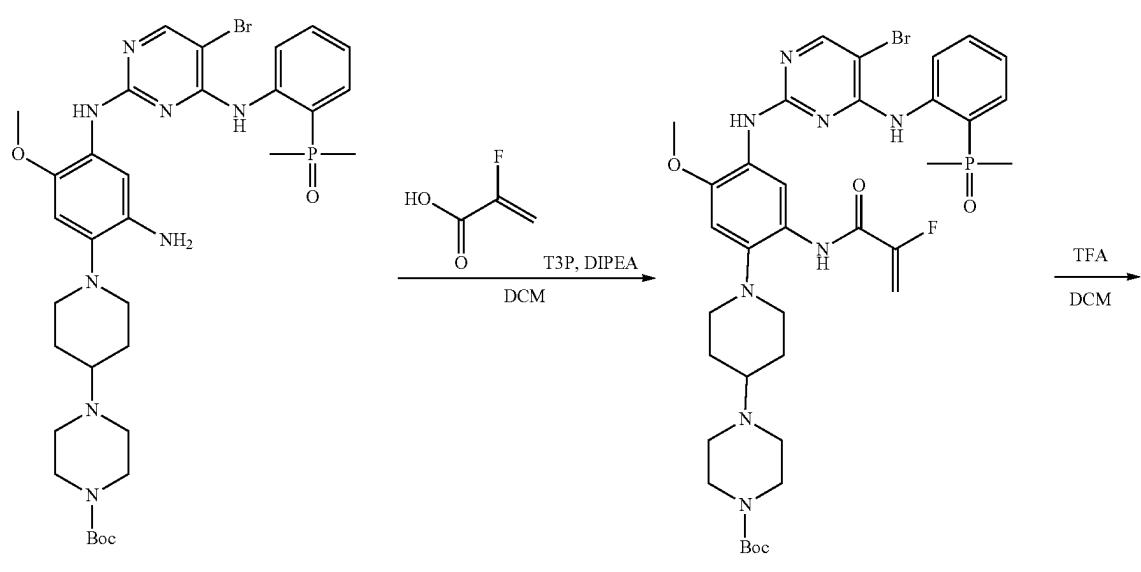
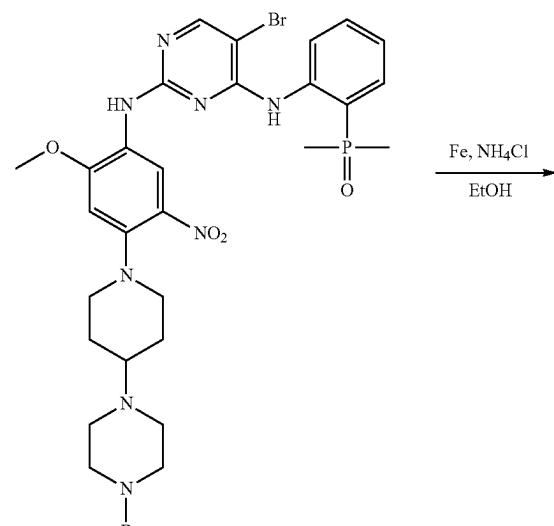
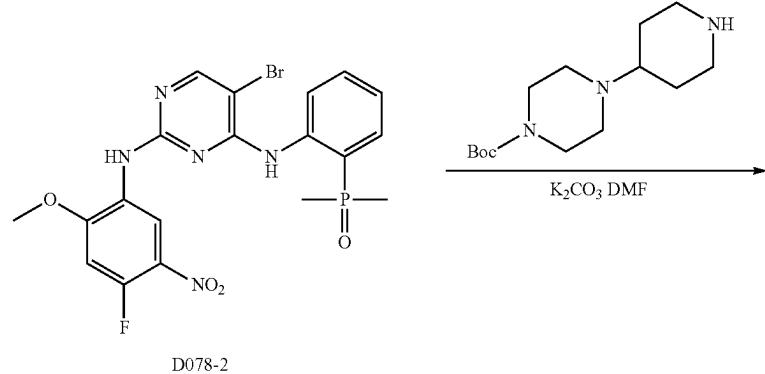
Step 7

[0549] M1 (713 mg, 2.2 mmol) and D058-6 (1.3 g, 2 mmol) were dissolved in a mixed solvent of 260 mL of anhydrous dichloromethane and 26 mL of anhydrous methanol. Under nitrogen protection, CH_3COOH (180 mg, 3 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Solid NaBH_3CN (251 mg, 4 mmol) was then added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample, and the mixture was purified by Flash to give a white solid pure product D058 (1.21 g, yield 63.0%). LCMS: $[M+H]^+=959$.

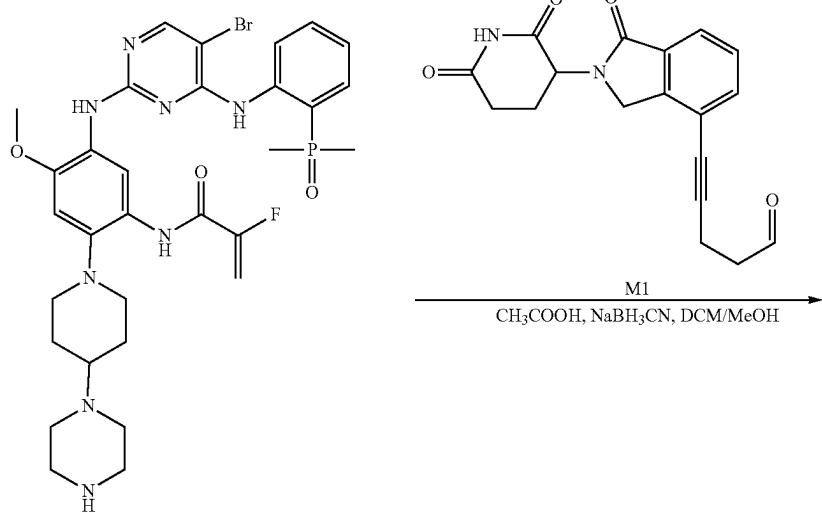
Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D078)



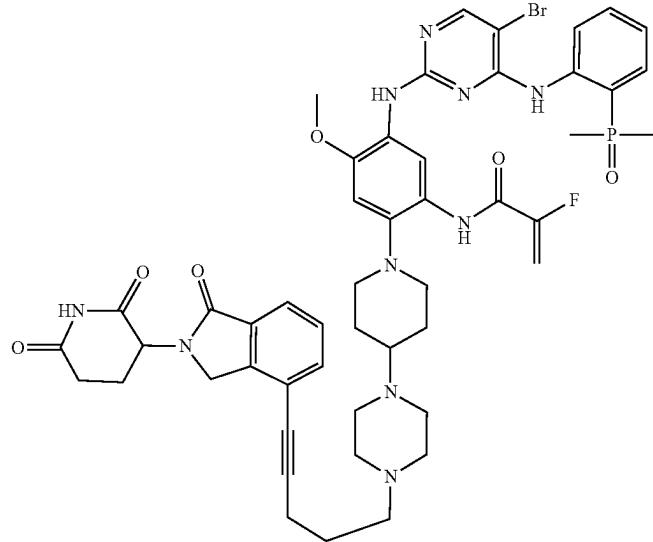
-continued



-continued



D078-6



D078

Step 1

[0550] 5-Bromo-2,4-dichloropyrimidine (5.13 g, 22.5 mmol), (2-aminophenyl) dimethylphosphine oxide (3.8 g, 22.5 mmol), NH_4HSO_4 (0.765 g, 2.25 mmol) and K_2CO_3 (3.73 g, 27.0 mmol) were dispersed in 60.0 mL of anhydrous DMF. The reaction was heated to 65° C. for 16 h. The reaction was completed as detected by TLC. The reaction solution was cooled to room temperature, and then filtered with suction, and the solid residue was washed with DMF. The filtrate was concentrated under reduced pressure to give a crude product, which was flash purified to give a light yellow solid product D078-1 (8.0 g). LCMS: $[\text{M}+\text{H}]^+=360$.

Step 2

[0551] D078-1 (8.0 g, 22.3 mmol) and 4-fluoro-2-methoxy-5-nitroaniline (4.14 g, 22.3 mmol) were dispersed

in 160 mL of tert butanol. Methanesulfonic acid (8.56 g, 89.1 mmol) was added to the reaction solution. The reaction was heated to 90° C. and refluxed for 16 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and then concentrated under reduced pressure to remove the solvent to give a crude product, which was flash purified to give a light yellow solid product D078-2 (9.1 g). LCMS: $[\text{M}+\text{H}]^+=510$.

Step 3

[0552] D078-2 (8.4 g, 16.5 mmol), tert-butyl 4-(piperidin-4-yl)piperazine-1-carboxylate (4.44 g, 16.5 mmol) and K_2CO_3 (6.83 g, 49.5 mmol) were dispersed in 150 mL of anhydrous DMF. The reaction was heated to 60° C. for 12 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and then

filtered with suction, and the solid residue was washed with DMF. The filtrate was concentrated under reduced pressure to give a crude product, which was flash purified to give a yellow solid product D078-3 (7.4 g). LCMS: $[M+H]^+=759$.

Step 4

[0553] D078-3 (7.4 g, 9.76 mmol), iron powder (3.28 g, 58.6 mmol) and NH_4Cl (26.1 g, 488 mmol) were dispersed in a mixed solvent of 150 mL of ethanol and 50 mL of water. The reaction was heated to 90° C. and refluxed for 2 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and filtered with diatomaceous earth by suction. The solid residue was washed with 100 mL of a mixed solvent of ethanol and water. The filtrate was collected and concentrated under reduced pressure to remove ethanol. The residue was extracted twice with a mixed solvent of methanol and dichloromethane (100 mL). The organic layers were combined and washed sequentially with water (2×50 mL) and saturated brine (1×50 mL). The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D078-4 (5.5 g). LCMS: $[M+H]^+=729$.

Step 5

[0554] D078-4 (5.0 g, 6.87 mmol), 2-fluoroacrylic acid (0.742 g, 8.24 mmol) and T3P (8.74 g, 13.74 mmol) were dispersed in 50 mL of anhydrous dichloromethane. Under N_2 protection, diisopropylethylamine (4.43 g, 34.35 mmol) was added to the reaction solution. The mixture was reacted at room temperature for 16 h. The reaction was completed as detected by LCMS. The reaction solution was diluted with 50 mL of dichloromethane and silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D078-5 (4.8 g). LCMS: $[M+H]^+=801$.

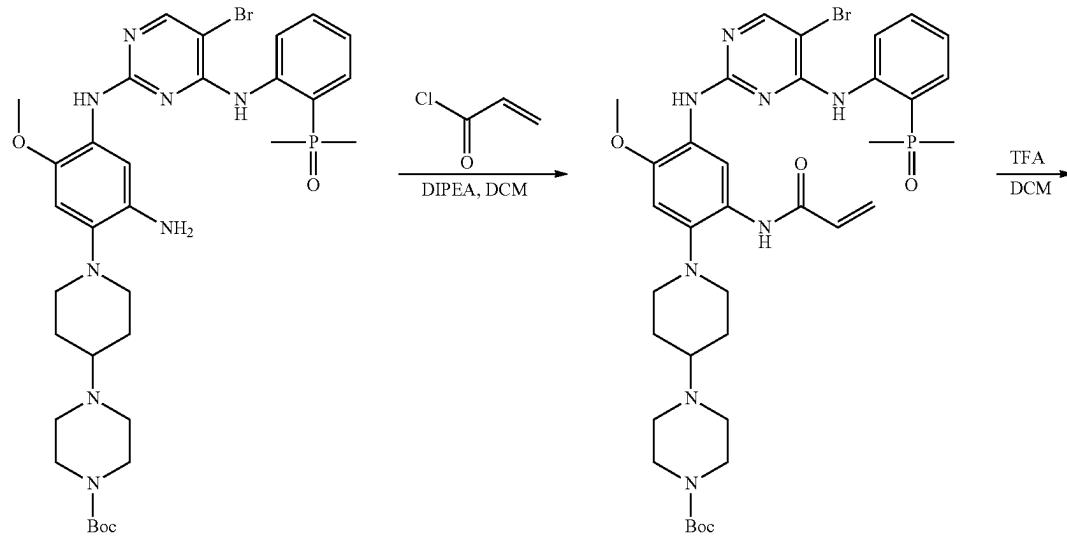
Step 6

[0555] D078-5 (4.8 g, 6.0 mmol) was dissolved in 80 mL of anhydrous dichloromethane. Under N_2 protection, 20 mL of trifluoroacetic acid was added to the reaction solution. The mixture was reacted at room temperature for 1.0 h. LCMS showed that the reaction was completed. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (150 mL), and then washed with saturated NaHCO_3 solution (2×60 mL) and saturated brine (1×60 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D078-6 (4.1 g). LCMS: $[M+H]^+=701$.

Step 7

[0556] M1 (1.95 g, 6.02 mmol) and D078-6 (3.58 g, 5.12 mmol) were dissolved in a mixed solvent of 100.0 mL of anhydrous dichloromethane and 10.0 mL of anhydrous methanol. Under nitrogen protection, CH_3COOH (542 mg, 9.03 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH_3CN (756 mg, 12.04 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to obtain the pure product D078 (3.1 g) as a white solid. LCMS: $[M+H]^+=1009$.

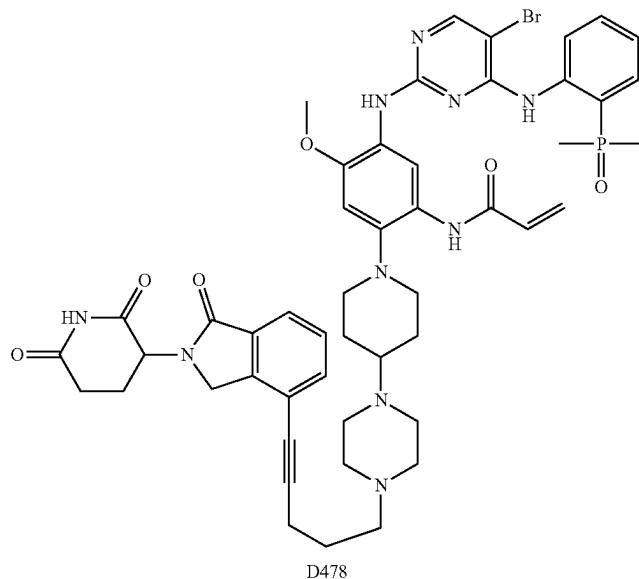
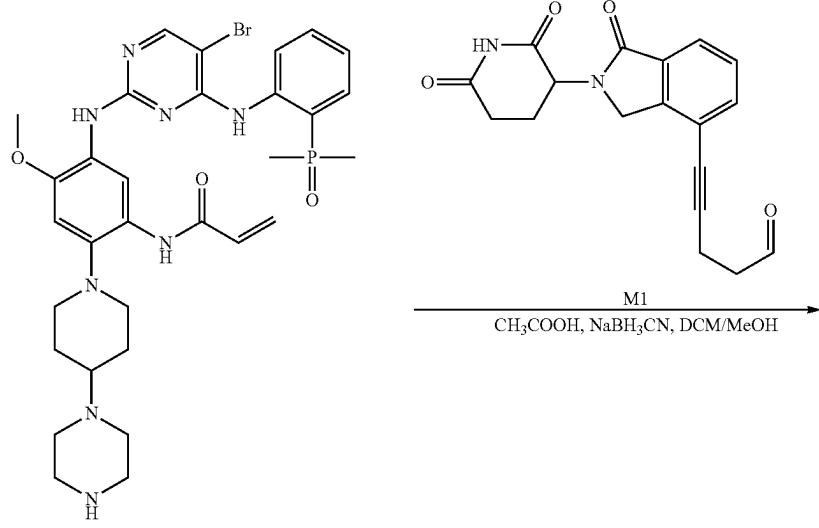
Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D478)



D078-4

D478-1

-continued

**Step 1**

[0557] D078-4 (145.6 mg, 0.2 mmol) and diisopropylethylamine (77.4 mg, 0.6 mmol) were dispersed in 15 mL of anhydrous dichloromethane. Under N₂ protection, acryloyl chloride (19.8 mg, 0.22 mmol, dissolved in 1.0 mL of dichloromethane) was added dropwise to the reaction solution. The mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was quenched with 0.5 mL of methanol, then diluted with 20 mL of dichloromethane. Silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D478-1 (135 mg). LCMS: [M+H]⁺=783.

Step 2

[0558] D478-1 (135 mg, 0.173 mmol) was dissolved in 10 mL of anhydrous dichloromethane. Under N₂ protection, 2.5

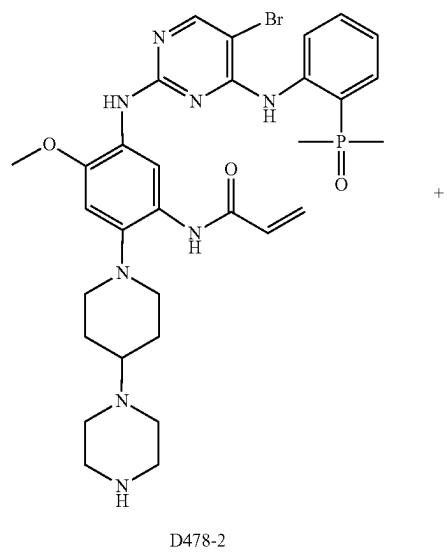
mL of trifluoroacetic acid was added to the reaction solution and the mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (50 mL), then washed with saturated NaHCO₃ solution (2×30 mL) and saturated brine (1×30 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D478-2 (110 mg). LCMS: [M+H]⁺=683.

Step 3

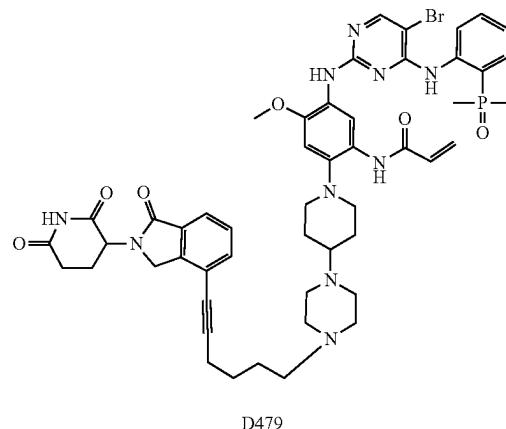
[0559] D478-2 (30 mg, 0.044 mmol) and M1 (17.1 mg, 0.053 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous

methanol. Under nitrogen protection, CH₃COOH (4.0 mg, 0.066 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.5 mg, 0.088 mmol) was added to the reaction solution. The mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to obtain the pure product D478 as a white solid (16 mg, yield 36.7%), LCMS: [M+H]⁺=991, 993.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D479)

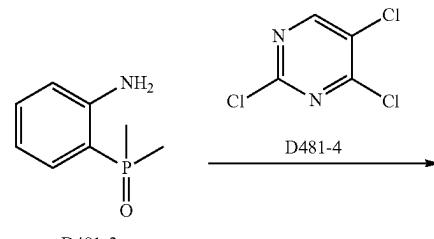
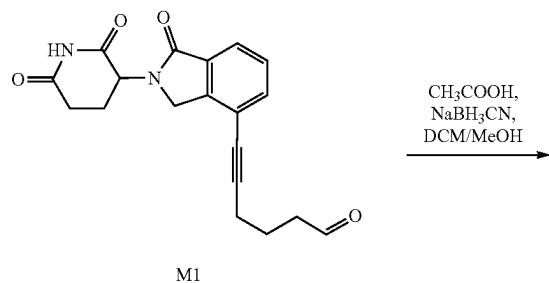
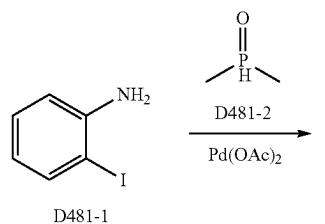


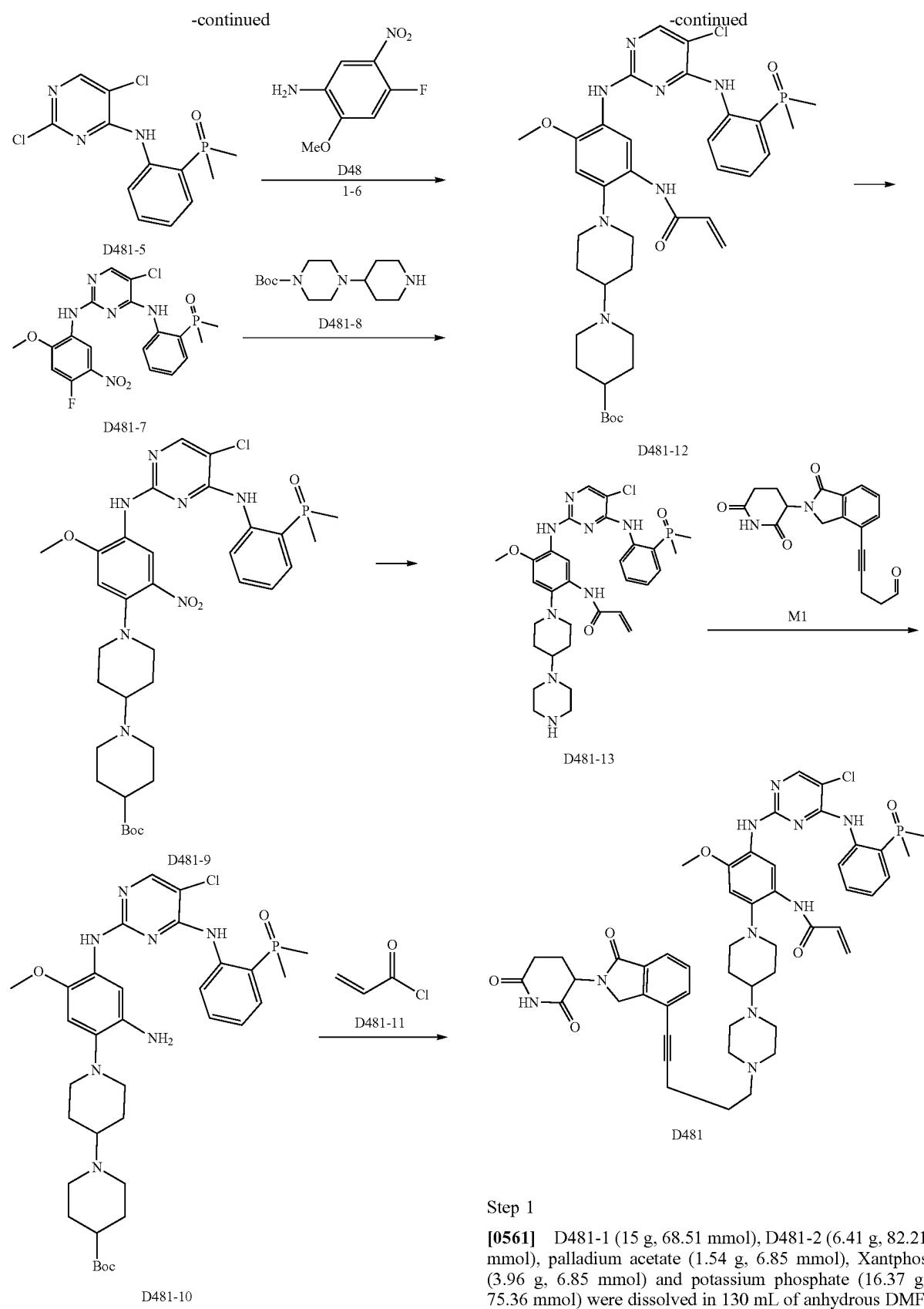
-continued



[0560] D478-2 (30 mg, 0.044 mmol) and M1 (17.9 mg, 0.053 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (4.0 mg, 0.066 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.5 mg, 0.088 mmol) was added to the reaction solution. The mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid product D479 (18 mg, yield 40.7%), LCMS: [M+H]⁺=1005, 1007.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D481)





Step 1

[0561] D481-1 (15 g, 68.51 mmol), D481-2 (6.41 g, 82.21 mmol), palladium acetate (1.54 g, 6.85 mmol), Xantphos (3.96 g, 6.85 mmol) and potassium phosphate (16.37 g, 75.36 mmol) were dissolved in 130 mL of anhydrous DMF. Under nitrogen protection, the mixture was stirred at 120° C.

for 6 hours. The reaction was cooled to room temperature. Ethyl acetate was added to the reaction. The mixture was stirred for 1 hour, and filtered. The filter cake was washed twice with ethyl acetate. The mother liquor was concentrated, then dissolved in a mixed solvent of water/concentrated hydrochloric acid (4/1), and washed three times with ethyl acetate. The aqueous phase was cooled to below 10° C. The pH was adjusted to 12 with 30% aqueous sodium hydroxide solution. The temperature of the aqueous phase was maintained below 20° C., and the aqueous phase was extracted with isopropanol/dichloromethane (1/3) 4 times. The organic phases were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure. The crude product is recrystallized with ethyl acetate/n-hexane (1/10) to obtain D481-3 (9.52 g, yield 82.2%), LCMS: $[M+H]^+=170$.

Step 2

[0562] D481-3 (9.52 g, 56.31 mmol), D481-4 (12.29 g, 67.57 mmol), potassium carbonate (9.34 g, 67.57 mmol) and tetrabutylammonium hydrogen sulfate (1.91 g, 5.63 mmol) were suspended in 200 mL of DMF. The mixture was stirred at 65° C. overnight under nitrogen protection. The reaction was cooled to room temperature, and filtered to remove solids. The filter cake was washed twice with DMF. The mother liquor was concentrated, and then layered in ethyl acetate/water (3.7/1). The aqueous phase was separated, and extracted twice with ethyl acetate. The organic phases were combined, washed once with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to obtain D481-5 (10 g). LCMS: $[M+H]^+=316$.

Step 3

[0563] D481-5 (1 g, 3.17 mmol), D481-6 (0.59 g, 3.17 mmol) and methanesulfonic acid (1.22 g, 12.70 mmol) were dissolved in 10 mL of tert butanol. Under nitrogen protection, the mixture was stirred at 90° C. overnight, and cooled to room temperature. The solvent was evaporated under reduced pressure. The crude product was purified by Flash to obtain D481-7 (1.4 g). LCMS: $[M+H]^+=466$.

Step 4

[0564] D481-7 (700 mg, 1.505 mmol), D481-8 (486 mg, 1.806 mmol) and cesium carbonate (1.47 g, 4.515 mmol) were dissolved in 10 mL of DMF. Under nitrogen protection, the mixture was stirred at 60° C. overnight, and cooled to room temperature. The solid was filtered out, and the solvent was evaporated under reduced pressure. The crude product was purified by Flash to obtain D481-9 (0.7 g). LCMS: $[M+H]^+=715$.

Step 5

[0565] D481-9 (914 mg, 1.28 mmol), iron powder (715 mg, 12.796 mmol) and ammonium chloride (411 mg, 7.678 mmol) were added to 80 mL of ethanol/water (3/1). The mixture was stirred at 100° C. for 1 hour, and cooled to room temperature. The solid was filtered out. The solid residue was washed twice with a mixed solvent of ethanol and water. The solvent was evaporated under reduced pressure, and the crude product was purified by Flash to obtain D481-10 (0.7 g). LCMS: $[M+H]^+=685$.

Step 6

[0566] D481-10 (670 mg, 0.979 mmol) and TEA (297 mg, 2.937 mmol) were dissolved in 50 mL of dichloromethane. The reaction was cooled down to -15° C. under nitrogen protection. A solution of D481-11 (80 mg, 0.881 mmol) in dichloromethane (5 mL) was slowly added to the mixture dropwise with stirring. The mixture was stirred at this temperature for another 1 hour. 1 mL of methanol was added to quench the reaction. The solvent was removed under reduced pressure. The residue was purified by Flash to obtain D481-12 (560 mg), LCMS: $[M+H]^+=739$.

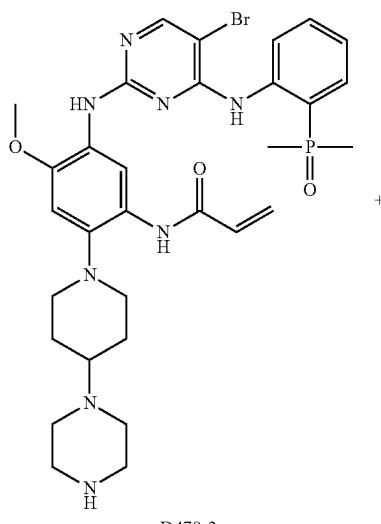
Step 7

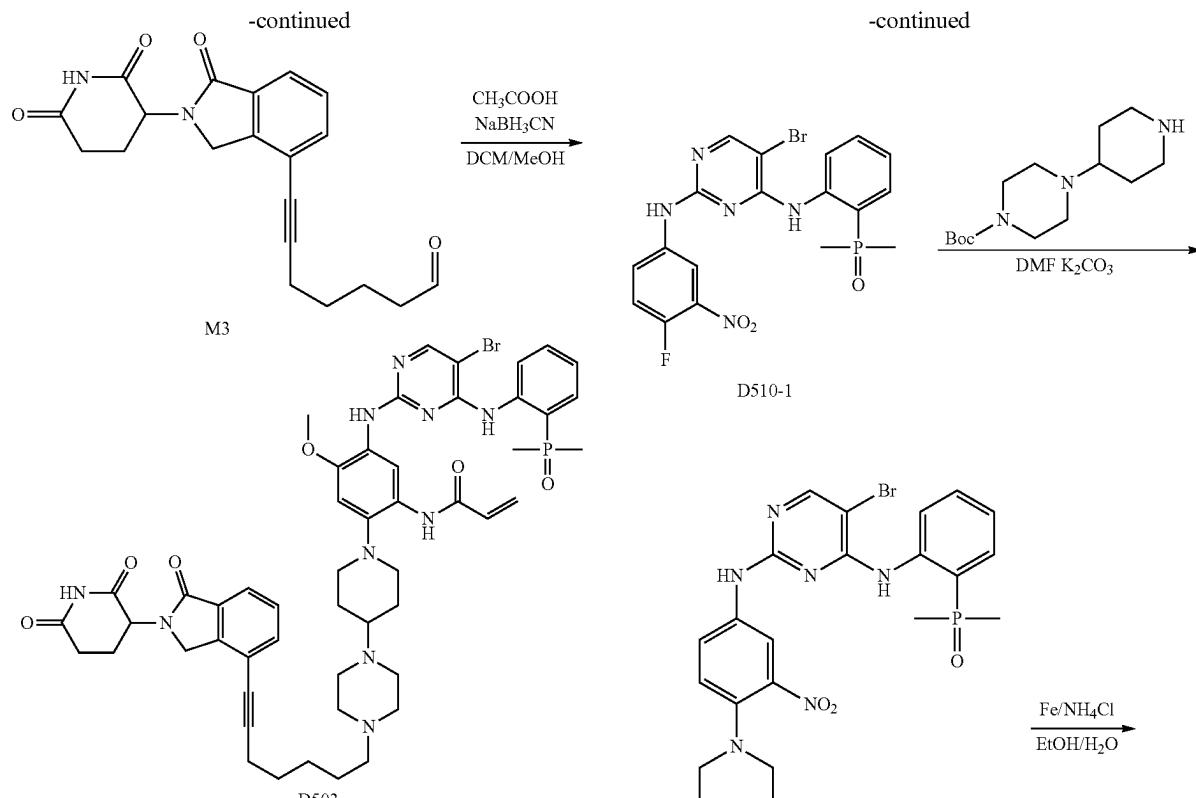
[0567] D481-12 (560 mg) was dissolved in 12 mL of dichloromethane, and trifluoroacetic acid (3 mL) was added with stirring. The mixture was stirred at room temperature for 1 hour under nitrogen protection. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D481-13 (460 mg, yield 95.0%), LCMS: $[M+H]^+=639$.

Step 8

[0568] D481-13 (30 mg, 0.093 mmol), M1 (71 mg, 0.111 mmol) and acetic acid (6.7 mg, 0.111 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). The mixture was stirred at room temperature for 1 hour under nitrogen. Sodium cyanoborohydride (8.7 mg, 0.139 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give an off-white solid compound D481 (22.6 mg, yield 50.8%), LCMS: $[M+H]^+=974$.

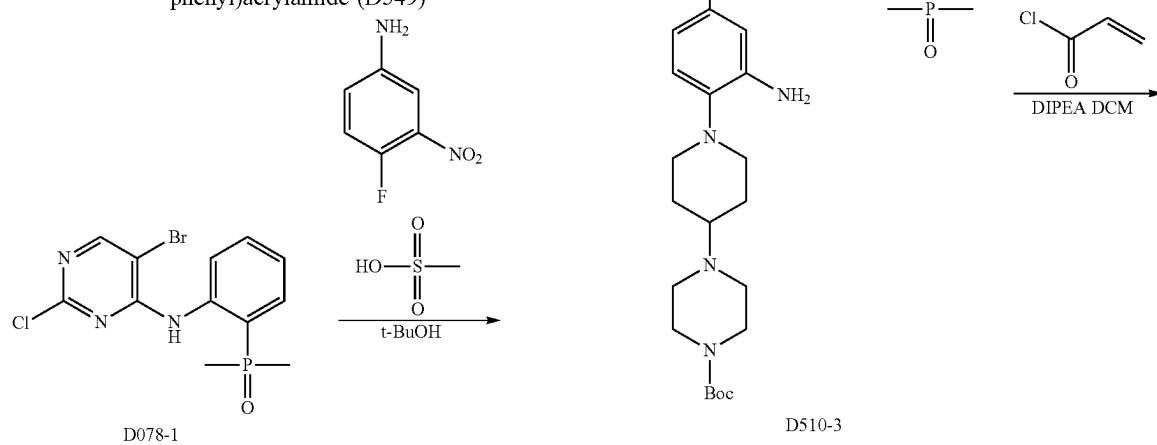
Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(7-(2,(6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)hept-6-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D503)

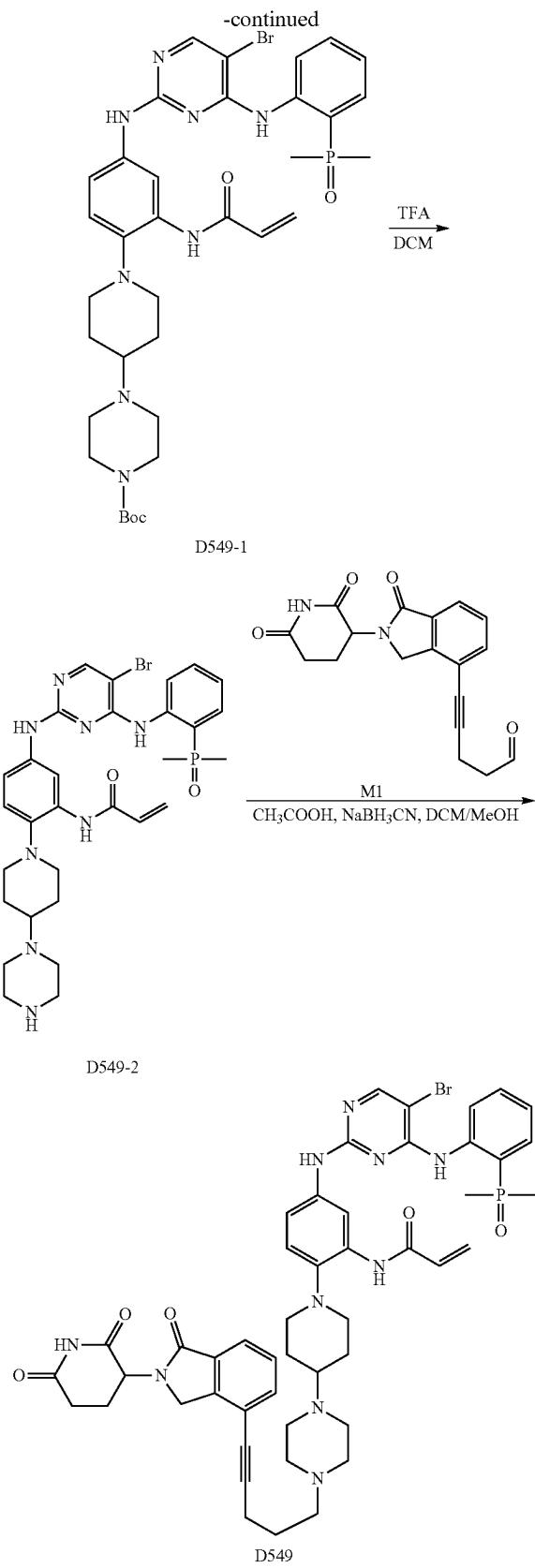




[0569] D478-2 (30 mg, 0.044 mmol) and M3 (18.7 mg, 0.053 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH_3COOH (4.0 mg, 0.066 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH_3CN (5.5 mg, 0.088 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D503 (17 mg, yield 37.9%). LCMS: $[\text{M}+\text{H}]^+=1019, 1021$.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenyl)acrylamide (D549)





Step 1

[0570] D078-1 (3.59 g, 10 mmol) and 4-fluoro-3-nitroaniline (1.72 g, 11 mmol) were dispersed in 70 mL of tert butanol, and methanesulfonic acid (3.84 g, 40 mmol) was added to the reaction solution. The reaction was heated to 90° C. for 16 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, and then concentrated under reduced pressure to remove the solvent to give a crude product, which was flash purified to give a light yellow solid product D510-1 (4.1 g, 85.6%). LCMS: $[\text{M}+\text{H}]^+=480$.

Step 2

[0571] D510-1 (4.1 g, 8.56 mmol), tert-butyl 4-(piperidin-4-yl)piperazine-1-carboxylate (2.3 g, 8.56 mmol) and K_2CO_3 (3.54 g, 25.7 mmol) were dispersed in 82 mL of anhydrous DMF. The reaction was heated to 60° C. for 12 h. The reaction was completed as detected by LCMS. The reaction solution was cooled to room temperature, filtered with suction, and the solid residue was washed with DMF. The filtrate was concentrated under reduced pressure to give a crude product, which was flash purified to give a yellow solid product D510-2 (5.6 g, 89.9%). LCMS: $[\text{M}+\text{H}]^+=729$.

Step 3

[0572] D510-2 (1.1 g, 1.51 mmol), iron powder (507 mg, 9.06 mmol) and NH_4Cl (4.04 g, 75.5 mmol) were dispersed in a mixed solvent of 45 mL of ethanol and 15 mL of water. The reaction was heated to 90° C. for 2 h. The reaction was completed as determined by LCMS. The reaction solution was cooled to room temperature, and filtered with diatomaceous earth. The solid residue was washed with a mixed solvent of ethanol and water (50 mL). The filtrate was collected and concentrated under reduced pressure to remove ethanol. The residue was extracted twice with a mixed solvent of methanol and dichloromethane (60 mL). The organic layers were combined and washed with water (2×30 mL) and saturated brine (1×30 mL) sequentially. The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D510-3 (760 mg, 72.1%). LCMS: $[\text{M}+\text{H}]^+=699$.

Step 4

[0573] D510-3 (139.6 mg, 0.2 mmol) and diisopropylethylamine (77.4 mg, 0.6 mmol) were dispersed in 15 mL of anhydrous dichloromethane. Under N_2 protection, acryloyl chloride (19.8 mg, 0.22 mmol, dissolved in 1.0 mL of dichloromethane) was added dropwise to the reaction solution. The mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was quenched with 0.5 mL of methanol, and then diluted with 20 mL of dichloromethane. Silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D549-1 (135 mg). LCMS: $[\text{M}+\text{H}]^+=753$.

Step 5

[0574] D549-1 (135 mg, 0.18 mmol) was dissolved in 10 mL of anhydrous dichloromethane. Under N_2 protection, 2.5 mL of trifluoroacetic acid was added to the reaction solution.

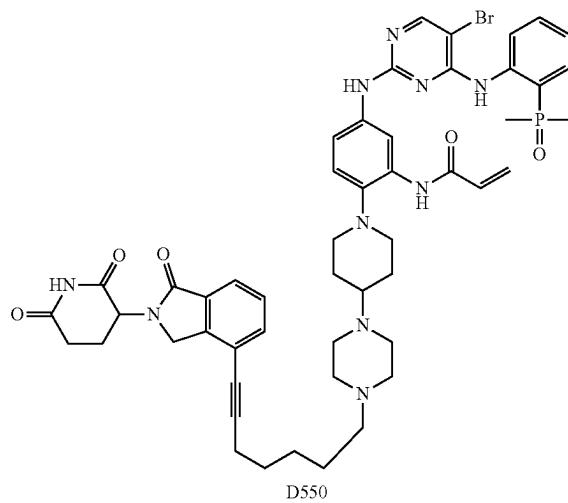
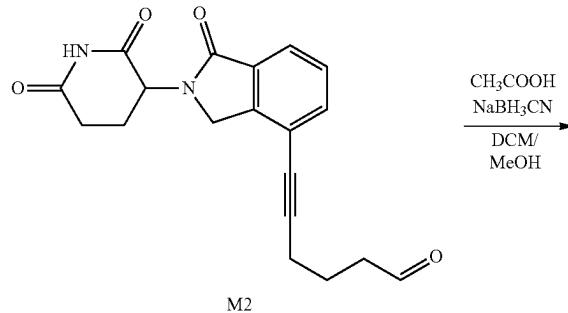
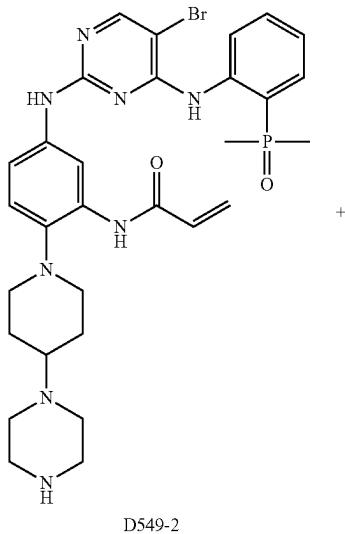
The mixture was reacted at room temperature for 1.0 h. LCMS showed that the reaction was completed. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (50 mL), and then washed with saturated NaHCO₃ solution (2×30 mL) and saturated brine (1×30 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D549-2 (110 mg). LCMS: [M+H]⁺=653.

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Step 6

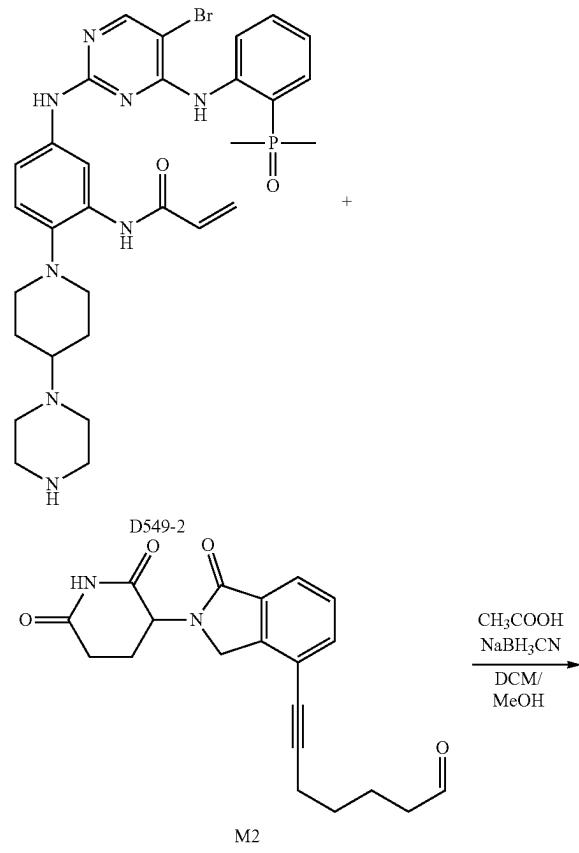
[0575] D549-2 (28.7 mg, 0.044 mmol) and M1 (17.1 mg, 0.053 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (4.0 mg, 0.066 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.5 mg, 0.088 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D549 (16 mg, yield 37.9%). LCMS: [M+H]⁺=961, 963.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenyl)acrylamide (D550)

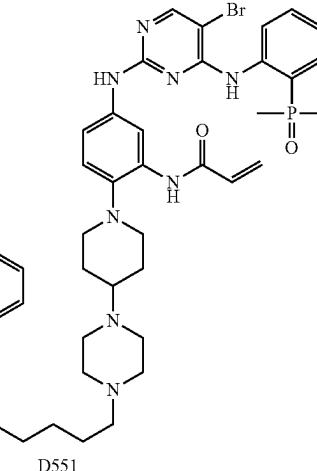


[0576] D549-2 (28.7 mg, 0.044 mmol) and M2 (17.9 mg, 0.053 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (4.0 mg, 0.066 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.5 mg, 0.088 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D550 (18.5 mg, yield 43.2%). LCMS: [M+H]⁺=975, 977.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(7-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hept-6-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenyl)acrylamide (D551)

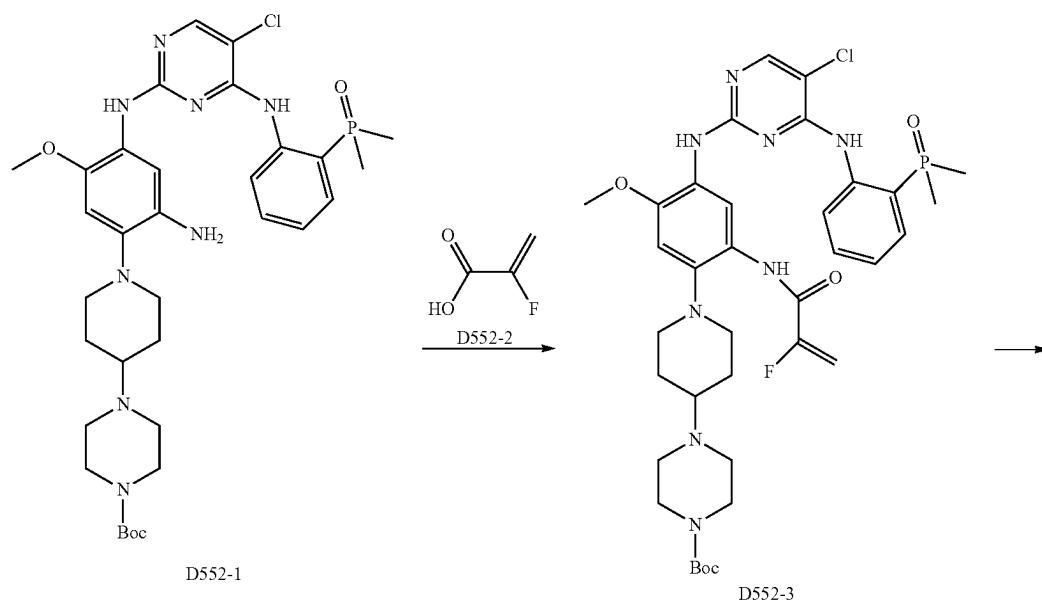


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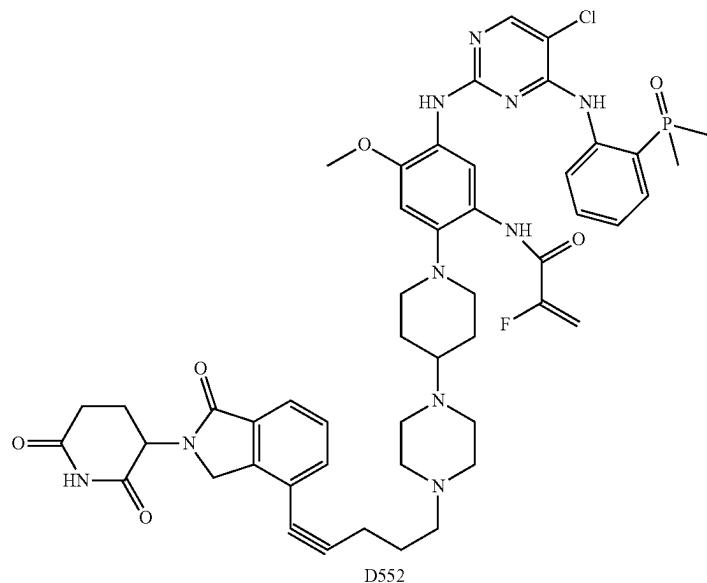
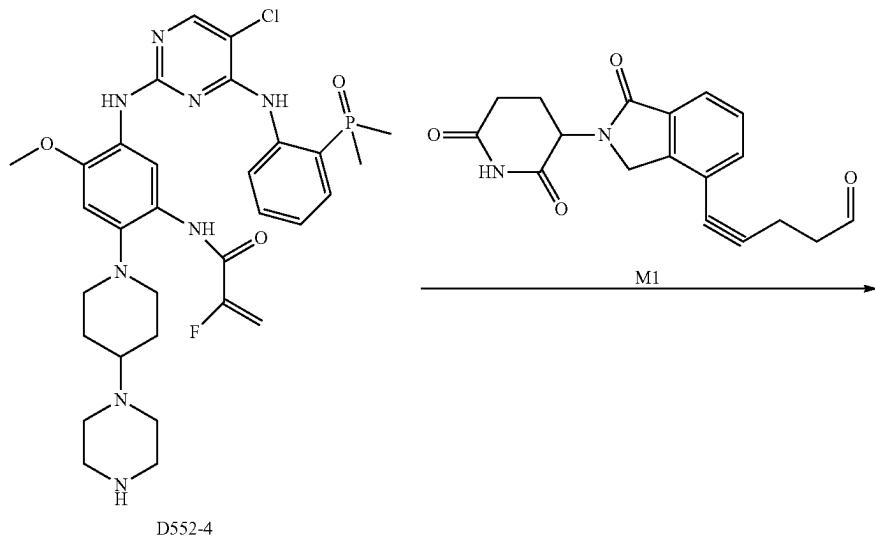


[0577] D549-2 (28.7 mg, 0.044 mmol) and M2 (18.7 mg, 0.053 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (4.0 mg, 0.066 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.5 mg, 0.088 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D551 (19 mg, yield 43.7%). LCMS: [M+H]⁺=989, 991.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D552)



-continued

**Step 1**

[0578] D552-1 (300 mg, 0.44 mmol), D552-2 (43 mg, 0.48 mmol), T3P (1.12 mL, 1.75 mmol) and DIEA (226 mg, 1.754 mmol) were dissolved in 10 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by Flash to give D552-3 (318 mg, yield 96.1%), LCMS: $[M+H]^+=757$.

Step 2

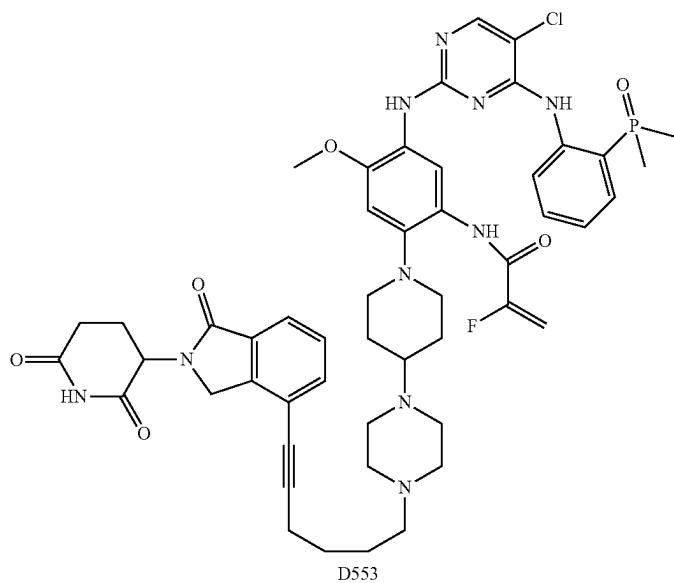
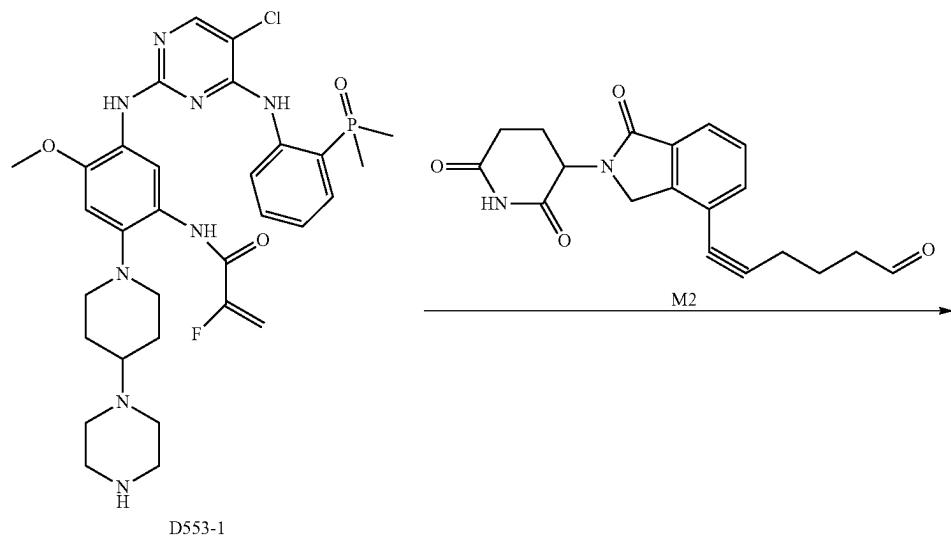
[0579] D552-3 (318 mg) was dissolved in 20 mL of dichloromethane, and trifluoroacetic acid (5 mL) was added with stirring. Under nitrogen protection, the mixture was

stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to give D552-4 (276 mg, yield 100%), LCMS: $[M+H]^+=657$.

Step 3

[0580] M1 (20 mg, 0.062 mmol), D552-4 (45 mg, 0.068 mmol) and acetic acid (4.4 mg, 0.074 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.8 mg, 0.093 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give an off-white solid D552 (20 mg, yield 33.3%), LCMS: $[M+H]^+=965$.

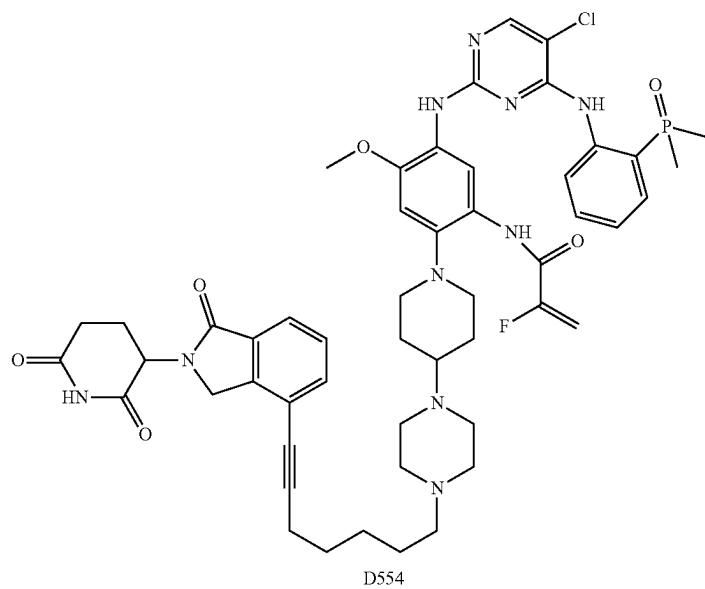
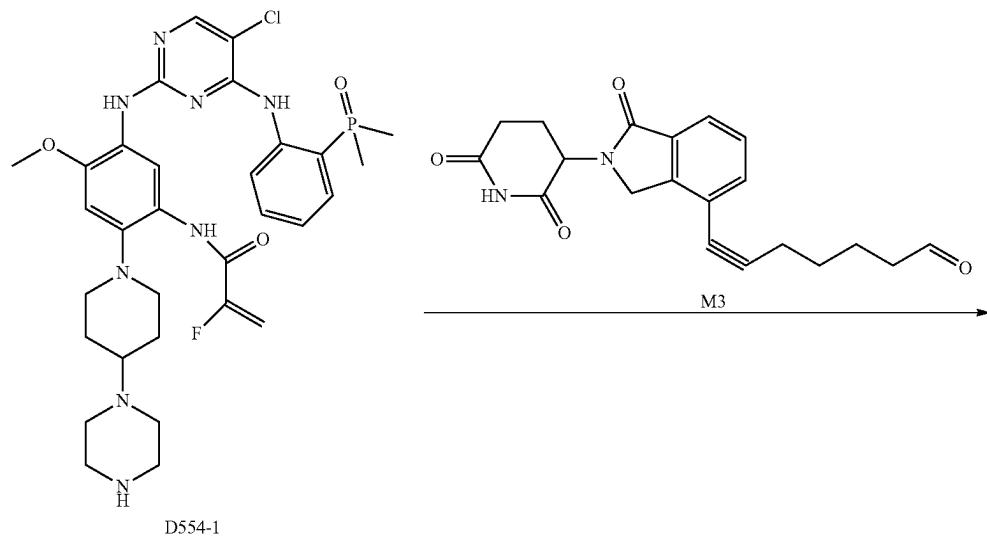
Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D553)



[0581] M2 (20 mg, 0.059 mmol), D553-1 (43 mg, 0.065 mmol) and acetic acid (4.3 mg, 0.071 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.6 mg,

0.089 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give an off-white solid compound D553 (13 mg, yield 22.4%), LCMS: $[M+H]^+=979$.

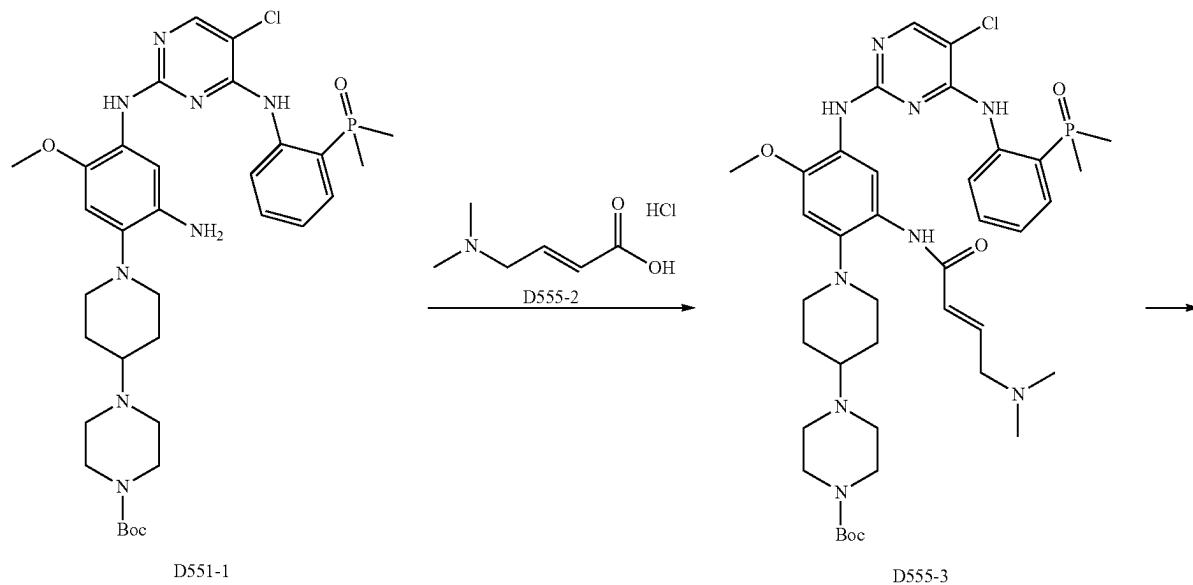
Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(7-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hept-6-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D554)



[0582] M3 (20 mg, 0.057 mmol), D554-1 (41 mg, 0.062 mmol) and acetic acid (4.1 mg, 0.068 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.4 mg,

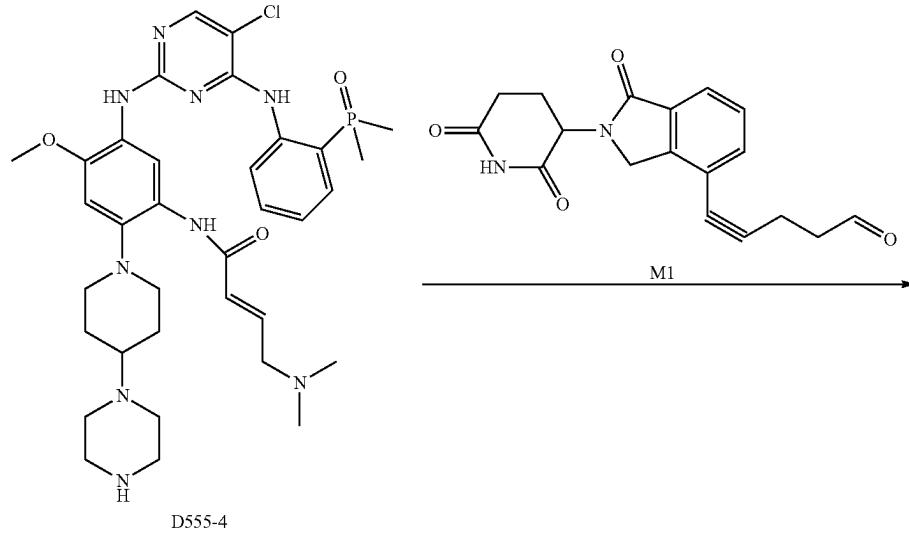
0.085 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give an off-white solid compound D554 (12 mg, yield 21.4%), LCMS: $[M+H]^+=993$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4-(dimethylamino)but-2-enamide
(D555)



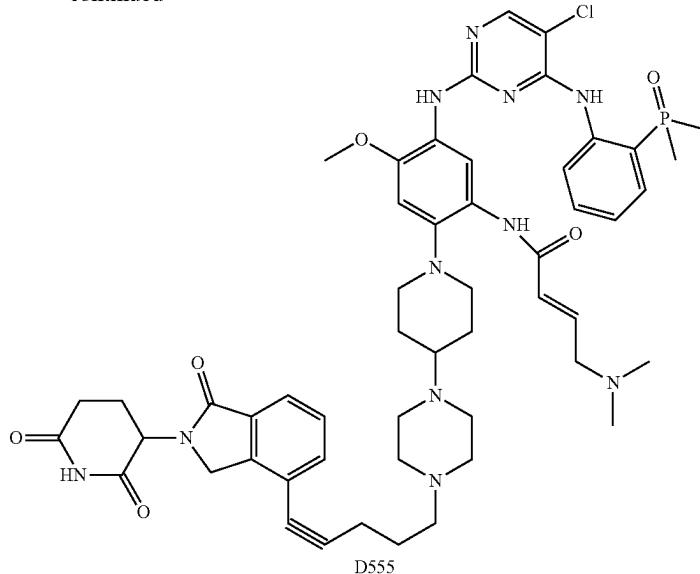
D551-1

D555-3



D555-4

-continued



Step 1

[0583] D555-1 (300 mg, 0.44 mmol), D555-2 (80 mg, 0.48 mmol), T3P (50% o EA, 1.12 mL, 1.75 mmol) and DIEA (283 mg, 2.19 mmol) were dissolved in 10 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by Flash to give D555-3 (303 mg, yield 86.8%), LCMS: $[M+H]^+=796$.

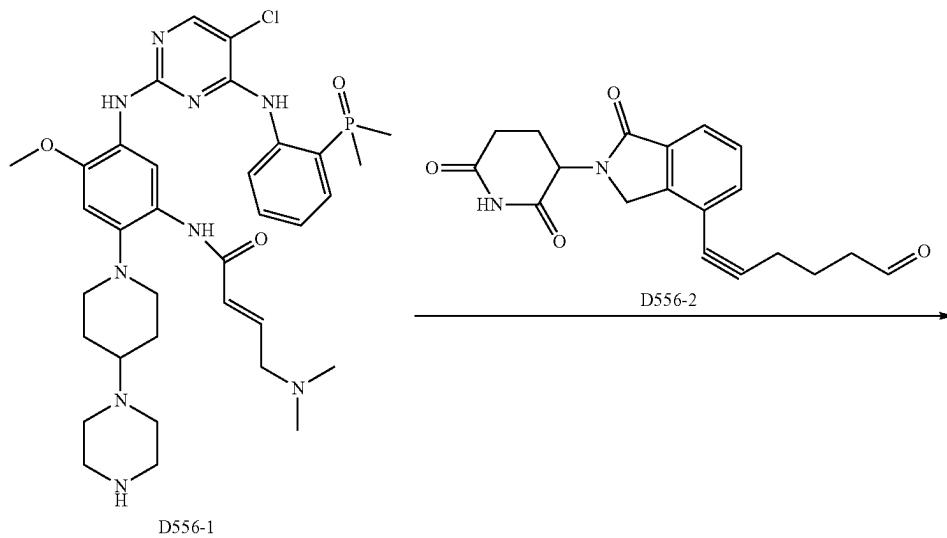
Step 2

[0584] D555-3 (303 mg) was dissolved in 20 mL of dichloromethane. Trifluoroacetic acid (5 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D555-4 (254 mg, yield 95.8%), LCMS: $[M+H]^+=696$.

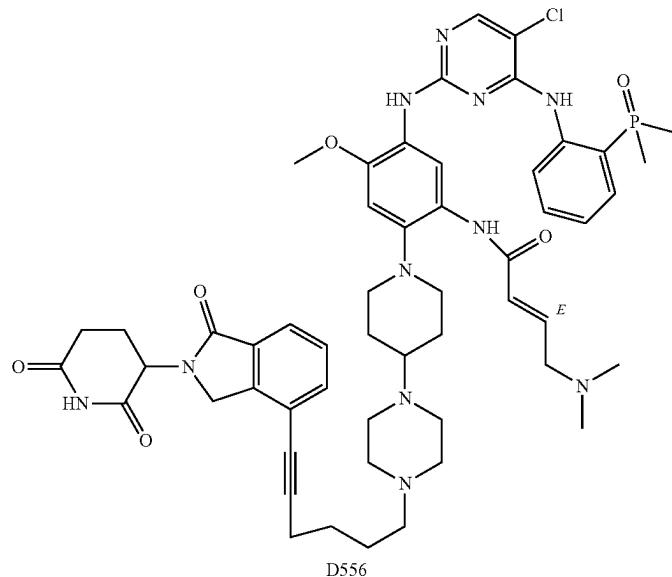
Step 3

[0585] M1 (20 mg, 0.062 mmol), D555-4 (47 mg, 0.068 mmol) and acetic acid (4.4 mg, 0.074 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.8 mg, 0.093 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give an off-white solid compound D555 (10 mg, yield 16.1%), LCMS: $[M+H]^+=1004$.

Preparation of (E)-N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-dimethoxyphenyl)-4-(dimethylamino)but-2-enamide (D556)



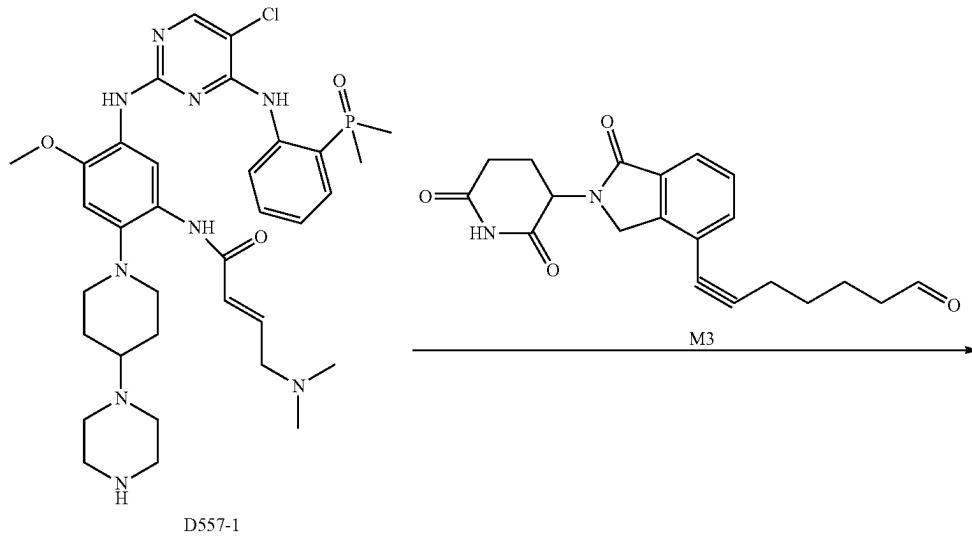
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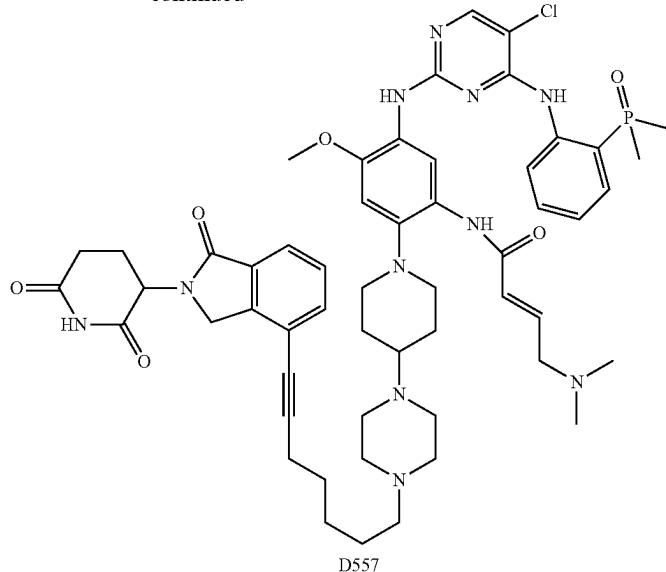
[0586] D556-1 (45 mg, 0.065 mmol), D556-2 (20 mg, 0.059 mmol) and acetic acid (4.3 mg, 0.071 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.6 mg, 0.089 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by

HPLC to give an off-white solid compound D556 (15 mg, yield 25.0%), LCMS: $[M+H]^+=1018$.

Preparation of (E)-N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(7-(2,6-dioxopiperidin-3-yl)-1-oxoisoinodolin-4-yl)hept-6-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-dimethoxyphenyl)-4-(dimethylamino)but-2-enamide (D557)

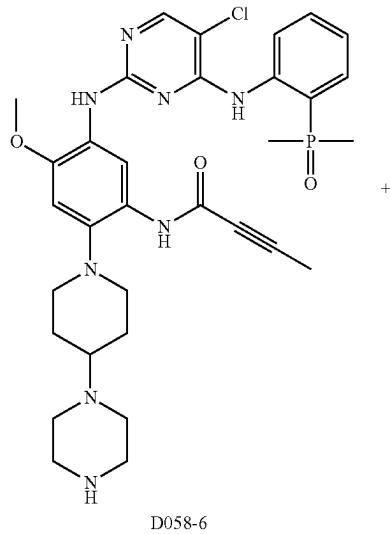


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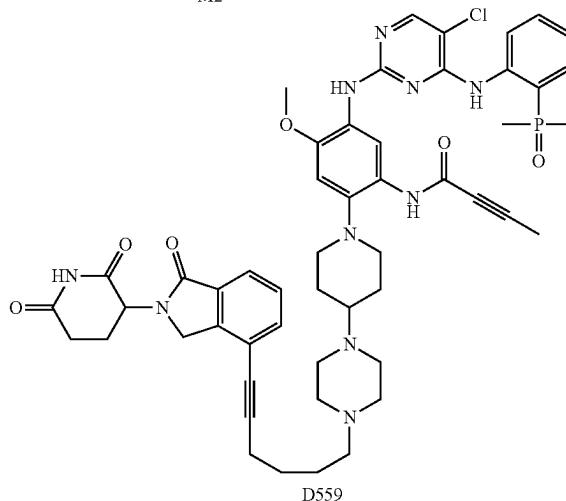
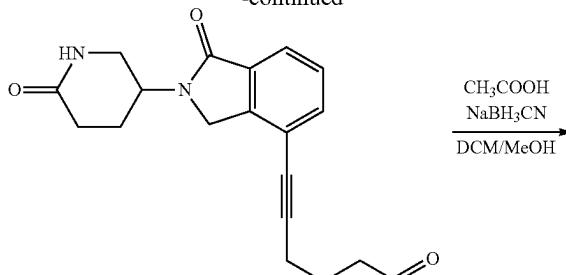


[0587] M3 (20 mg, 0.057 mmol), D557-1 (43 mg, 0.062 mmol) and acetic acid (4.1 mg, 0.068 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.4 mg, 0.085 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give an off-white solid D557 (15 mg, yield 25.9%), LCMS: $[M+H]^+$ =1032.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide (D559)



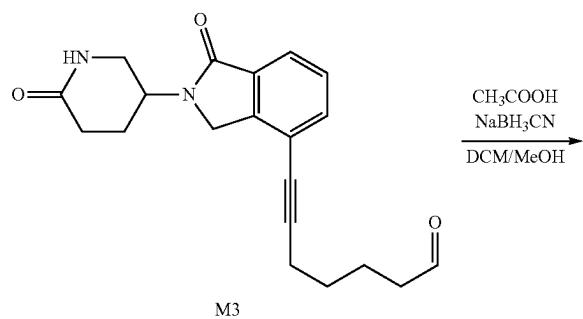
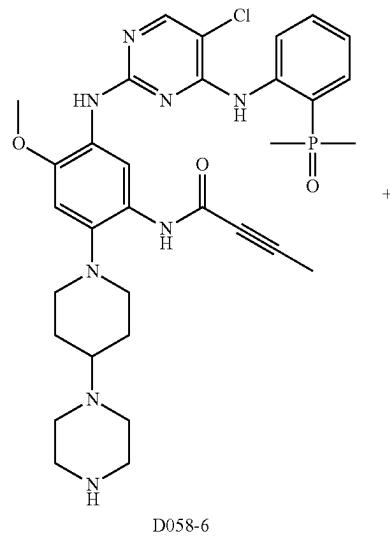
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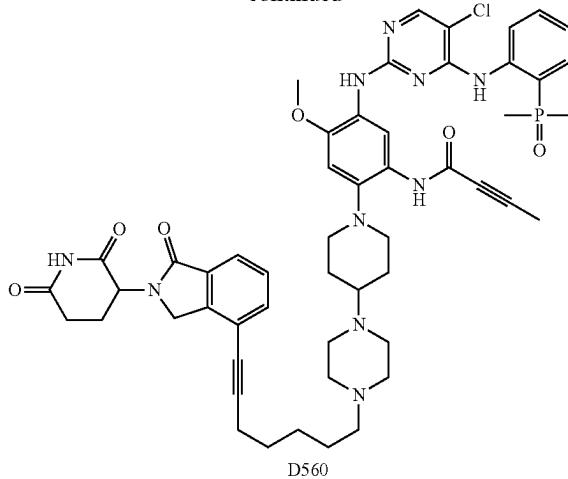
[0588] M2 (50.7 mg, 0.15 mmol) and D058-6 (87.8 mg, 0.135 mmol) were dissolved in a mixed solvent of 15 mL of anhydrous dichloromethane and 1.5 mL of anhydrous methanol. Under nitrogen protection, CH_3COOH (13.5 mg, 0.225 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH_3CN (18.8 mg, 0.3

mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to obtain the pure product D559 (36 mg, yield 24.7% o) as a white solid. LCMS: $[M+H]^+=973$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(7-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hept-6-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide (D560)

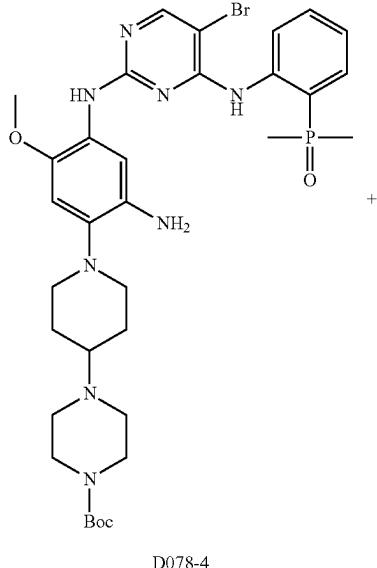


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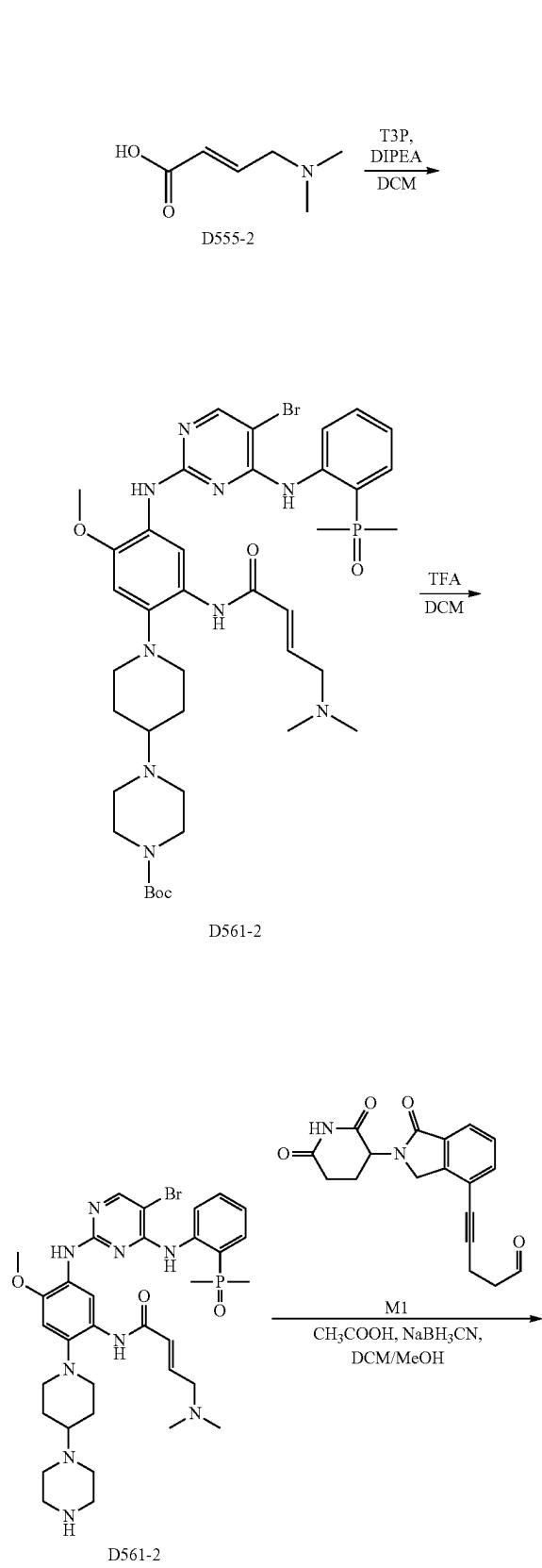


[0589] M3 (52.8 mg, 0.15 mmol) and D058-6 (87.8 mg, 0.135 mmol) were dissolved in a mixed solvent of 15 mL of anhydrous dichloromethane and 1.5 mL of anhydrous methanol. Under nitrogen protection, CH_3COOH (13.5 mg, 0.225 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH_3CN (18.8 mg, 0.3 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to obtain the pure product D560 (41 mg, yield 27.7%) as a white solid. LCMS: $[M+H]^+=987$.

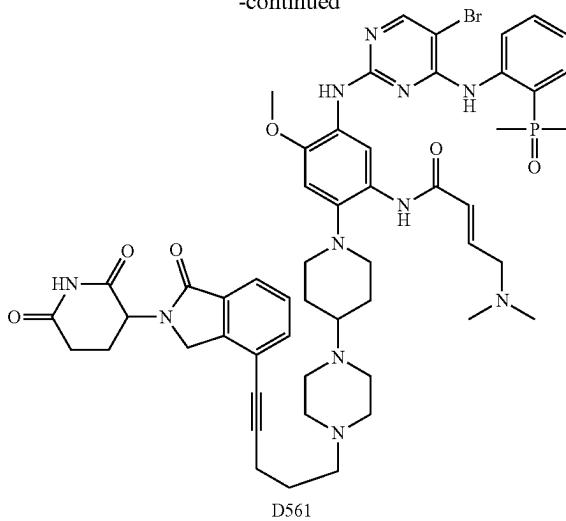
Preparation of N-(5-((5-bromo-4-((2-(dimethylaminophenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4-(dimethylamino)but-2-enamide (D561)



-continued



-continued



Step 1

[0590] D078-4 (145.6 mg, 0.2 mmol), D555-2 (25.8 mg, 0.2 mmol) and T3P (254 mg, 0.4 mmol) were dispersed in 4.0 mL of anhydrous dichloromethane. Under N₂ protection, diisopropylethylamine (129 g, 1.0 mmol) was added to the reaction solution. The mixture was reacted at room temperature for 2.0 h. The reaction was completed as detected by LCMS. The reaction solution was diluted with 50 mL of dichloromethane. Silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D561-1 (141 mg). LCMS: [M+H]⁺=840.

Step 2

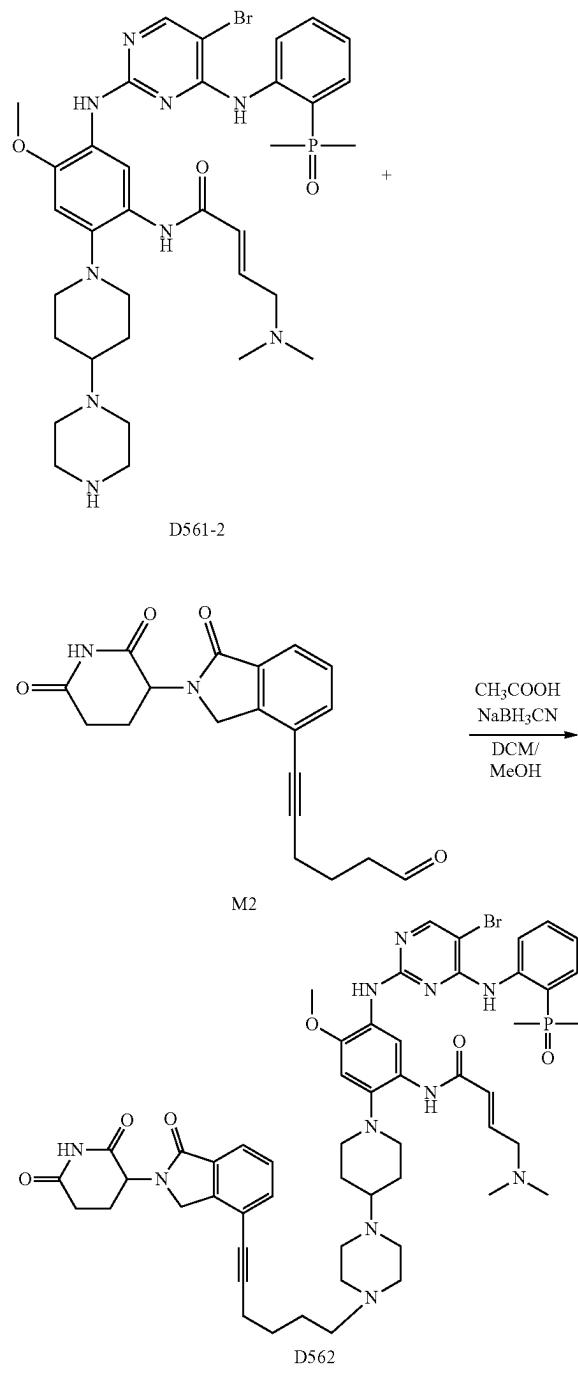
[0591] D561-1 (141 mg, 0.168 mmol) was dissolved in 10 mL of anhydrous dichloromethane. Under N₂ protection, 2.5 mL of trifluoroacetic acid was added to the reaction solution. The mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (50 mL), and then washed with saturated NaHCO₃ solution (2×30 mL) and saturated brine (1×30 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered with suction. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D561-2 (110 mg). LCMS: [M+H]⁺=740.

Step 3

[0592] D561-2 (30 mg, 0.041 mmol) and M1 (15.9 mg, 0.049 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (3.7 mg, 0.062 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.1 mg, 0.082 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample.

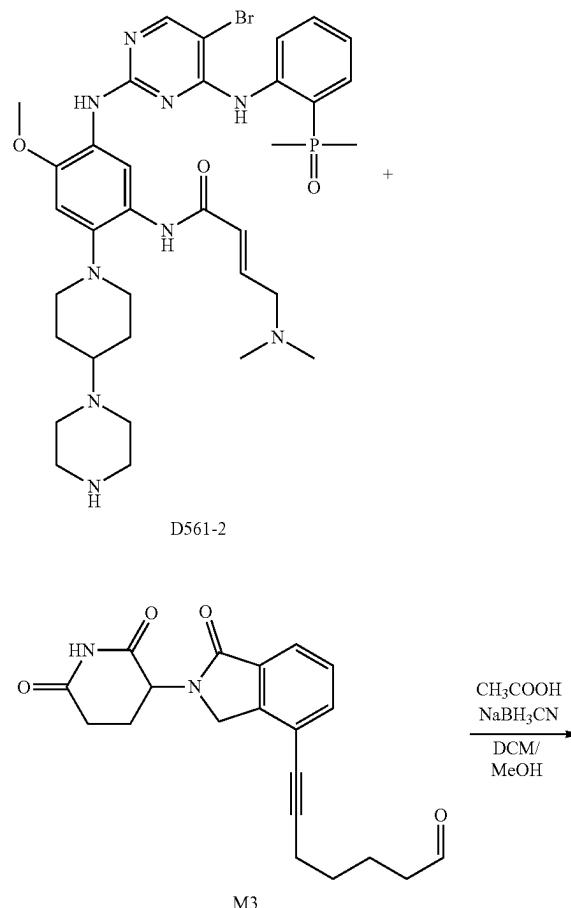
The mixture was purified by Flash to give a white solid pure product D561 (11.5 mg, yield 26.8%). LCMS: [M+H]⁺ =1048, 1050.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-dimethoxyphenyl)-4-(dimethylamino)but-2-enamide (D562)

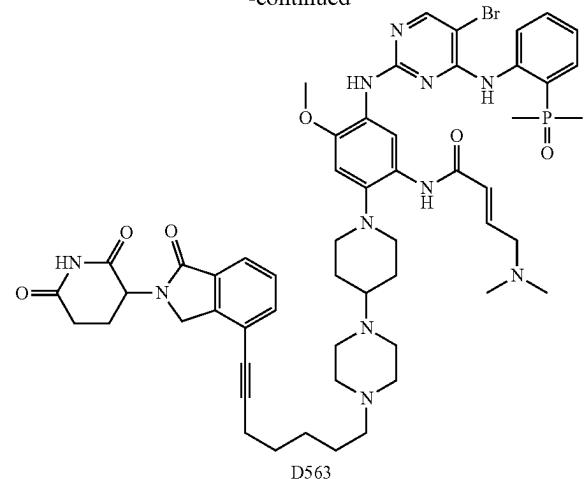


[0593] D561-2 (30 mg, 0.041 mmol) and M2 (16.6 mg, 0.049 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (3.7 mg, 0.062 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then solid NaBH₃CN (5.1 mg, 0.082 mmol) was added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D562 (15.5 mg, yield 35.6%). LCMS: [M+H]⁺ =1062, 1064.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(7-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hept-6-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-dimethoxyphenyl)-4-(dimethylamino)but-2-enamide (D563)

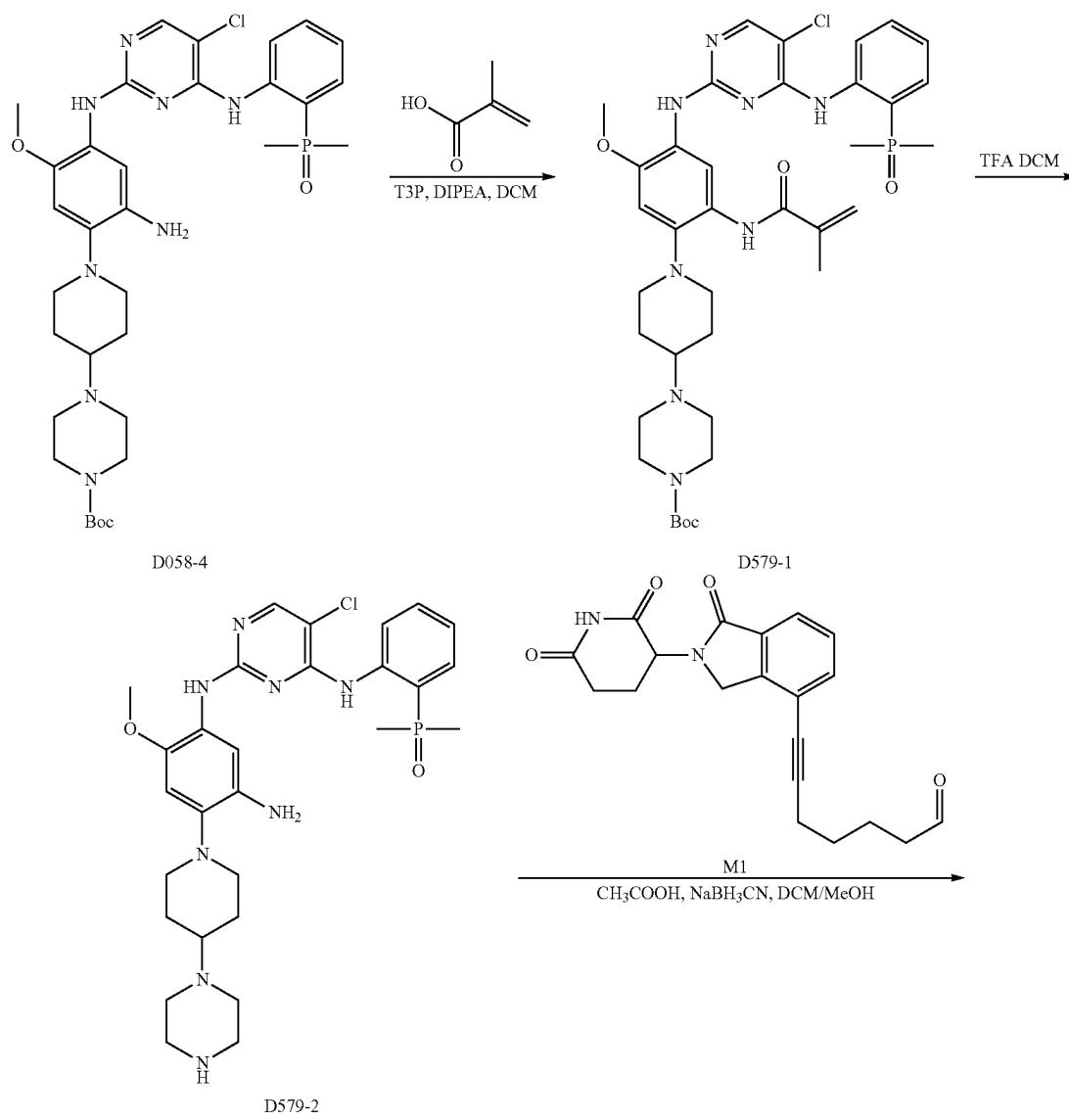


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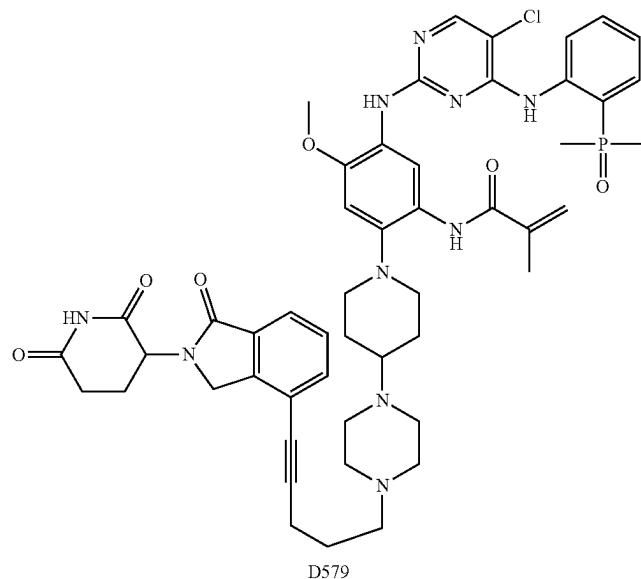


[0594] D561-2 (30 mg, 0.041 mmol) and M3 (17.2 mg, 0.049 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (3.7 mg, 0.062 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Solid NaBH₃CN (5.1 mg, 0.082 mmol) was then added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D563 (16.5 mg, yield 31.3%). LCMS: [M+H]⁺=1076, 1078.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)methacrylamide (D579)



-continued



Step 1

[0595] D058-4 (136.8 mg, 0.2 mmol), methacrylic acid (17.2 mg, 0.2 mmol) and T3P (254 mg, 0.4 mmol) were dispersed in 5.0 mL of anhydrous dichloromethane. Under N₂ protection, diisopropylethylamine (129 mg, 1.0 mmol) was added to the reaction solution. The mixture was reacted at room temperature for 2.0 h. The reaction was completed as detected by LCMS. The reaction solution was diluted with 15 mL of dichloromethane and silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D579-1 (120 mg). LCMS: [M+H]⁺=753.

Step 2

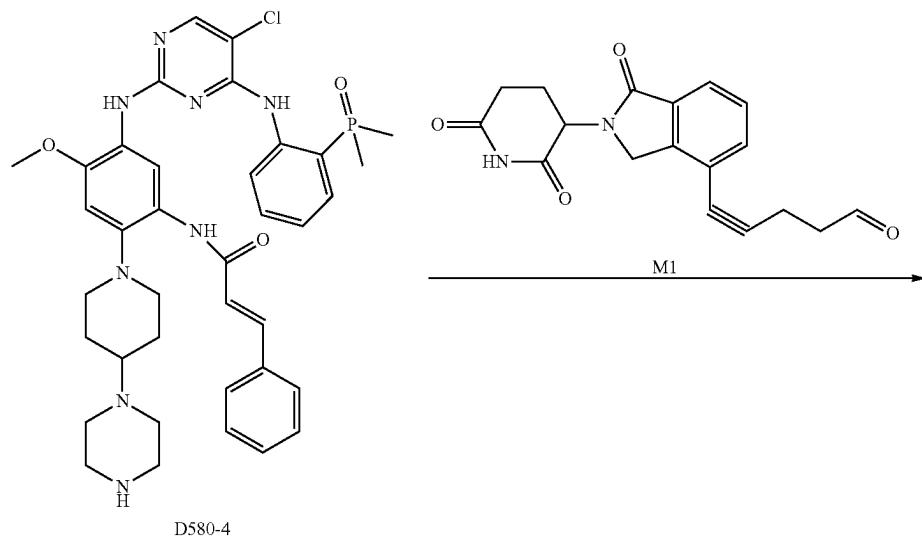
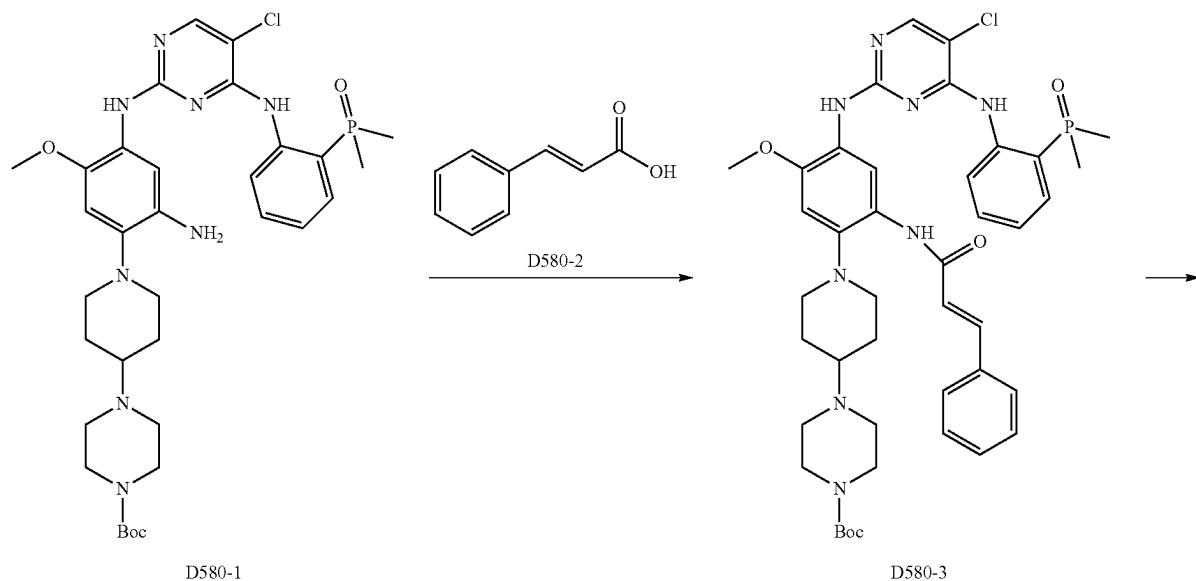
[0596] D579-1 (120 mg, 0.16 mmol) was dissolved in 10 mL of anhydrous DCM. Under N₂ protection, 2.5 mL of trifluoroacetic acid was added to the reaction solution. The mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (40 mL), and then washed with saturated

NaHCO₃ solution (2×30 mL) and saturated brine (1×30 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D579-2 (88 mg). LCMS: [M+H]⁺=653.

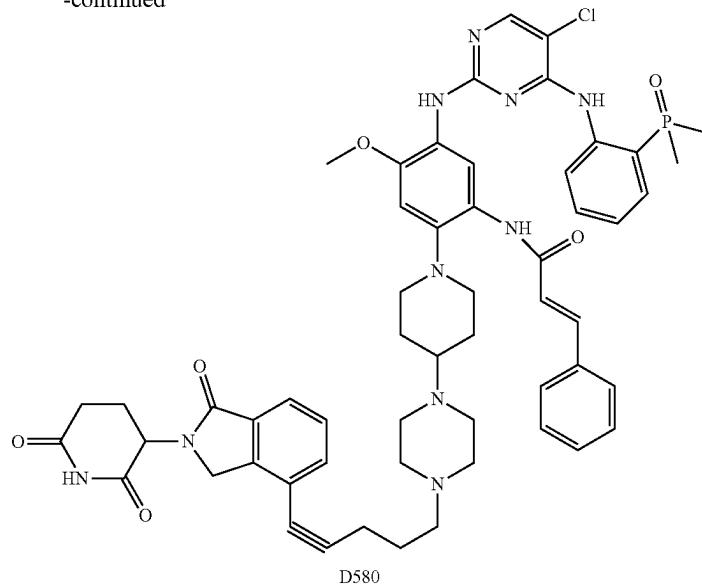
Step 3

[0597] M1 (52.5 mg, 0.162 mmol) and D579-2 (88 mg, 0.135 mmol) were dissolved in a mixed solvent of 15 mL of anhydrous dichloromethane and 1.5 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (12.2 mg, 0.203 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Solid NaBH₃CN (17.0 mg, 0.27 mmol) was then added to the reaction solution and the mixture was reacted at room temperature for another 2 h. The reaction was completed as detected by LCMS and thin layer chromatography. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D579 (51 mg, yield 39.3%). LCMS: [M+H]⁺=961.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)cinnamamide (D580)



-continued

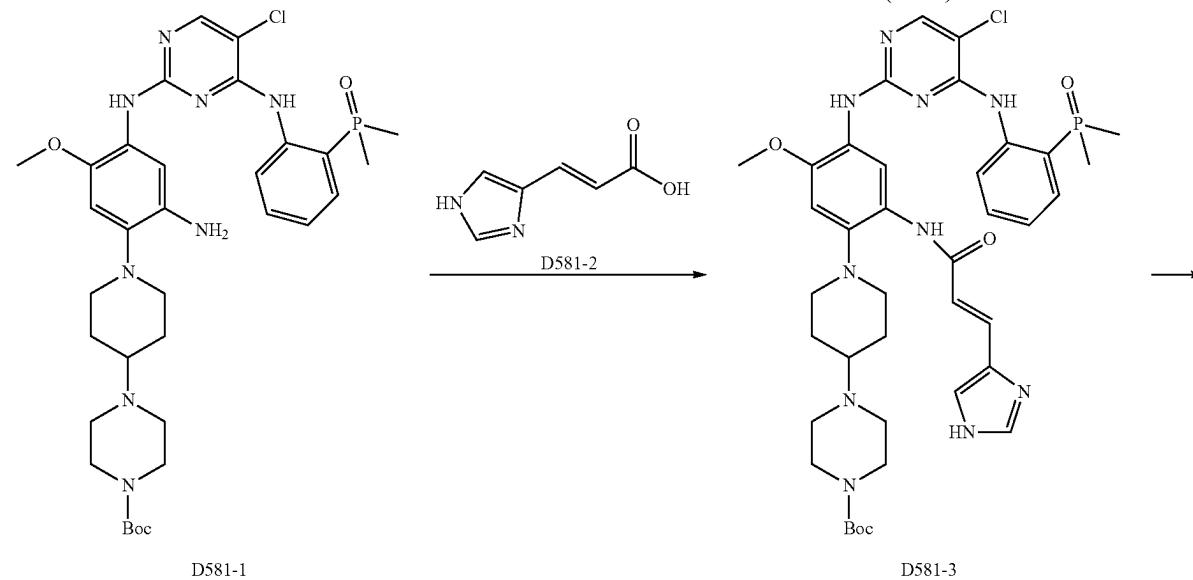


Step 1

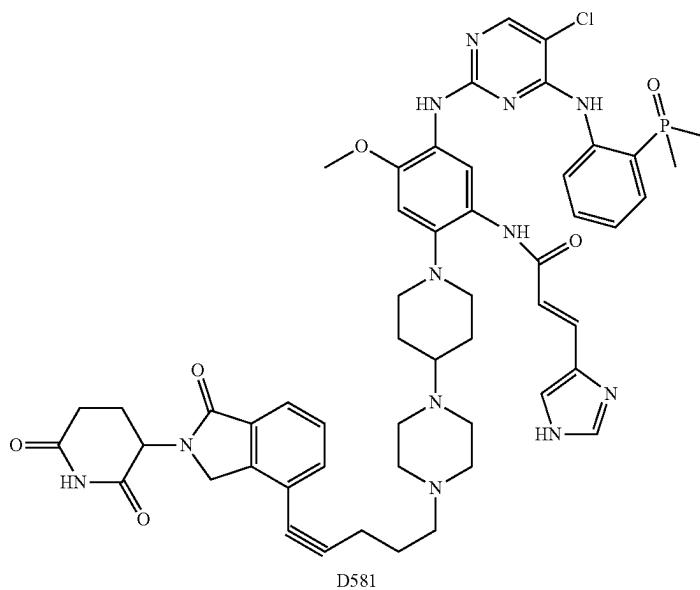
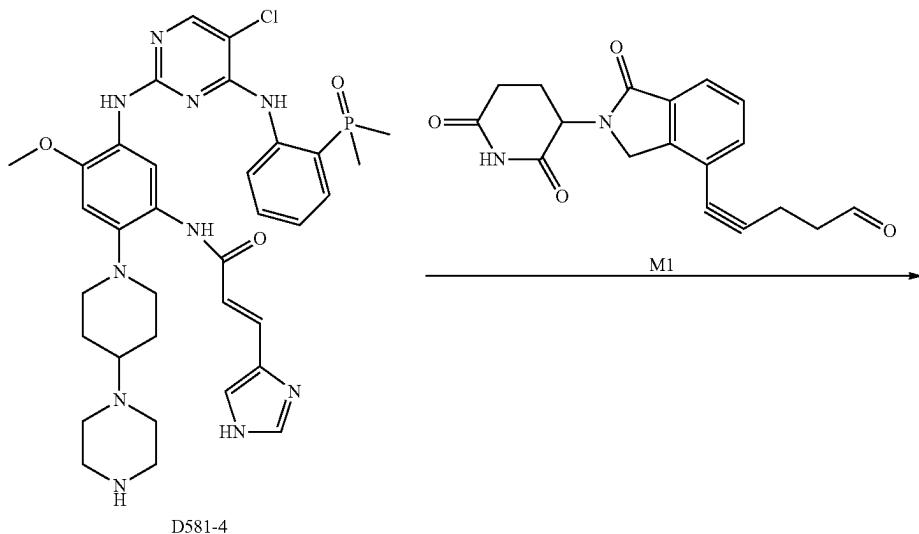
[0598] D580-1 (80 mg, 0.117 mmol), D580-2 (19 mg, 0.129 mmol), T3P (50% EA, 149 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours, and purified by thin layer chromatography to obtain D580-3 (75 mg, yield 78.9%), LCMS: $[M+H]^+=815$.

Step 2

[0599] D580-3 (75 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D580-4 (64 mg, yield 97.0%), LCMS: $[M+H]^+=715$.



-continued

**Step 1**

[0601] D581-2 (24 mg, 0.174 mmol) and HATU (77 mg, 0.203 mmol) were dissolved in 2 mL of tetrahydrofuran. Under nitrogen, the mixture was stirred at room temperature for 30 minutes. A solution of D581-1 (80 mg, 0.117 mmol) and DIEA (45 mg, 0.351 mmol) in 2 mL of tetrahydrofuran was added dropwise. The mixture was heated to 60° C. and stirred for 64 hours. The mixture was cooled to room temperature and the solvent was removed under reduced

pressure. The residue was purified by Flash (dichloromethane/methanol) to give D581-3 (60 mg, yield 63.8%), LCMS: $[M+H]^+=805$.

Step 2

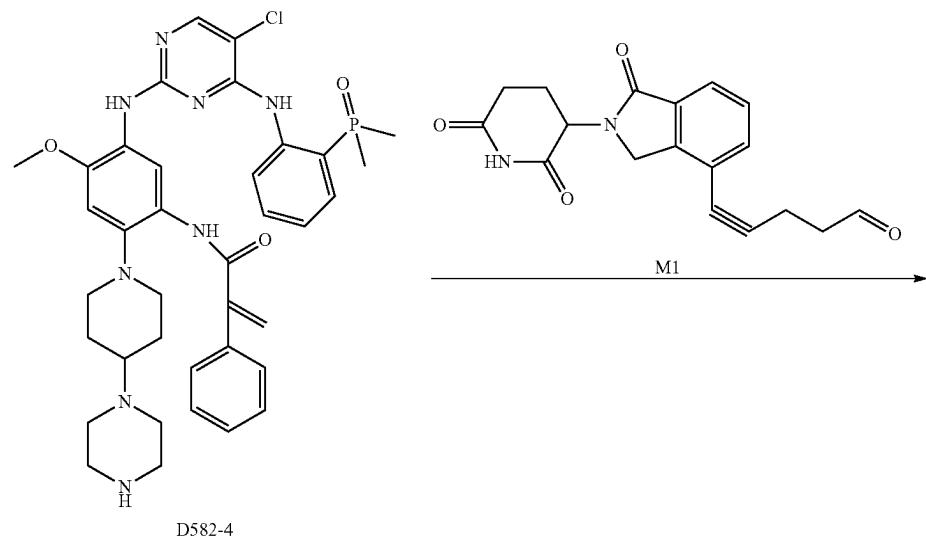
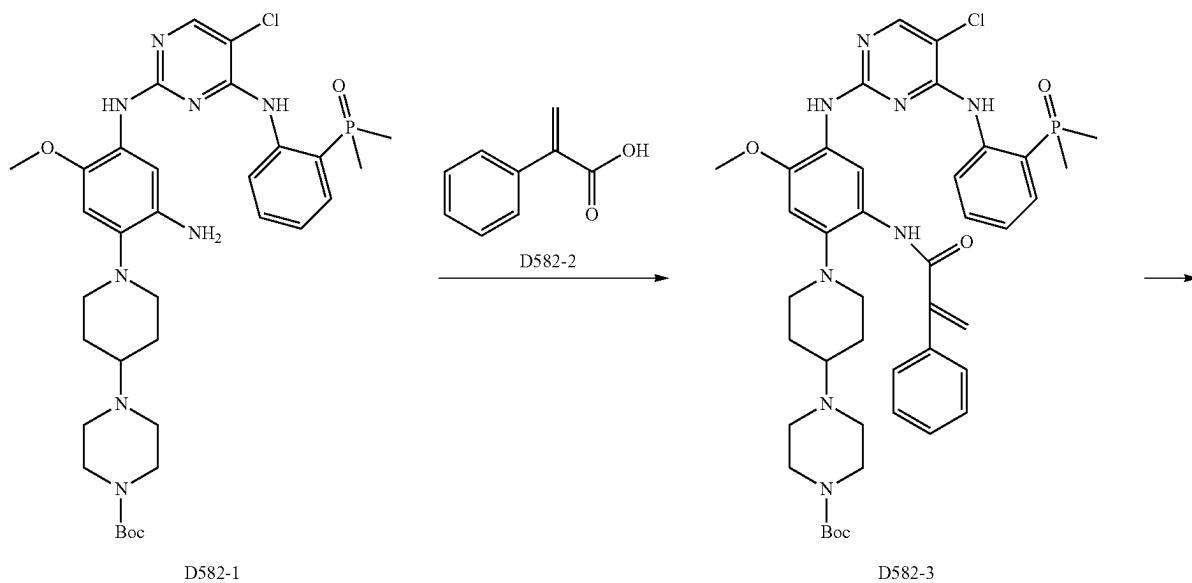
[0602] D581-3 (60 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D581-4 (38 mg, yield 52.5%), LCMS: $[M+H]^+=705$.

Step 3

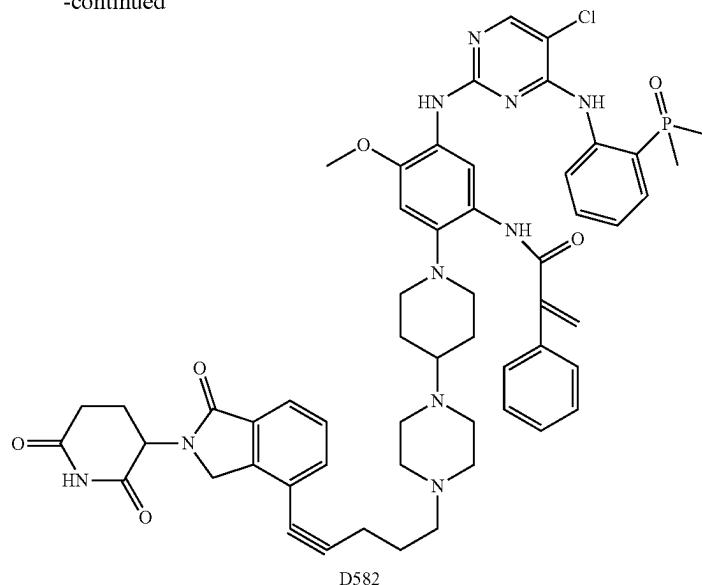
[0603] D581-4 (38.2 mg, 0.054 mmol), M1 (19.3 mg, 0.060 mmol) and acetic acid (3.9 mg, 0.065 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.1 mg, 0.081 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give compound D581 (15 mg, yield 27.3%), LCMS: $[M+H]^+=1013$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-phenylacrylamide (D582)



-continued

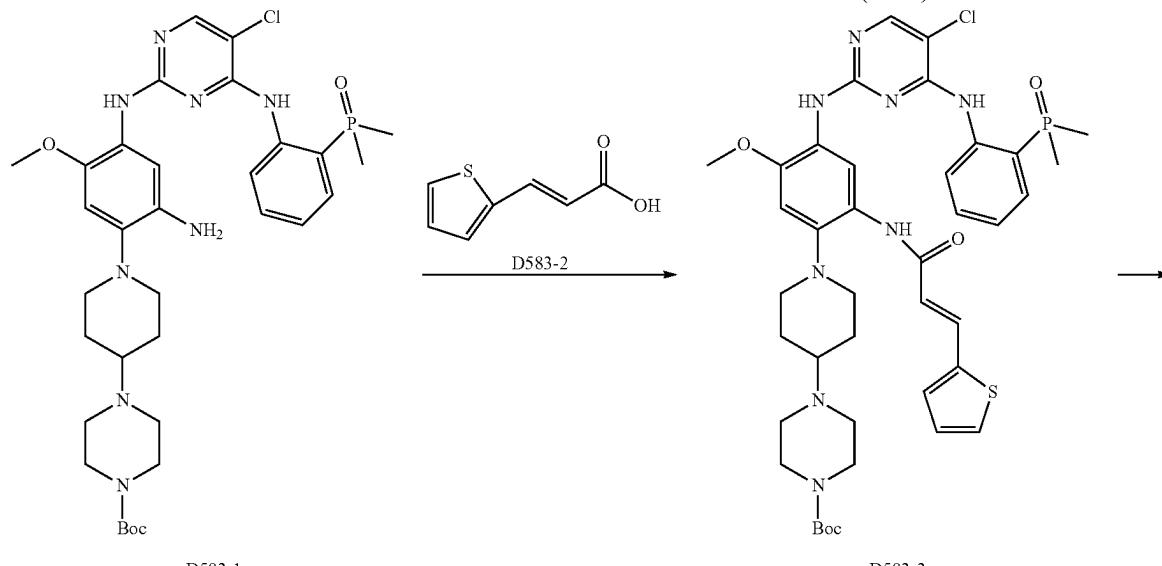


Step 1

[0604] D582-1 (80 mg, 0.117 mmol), D582-2 (19 mg, 0.129 mmol), T3P (50% EA, 149 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by thin layer chromatography to obtain D582-3 (69 mg, yield 72.6%), LCMS: $[M+H]^+=815$.

Step 2

[0605] D582-3 (69 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D582-4 (50 mg, yield 83.3%), LCMS: $[M+H]^+=715$.



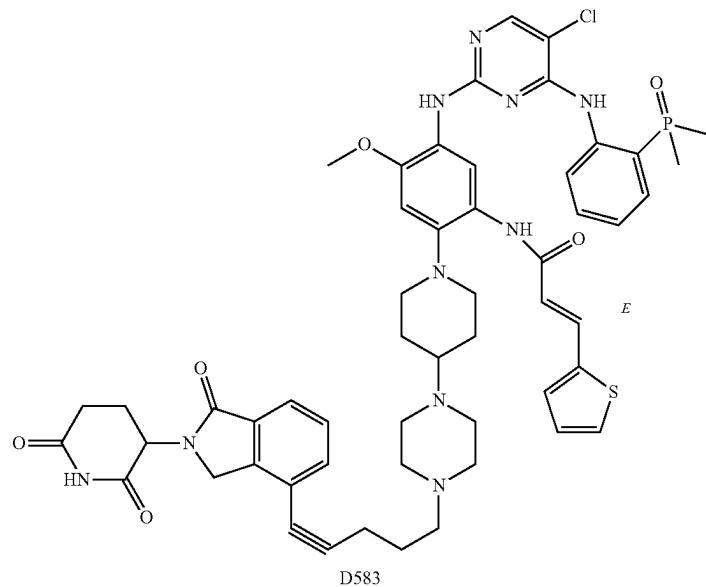
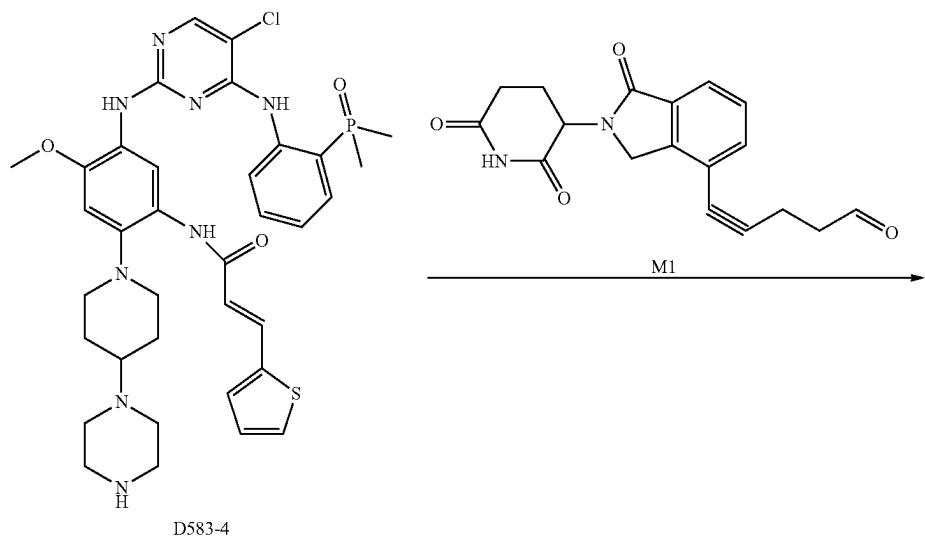
Step 3

[0606] D582-4 (55 mg, 0.077 mmol), M1 (22.7 mg, 0.070 mmol) and acetic acid (5.0 mg, 0.084 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.6 mg, 0.105 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D582 (25 mg, yield 34.9%), LCMS: $[M+H]^+=1023$.

Preparation of (E)-N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-3-(thiophen-2-yl)acrylamide (D583)

D583-3

-continued

**Step 1**

[0607] D583-1 (80 mg, 0.117 mmol), D583-2 (20 mg, 0.129 mmol), T3P (149 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by thin layer chromatography to obtain D583-3 (66 mg, yield 68.8%), LCMS: $[M+H]^+=821$.

Step 2

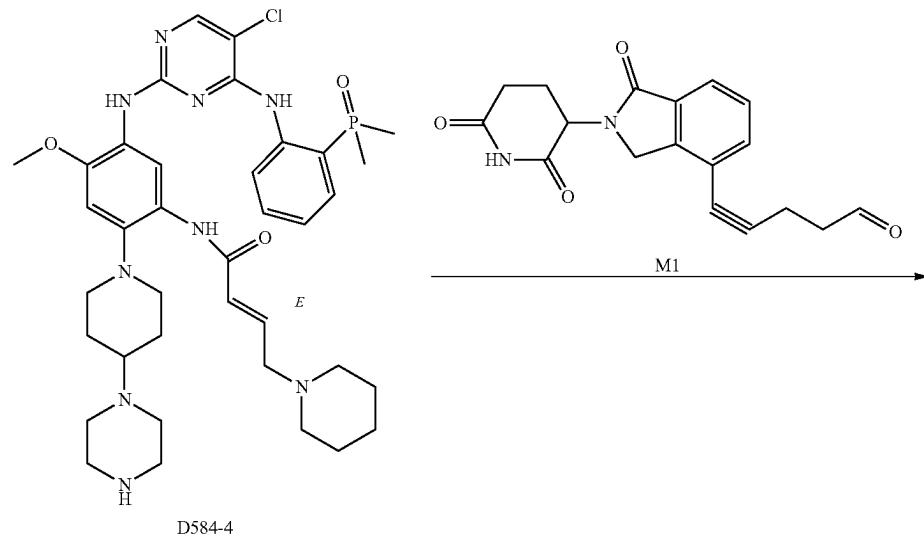
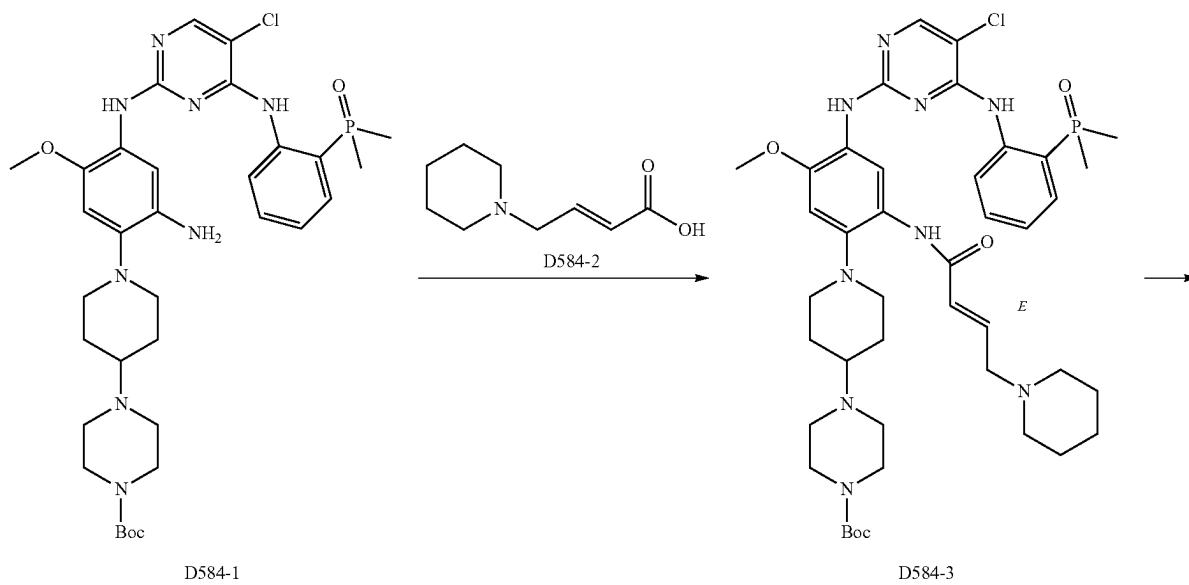
[0608] D583-3 (66 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D583-4 (22 mg, yield 37.9%), LCMS: $[M+H]^+=721$.

Step 3

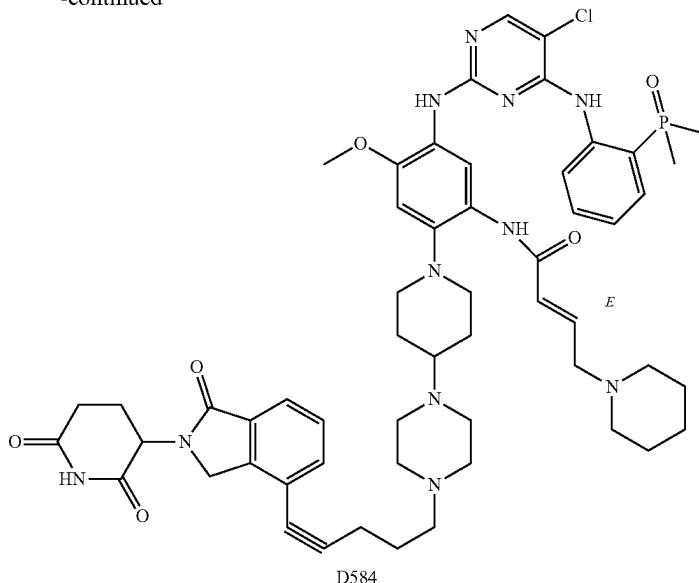
[0609] D583-4 (53.4 mg, 0.074 mmol), M1 (21.8 mg, 0.067 mmol) and acetic acid (4.9 mg, 0.081 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.3 mg, 0.101 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give compound D583 (25 mg, yield 36.2%), LCMS: [M+H]⁺=1029.

Preparation of (E)-N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisoinolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4-(piperidin-1-yl)but-2-enamide (D584)



-continued

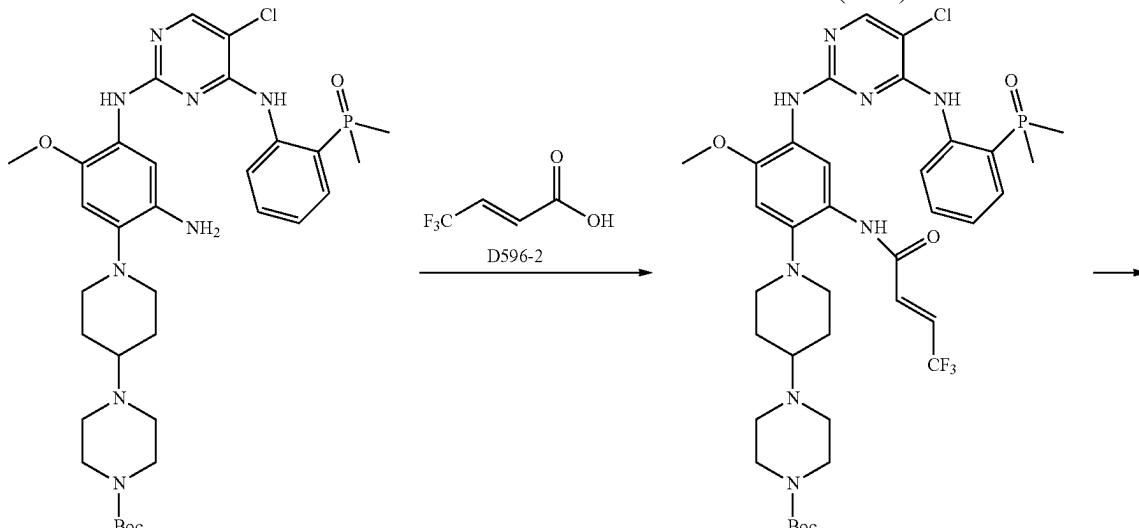


Step 1

[0610] D584-1 (80 mg, 0.117 mmol), D584-2 (26 mg, 0.129 mmol), T3P (149 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by thin layer chromatography to obtain D584-3 (68 mg, yield 70.1%), LCMS: $[M+H]^+$ =836.

Step 2

[0611] D584-3 (68 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D584-4 (15 mg, yield 25.0%), LCMS: $[M+H]^+$ = 736.

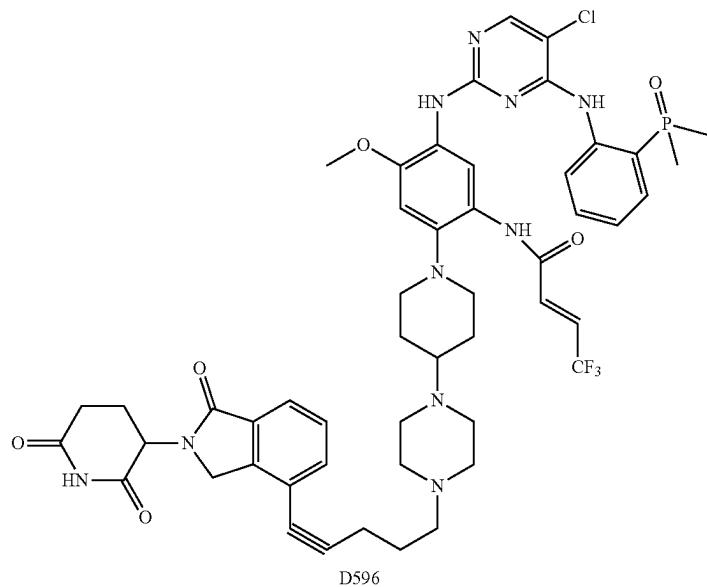
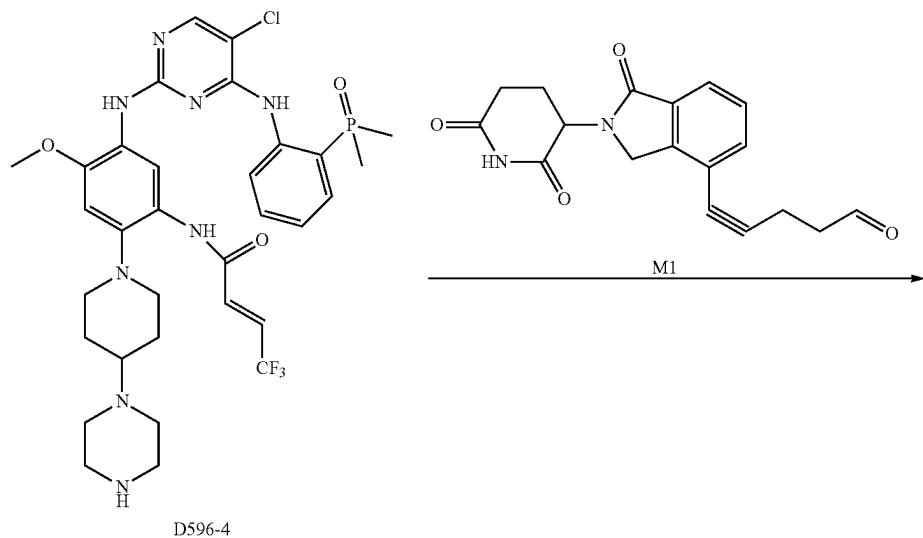


Step 3

[0612] D584-4 (37.3 mg, 0.051 mmol), M1 (15.0 mg, 0.046 mmol) and acetic acid (3.3 mg, 0.056 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (4.4 mg, 0.069 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40°C., and the crude product was purified by HPLC to give compound D584 (18 mg, yield 37.5%), LCMS: $[\text{M}+\text{H}]^+=1043$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisobutyl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide (D596)

-continued

**Step 1**

[0613] D596-1 (80 mg, 0.117 mmol), D596-2 (18 mg, 0.129 mmol), T3P (149 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by thin layer chromatography to obtain D596-3 (62 mg, yield 66.0%), LCMS: $[M+H]^+=807$.

Step 2

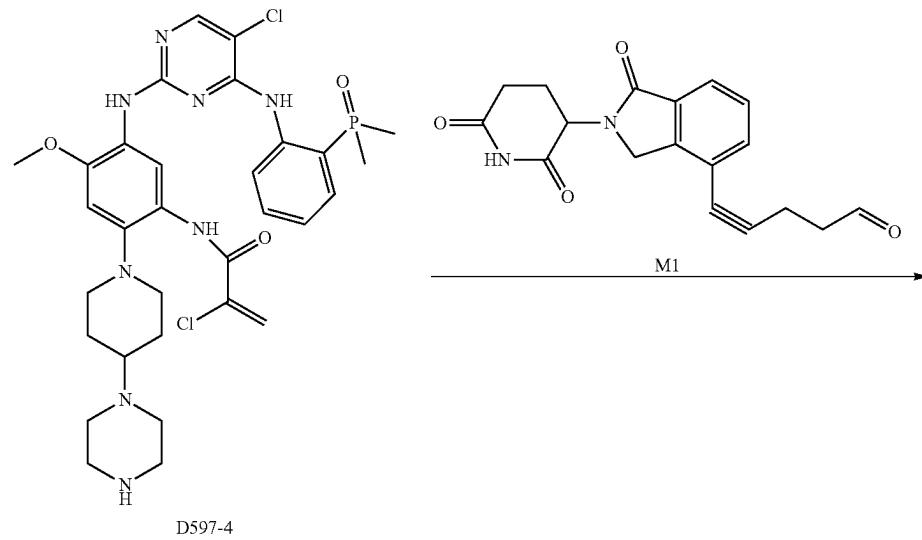
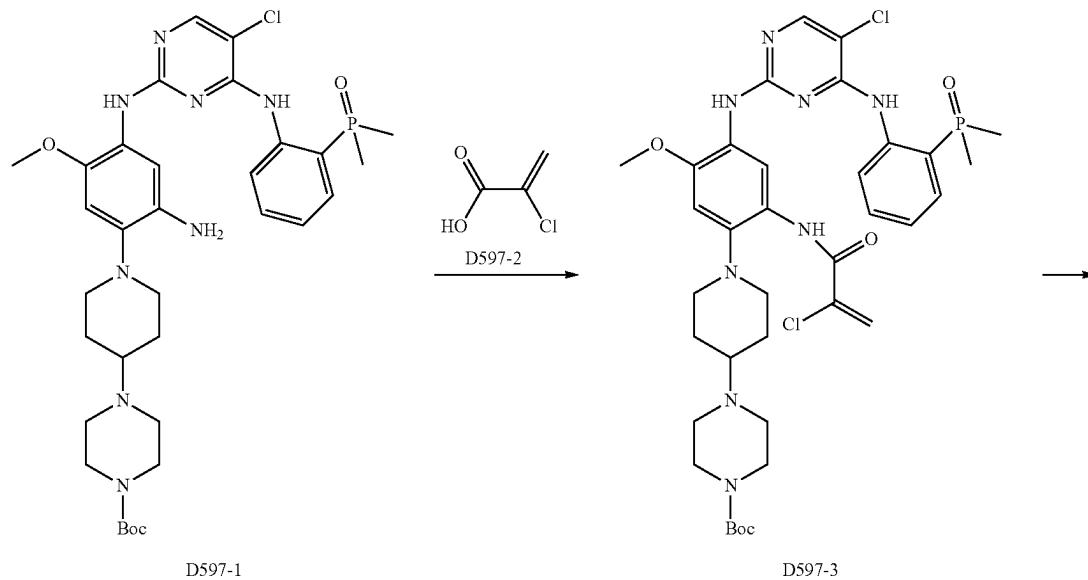
[0614] D596-3 (62 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D596-4 (54 mg, yield 100%), LCMS: $[M+H]^+=707$.

Step 3

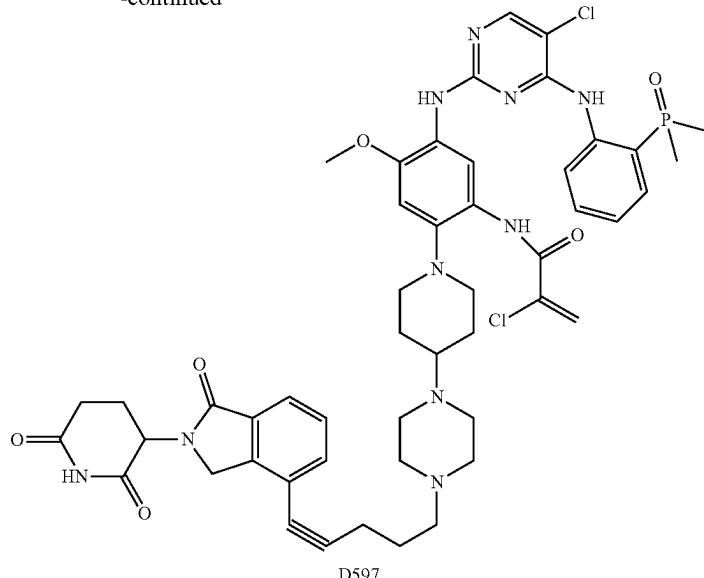
[0615] D596-4 (56.7 mg, 0.080 mmol), M1 (28.6 mg, 0.088 mmol) and acetic acid (5.8 mg, 0.096 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (7.6 mg, 0.120 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give D596 (15 mg, yield 18.5%), LCMS: [M+H]⁺ = 1015.

Preparation of 2-chloro-N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D597)



-continued



Step 1

[0616] D597-1 (80 mg, 0.117 mmol), D597-2 (13.6 mg, 0.129 mmol), T3P (149 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by thin layer chromatography to obtain D597-3 (40 mg, yield 44.4%), LCMS: $[M+H]^+$ =773.

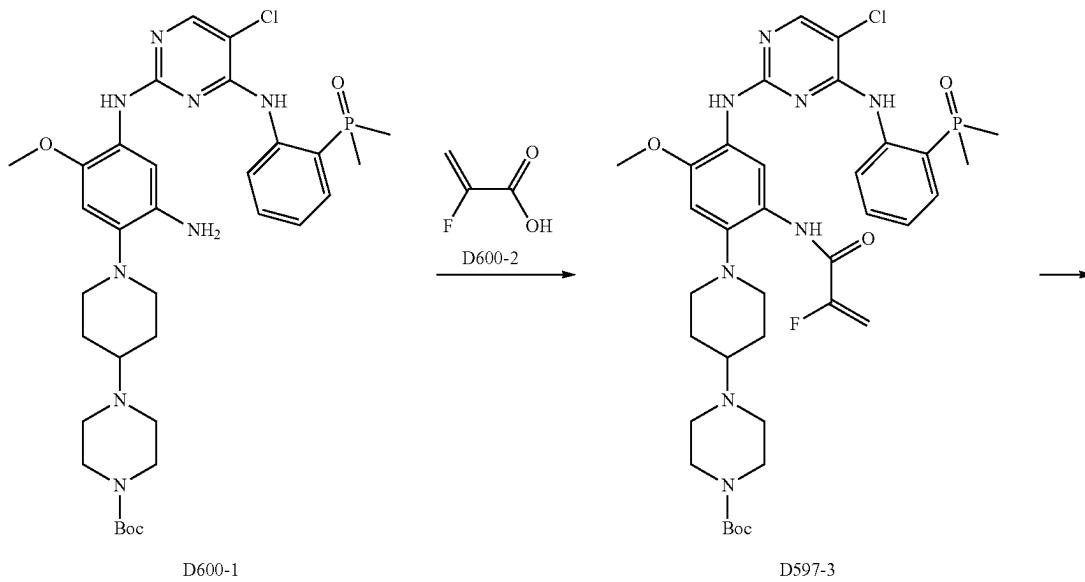
Step 2

[0617] D597-3 (40 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D597-4 (29 mg, yield 85.3%), LCMS: $[M+H]^+$ = 673.

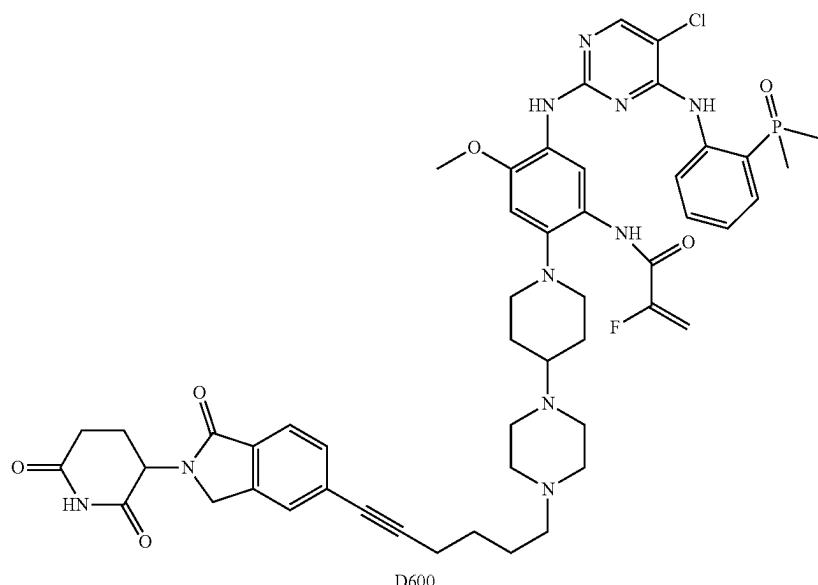
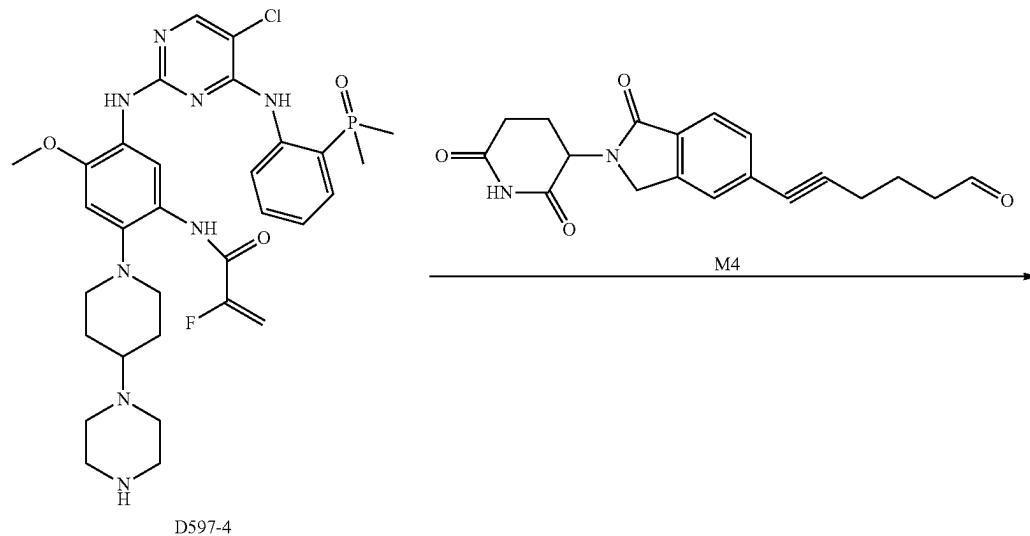
Step 3

[0618] D597-4 (29 mg, 0.043 mmol), M1 (15.4 mg, 0.047 mmol) and acetic acid (3.1 mg, 0.052 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (4.1 mg, 0.065 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D597 (13 mg, yield 31.0%), LCMS: $[\text{M}+\text{H}]^+ = 981$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D600)



-continued

**Step 1**

[0619] D600-1 (100 mg, 0.146 mmol), D600-2 (15.8 mg, 0.175 mmol), T3P (372 mg, 0.585 mmol) and TEA (59 mg, 0.585 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by thin layer chromatography to obtain D600-3 (91 mg, yield 82.4%), LCMS: $[M+H]^+=757$.

Step 2

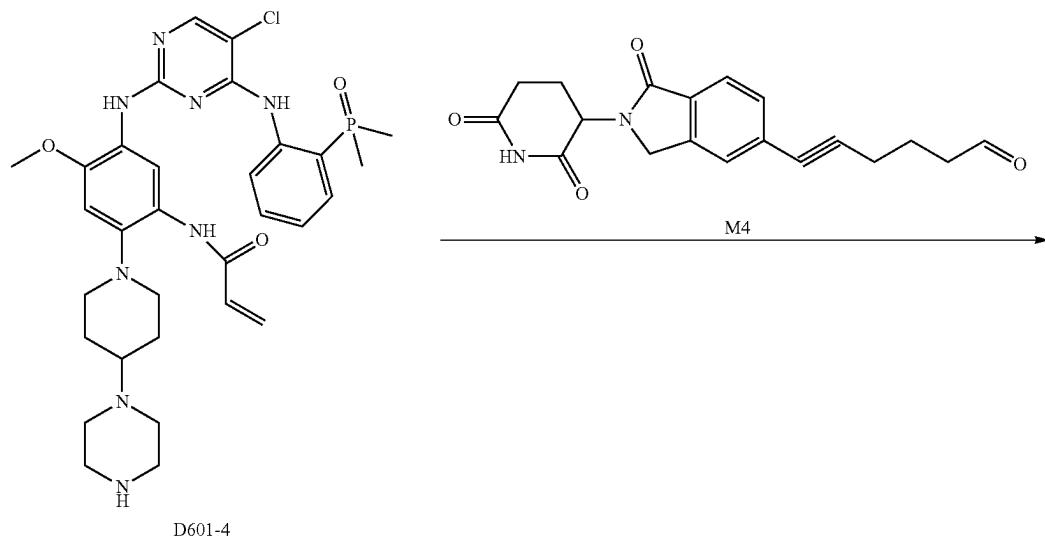
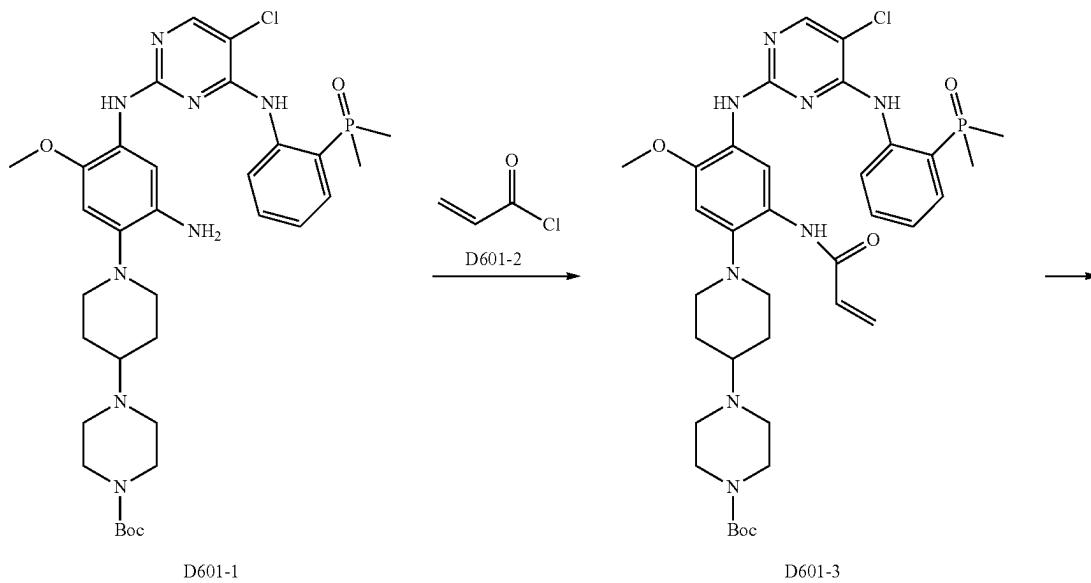
[0620] D600-3 (91 mg) was dissolved in 4 mL of dichloromethane, and trifluoroacetic acid (1 mL) was added under stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D600-4 (66 mg, yield 83.5%), LCMS: $[M+H]^+=657$.

Step 3

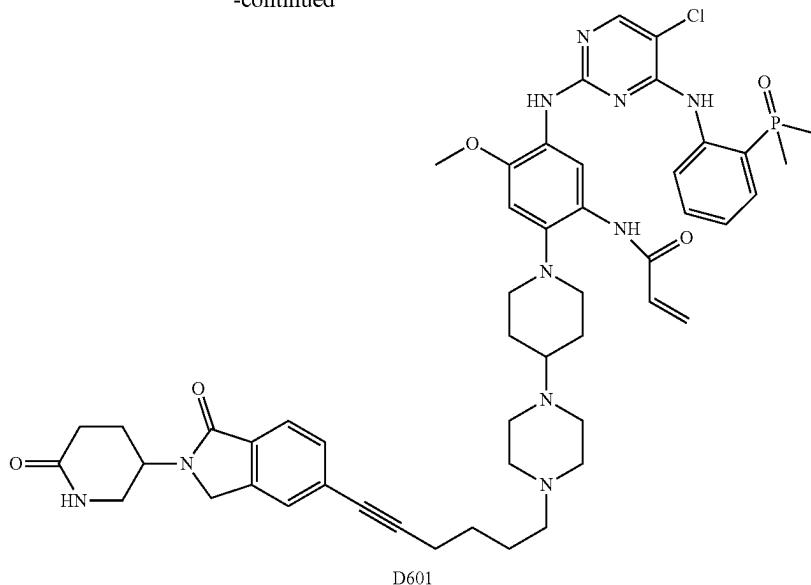
[0621] D600-4 (66 mg, 0.101 mmol), M4 (37 mg, 0.111 mmol) and acetic acid (7.2 mg, 0.121 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (9.5 mg, 0.151 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to obtain D600 (10 mg, yield 10.2%), LCMS: [M+H]⁺=979.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D601)



-continued



Step 1

[0622] D601-1 (100 mg, 0.146 mmol) and TEA (44 mg, 0.438 mmol) were dissolved in 20 mL of dichloromethane. Under nitrogen protection, a solution of D601-2 (14.5 mg, 0.161 mmol) in 1 mL of dichloromethane was added drop-wise at -12° C. The temperature was maintained and the mixture was stirred for 1.5 hours. Methanol was added to quench the reaction. The solvent was evaporated and the crude product was purified by thin layer chromatography to obtain D601-3 (69 mg, yield 63.9%). LCMS: $[M+H]^+$ =739.

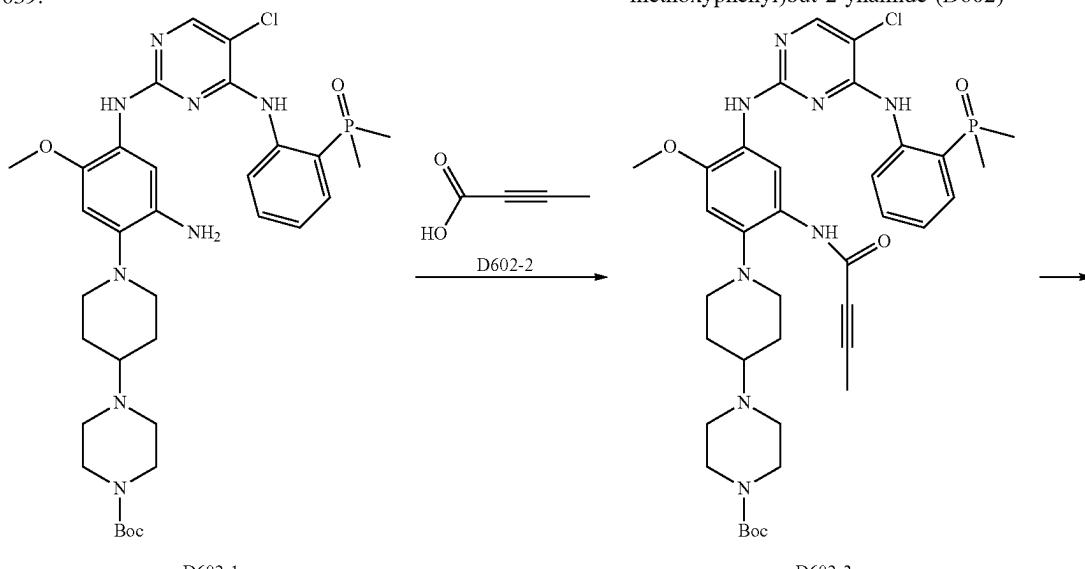
Step 2

[0623] D601-3 (69 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring, and the mixture was stirred at room temperature for 1.5 hours under nitrogen protection. The solvent was removed under reduced pressure and the residue was purified by Flash to give D601-4 (51 mg, yield 60.0%), LCMS: $[\text{M}+\text{H}]^+ = 639$.

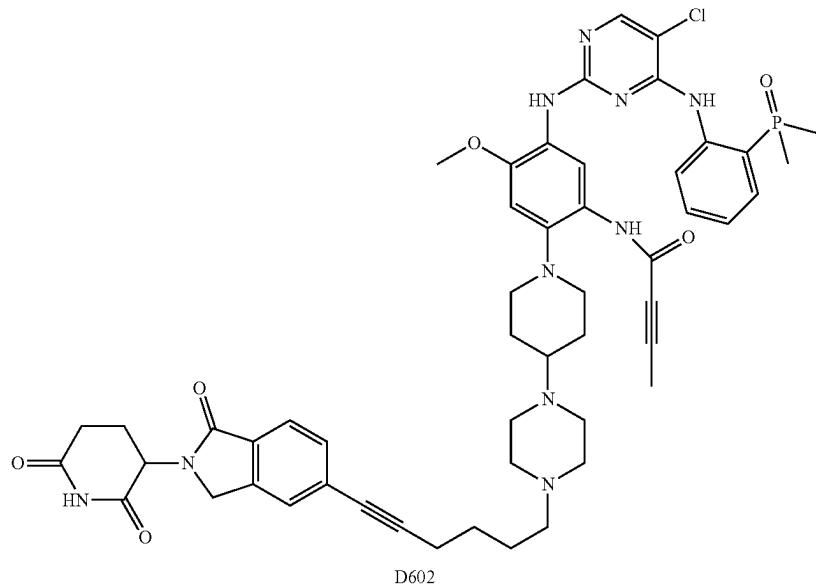
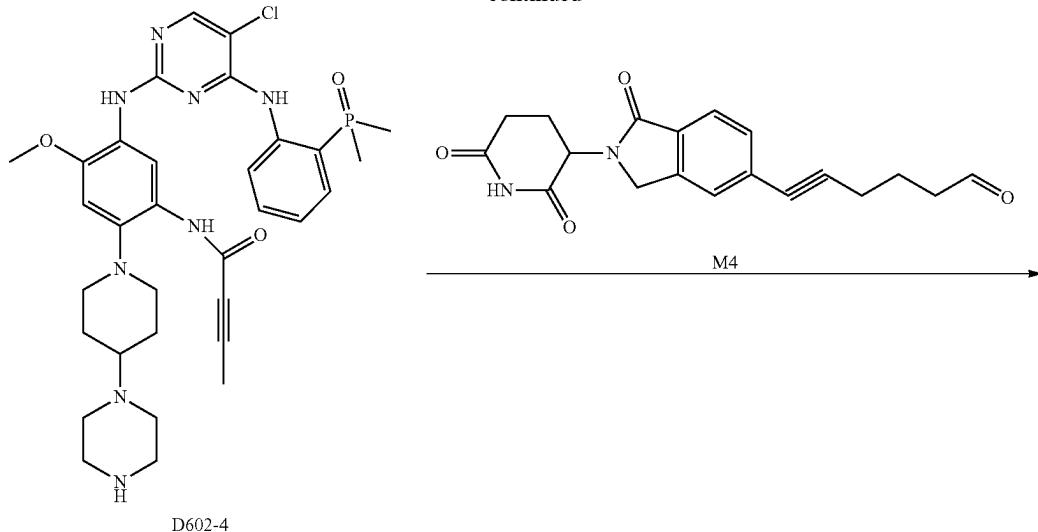
Step 3

[0624] D601-4 (51 mg, 0.080 mmol), M4 (30 mg, 0.088 mmol) and acetic acid (5.8 mg, 0.096 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (7.5 mg, 0.120 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D601 (25 mg, yield 32.5%), LCMS: $[\text{M}+\text{H}]^+ = 961$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-5-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide (D602)



-continued



Step 1

[0625] D602-1 (100 mg, 0.146 mmol), D602-2 (14.7 mg, 0.175 mmol), T3P (50% EA, 372 mg, 0.585 mmol) and TEA (59 mg, 0.585 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The crude product was purified by thin layer chromatography to give D602-3 (75 mg, yield 68.2%), LCMS: $[M+H]^+=751$.

Step 2

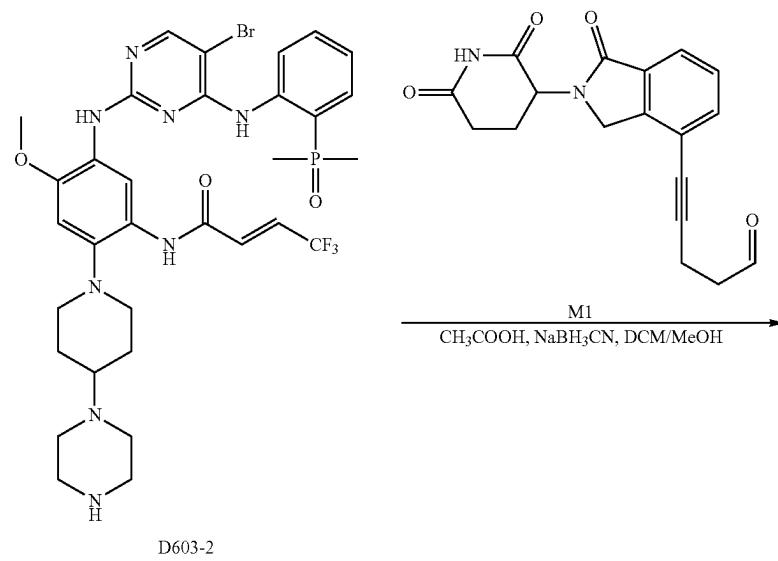
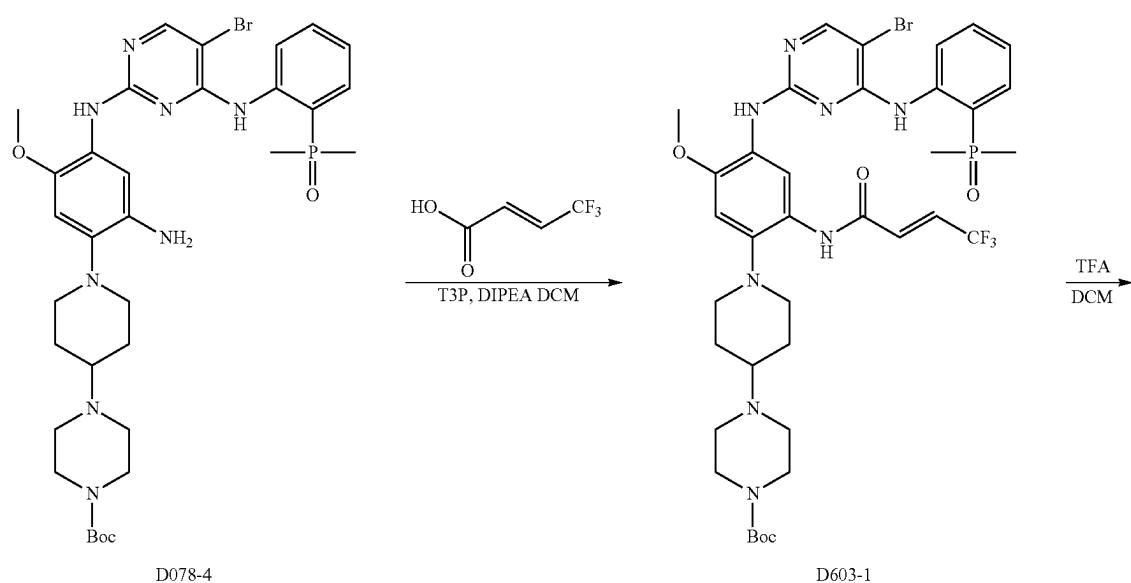
[0626] D602-3 (75 mg) was dissolved in 4 mL of dichloromethane, and trifluoroacetic acid (1 mL) was added with stirring. The mixture was stirred at room temperature for 1.5 hours under nitrogen protection. The solvent was removed

under reduced pressure and the residue was purified by Flash to obtain D602-4 (55 mg, yield 84.6%), LCMS: $[M+H]^+=651$.

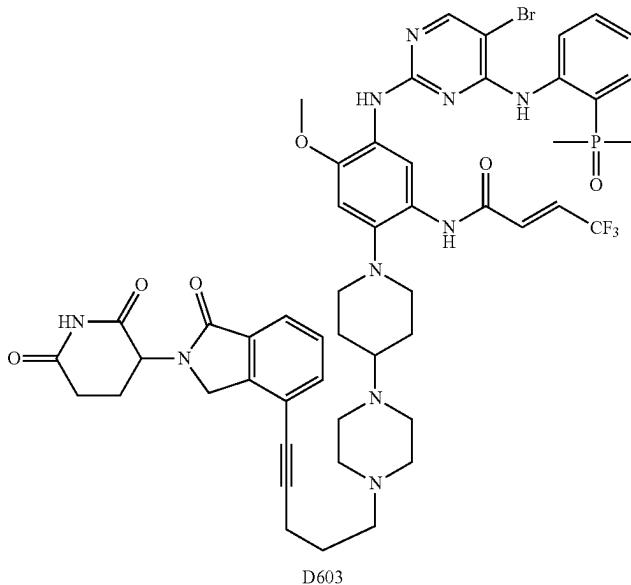
Step 3

[0627] D602-4 (55 mg, 0.085 mmol), M4 (32 mg, 0.093 mmol) and acetic acid (6.1 mg, 0.101 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (8.0 mg, 0.127 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D602 (20 mg, yield 24.4%), LCMS: $[M+H]^+=973$.

Preparation of (E)-N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide
(D603)



-continued



Step 1

[0628] D078-4 (145.6 mg, 0.2 mmol), (E)-4,4,4-trifluoro-2-butenoic acid (42 mg, 0.3 mmol) and T3P (254 mg, 0.4 mmol) were dispersed in 5.0 mL of anhydrous dichloromethane. Under N₂ protection, diisopropylethylamine (129 mg, 1.0 mmol) was added to the reaction solution and reacted at room temperature for 2.0 h. The reaction was completed as detected by LCMS. The reaction solution was diluted with 30 mL of dichloromethane. Silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D603-1 (128 mg, yield 75.0%). LCMS: [M+H]⁺=851.

Step 2

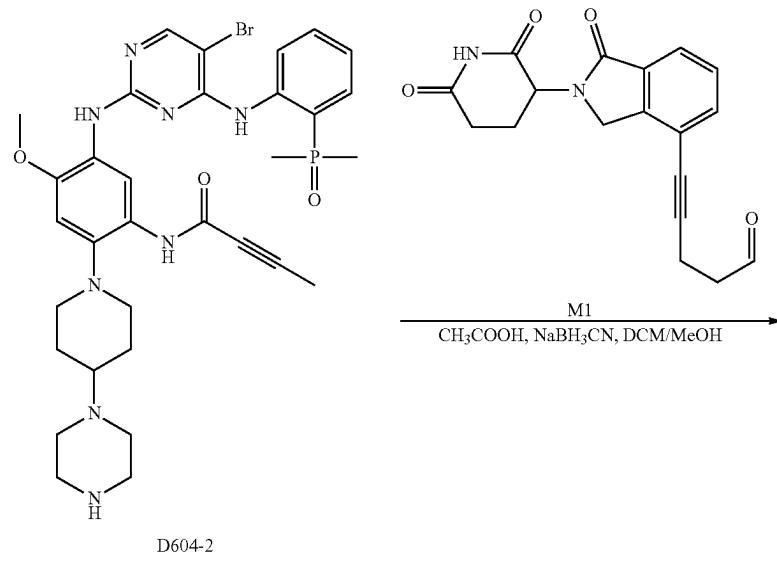
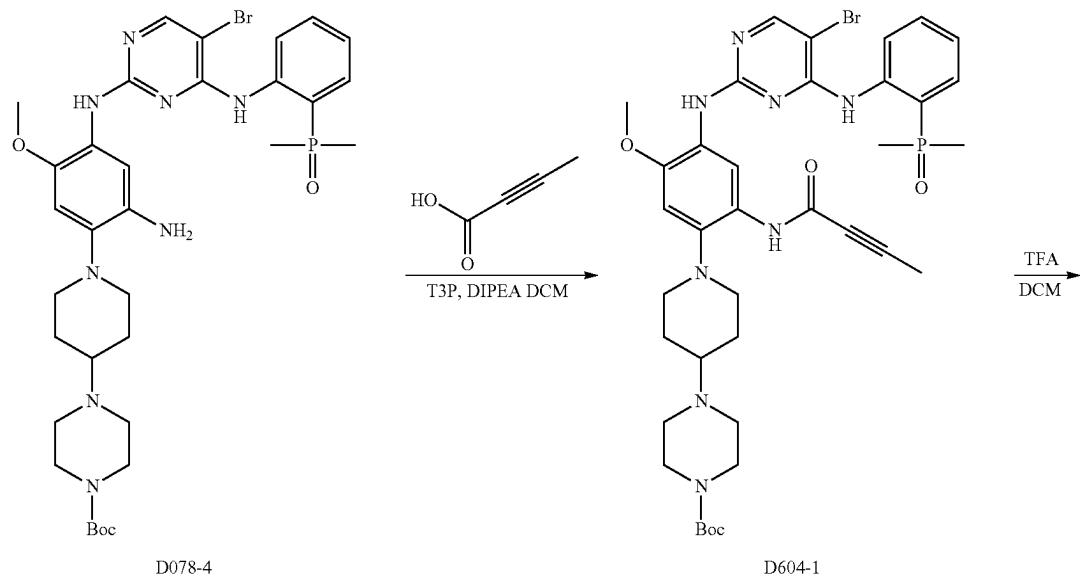
[0629] D603-1 (128 mg, 0.15 mmol) was dissolved in 10 mL of anhydrous dichloromethane. Under N₂ protection, 2.5 mL of trifluoroacetic acid was added to the reaction solution and the mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was concentrated under reduced pressure. The residue was redissolved in 30 mL of a mixed solvent (MeOH:DCM=1:20), then washed with saturated NaHCO₃

solution (2×20 mL) and saturated brine (1×20 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D603-2 (95 mg, yield 84.4%). LCMS: [M+H]⁺=751.

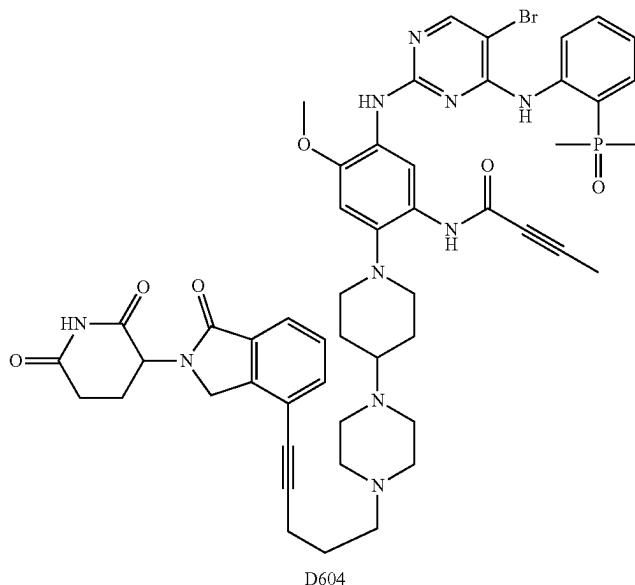
Step 3

[0630] D603-2 (95 mg, 0.127 mmol) and M1 (53.4 mg, 0.165 mmol) were dissolved in a mixed solvent of 10.0 mL of anhydrous dichloromethane and 1.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (11.4 mg, 0.191 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Solid NaBH₃CN (16.0 mg, 0.254 mmol) was then added to the reaction solution and the mixture was reacted at room temperature for another 2 h. LCMS and TLC showed that the reaction was completed. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D603 (35 mg, yield 26.1%). LCMS: [M+H]⁺=1059, 1061.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide (D604)



-continued



Step 1

[0631] D078-4 (3.2 g, 4.4 mmol), but-2-yneic acid (0.37 g, 4.4 mmol) and T3P (4.47 g, 8.8 mmol) were dispersed in 32 mL of anhydrous dichloromethane. Under N₂ protection, diisopropylethylamine (2.84 g, 22.0 mmol) was added to the reaction solution. The mixture was reacted at room temperature for 2.0 h. The reaction was completed as detected by LCMS. The reaction solution was diluted with 50 mL of dichloromethane and silica gel was directly added to the sample. The mixture was purified by Flash to give a yellow solid product D604-1 (3.1 g). LCMS: [M+H]⁺=795.

Step 2

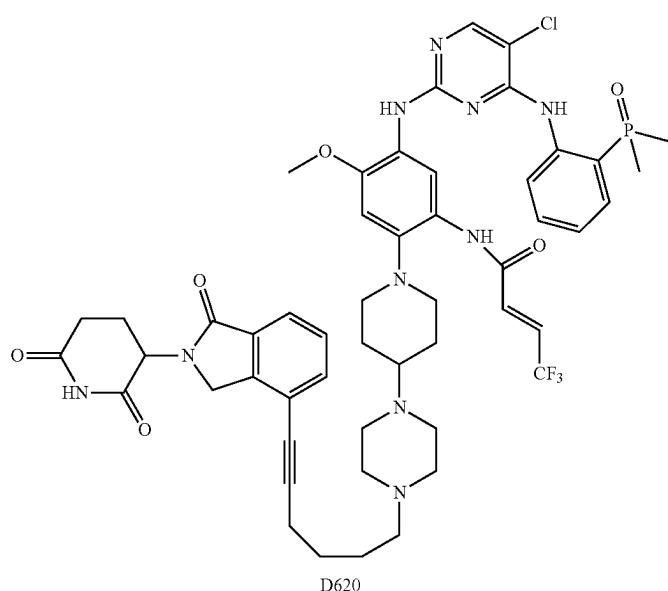
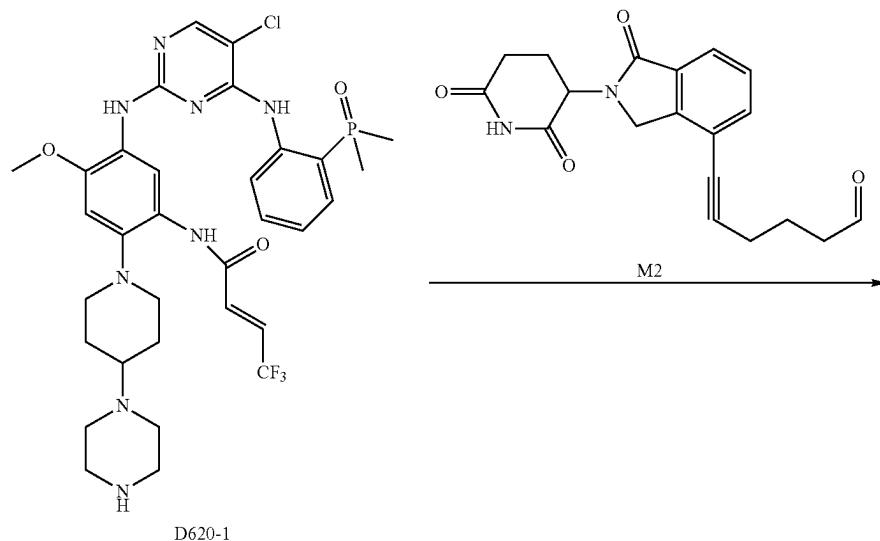
[0632] D604-1 (3.1 g, 3.9 mmol) was dissolved in 60 mL of anhydrous dichloromethane. Under N₂ protection, 15 mL of trifluoroacetic acid was added to the reaction solution and the mixture was reacted at room temperature for 1.0 h. The reaction was completed as detected by LCMS. The reaction solution was concentrated under reduced pressure. The residue was redissolved in a mixed solvent of methanol and dichloromethane (100 mL), then washed with saturated

NaHCO₃ solution (2×60 mL) and saturated brine (1×60 mL) in sequence. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to remove the solvent to give a crude product, which was purified by Flash to give a yellow solid product D604-2 (2.1 g). LCMS: [M+H]⁺=701.

Step 3

[0633] D604-2 (2.1 g, 3.03 mmol) and M1 (0.94 g, 3.33 mmol) were dissolved in a mixed solvent of 160.0 mL of anhydrous dichloromethane and 16.0 mL of anhydrous methanol. Under nitrogen protection, CH₃COOH (238 mg, 4.55 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Solid NaBH₃CN (332 mg, 6.06 mmol) was then added to the reaction solution and the mixture was reacted at room temperature for another 2 h. LCMS and TLC showed that the reaction was completed. Silica gel was directly added to the sample. The mixture was purified by Flash to give a white solid pure product D604 (1.6 g, yield 52.8%). LCMS: [M+H]⁺=1003, 1005.

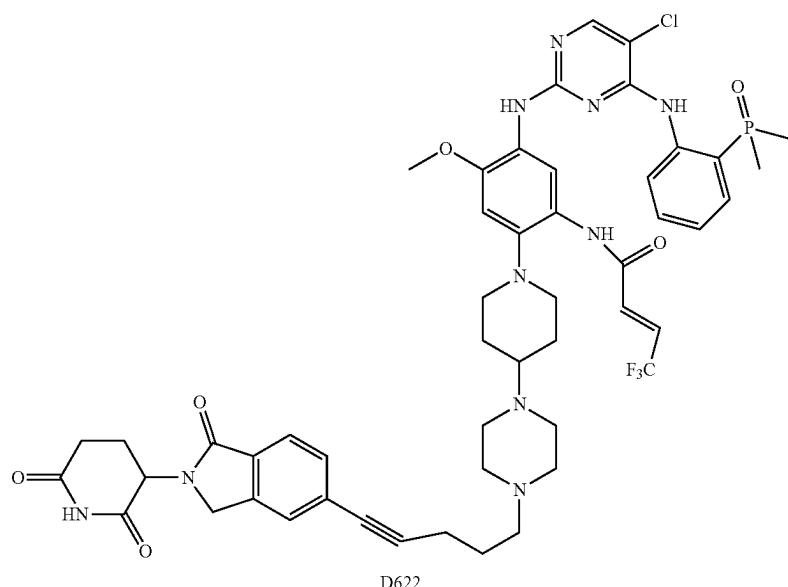
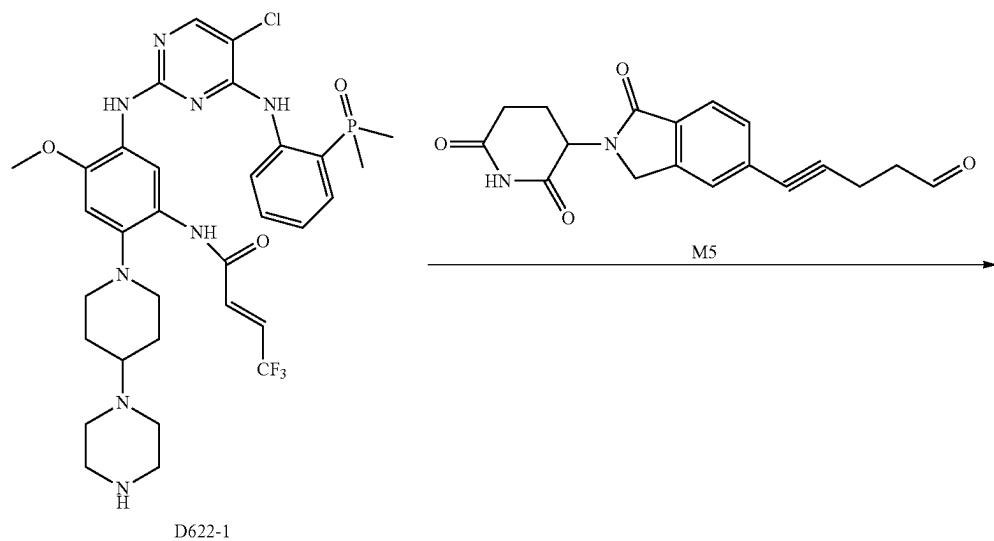
Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide (D620)



[0634] D620-1 (50 mg, 0.071 mmol), M2 (29 mg, 0.085 mmol) and acetic acid (5.1 mg, 0.085 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.7 mg,

0.106 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D620 (24 mg, yield 32.9%), LCMS: [M+H]⁺=1029.

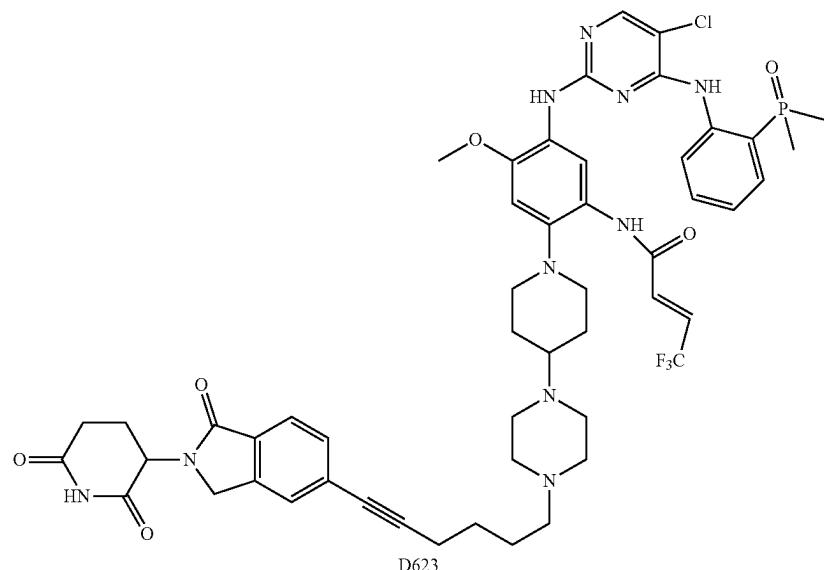
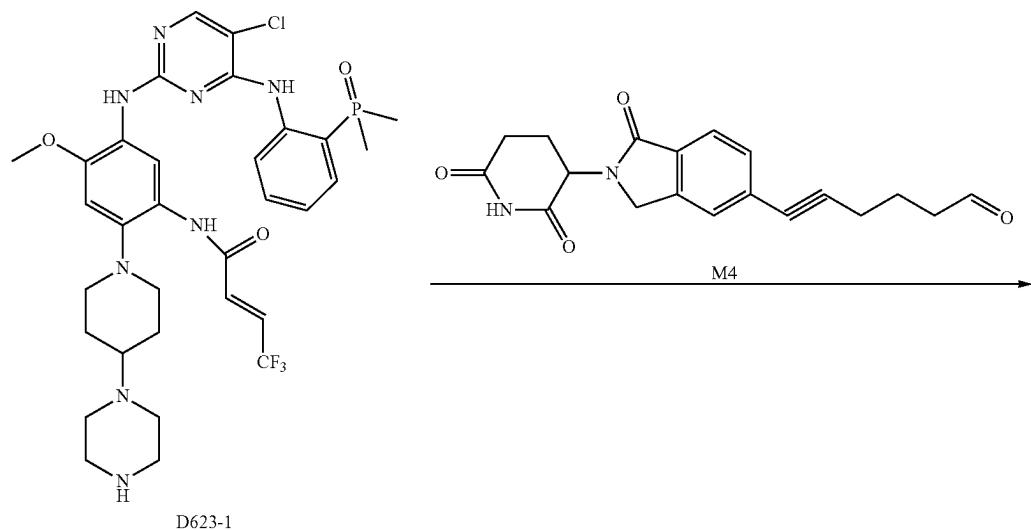
Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide (D622)



[0635] D622-1 (22 mg, 0.031 mmol), M5 (12 mg, 0.037 mmol) and acetic acid (2.2 mg, 0.037 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (2.9 mg,

0.047 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D622 (12 mg, yield 37.5%), LCMS: $[M+H]^+=1015$.

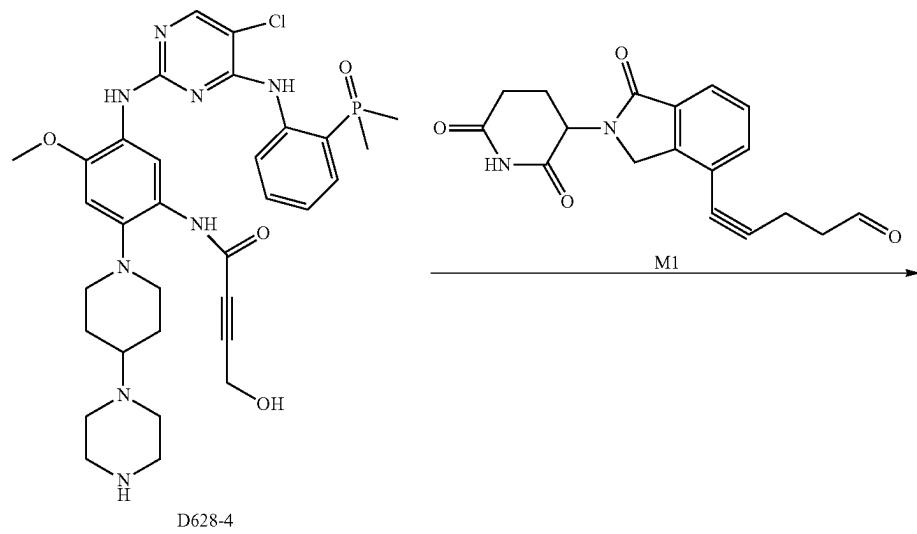
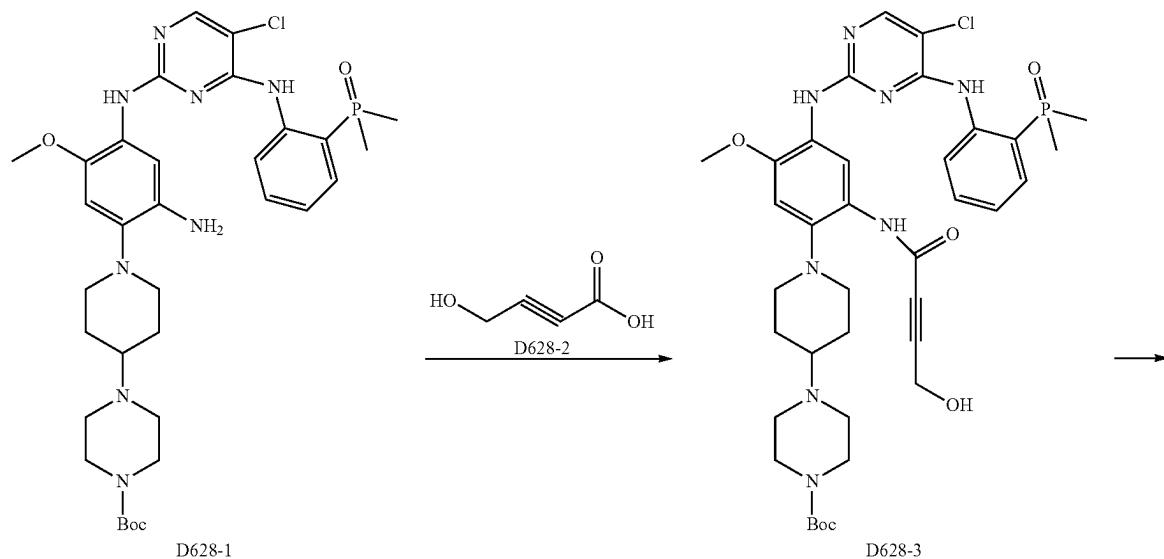
Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(6-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)hex-5-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide (D623)



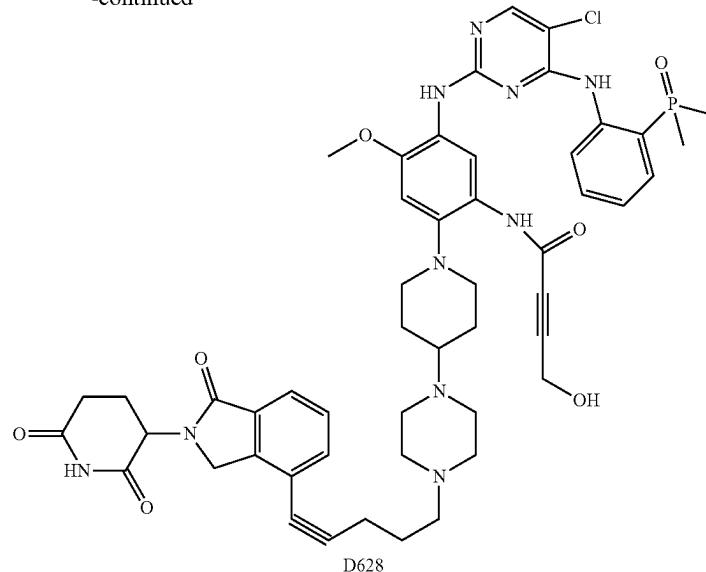
[0636] D623-1 (50 mg, 0.071 mmol), M4 (29 mg, 0.085 mmol) and acetic acid (5.1 mg, 0.037 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.7 mg,

0.106 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D623 (20 mg, yield 27.5%), LCMS: [M+H]⁺=1029.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4-hydroxybut-2-ynamide (D628)



-continued



Step 1

[0637] D628-1 (200 mg, 0.292 mmol), D628-2 (35.1 mg, 0.351 mmol), pyridine (92 mg, 1.170 mmol) and EDCI (224 mg, 1.170 mmol) were dissolved in 3 mL of DMF. Under nitrogen protection, the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by Flash to give D628-3 (100 mg, yield 44.6%), LCMS: $[M+H]^+=767$.

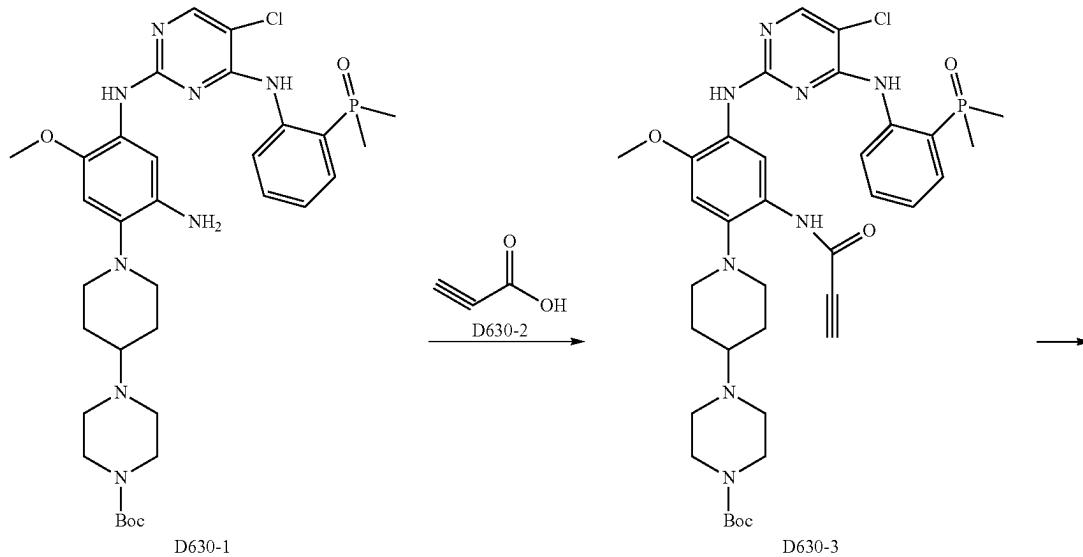
Step 2

[0638] D628-3 (100 mg) was dissolved in 8 mL of dichloromethane. Trifluoroacetic acid (2 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D628-4 (50 mg, yield 57.5%), LCMS: $[M+H]^+=667$.

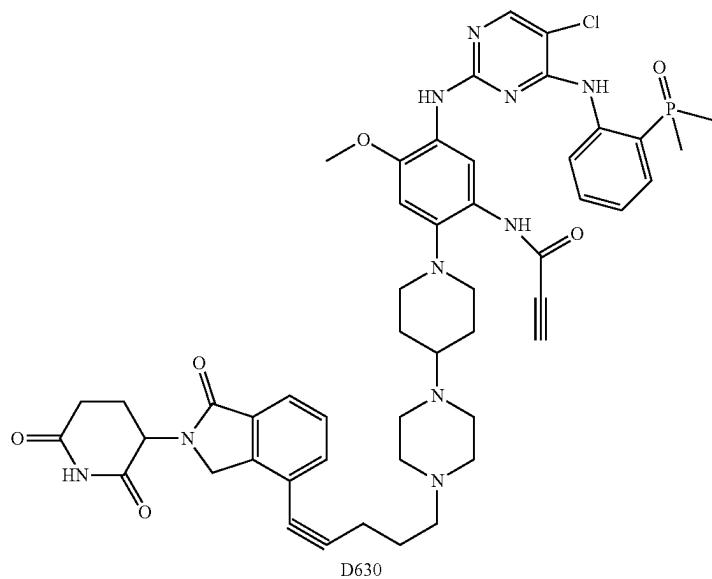
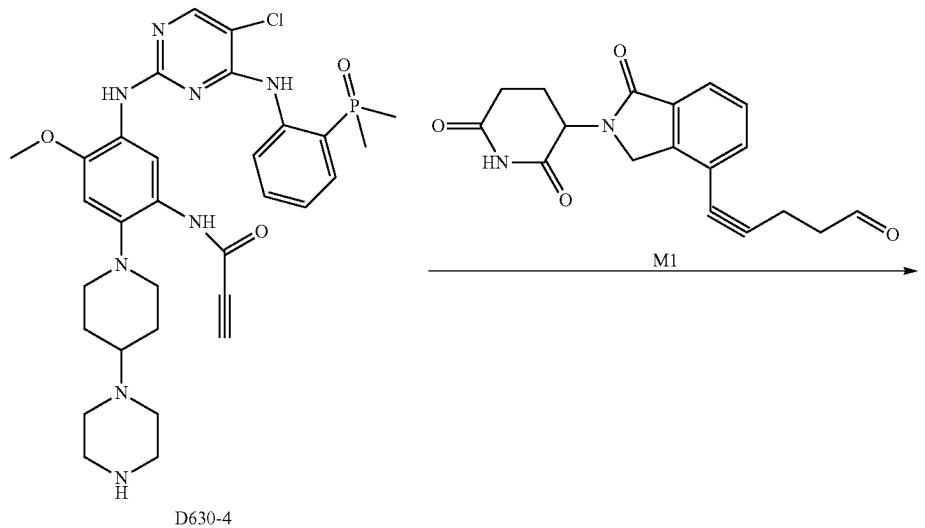
Step 3

[0639] D628-4 (50 mg, 0.075 mmol), M1 (27 mg, 0.083 mmol) and acetic acid (5.4 mg, 0.090 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (7.1 mg, 0.113 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D628 (11 mg, yield 15.1%), LCMS: $[M+H]^+=975$.

Preparation of N-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)propynamide (D630)



-continued

**Step 1**

[0640] D630-1 (80 mg, 0.117 mmol), D630-2 (9.8 mg, 0.140 mmol), T3P (296 mg, 0.468 mmol) and TEA (47 mg, 0.468 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D630-3 (57 mg, yield 66.3%), LCMS: $[M+H]^+=737$.

Step 2

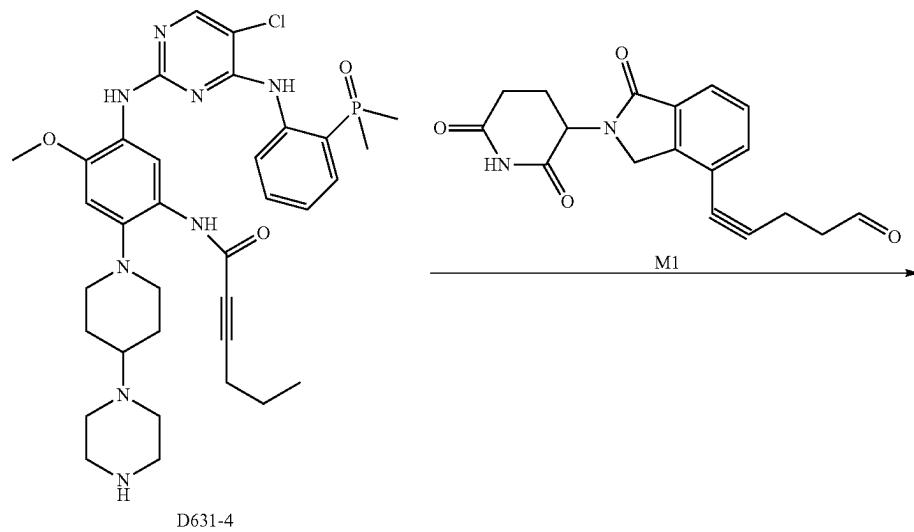
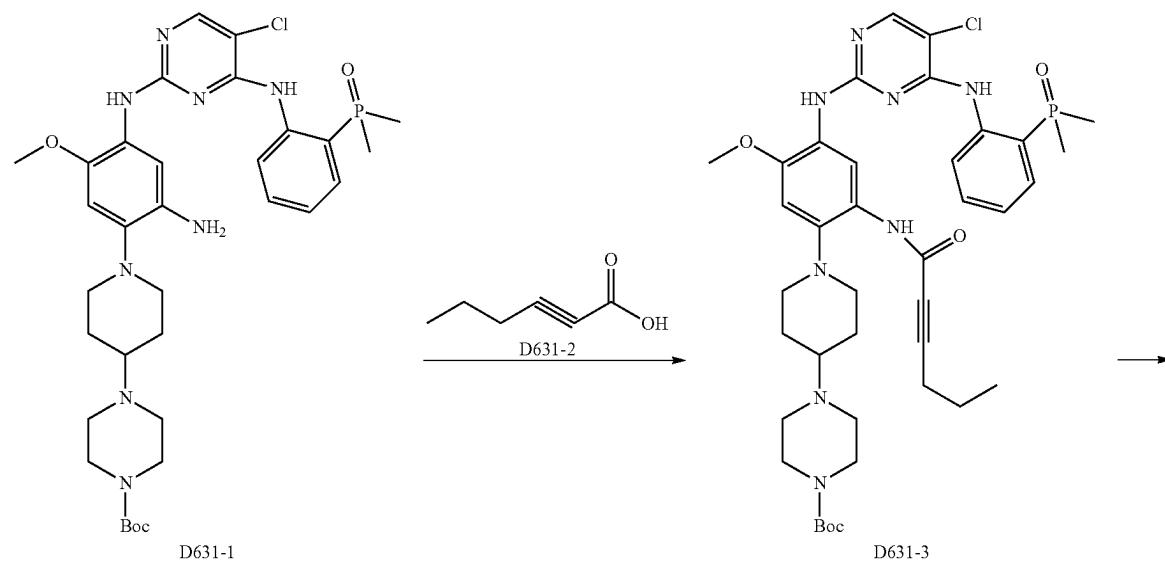
[0641] D630-3 (57 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D630-4 (47 mg, yield 95.9%), LCMS: $[M+H]^+=637$.

Step 3

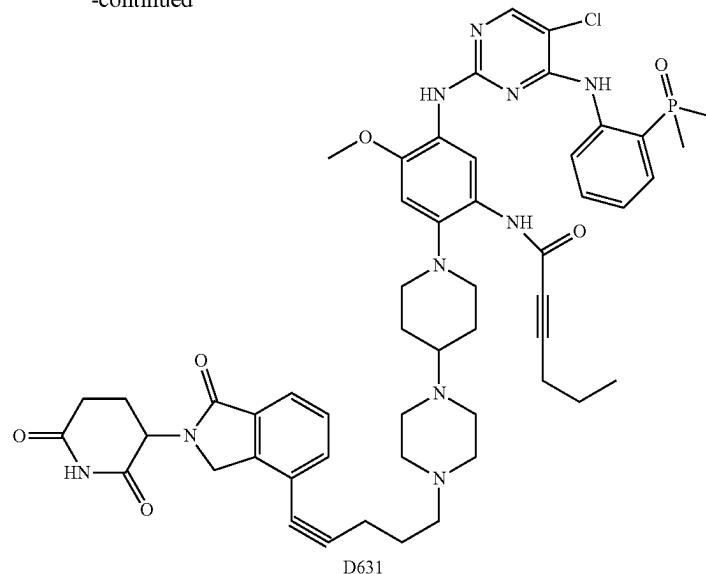
[0642] D630-4 (47 mg, 0.067 mmol), M1 (24 mg, 0.073 mmol) and acetic acid (4.8 mg, 0.080 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.3 mg, 0.100 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give compound D630 (2.14 mg, yield 3.1%), LCMS: $[M+H]^+=945$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)hex-2-ynamide (D631)



-continued



Step 1

[0643] D631-1 (100 mg, 0.146 mmol), D631-2 (20 mg, 0.175 mmol), T3P (372 mg, 0.585 mmol) and TEA (59 mg, 0.585 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D631-3 (70 mg, yield 61.4%), LCMS: $[M+H]^+=779$.

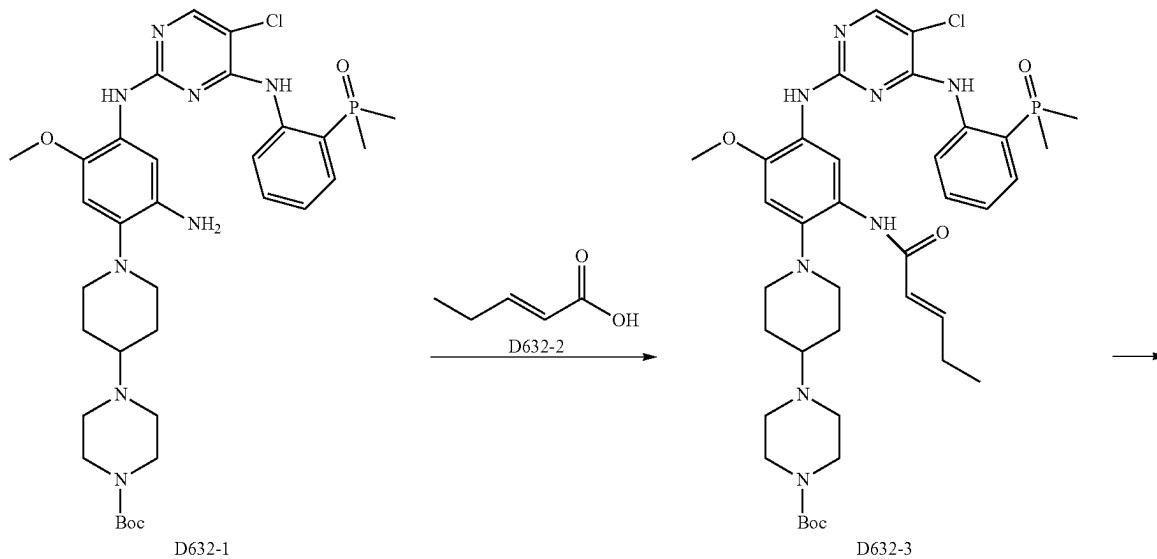
Step 2

[0644] D631-3 (70 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D631-4 (56 mg, yield 91.8%), LCMS: $[M+H]^+=679$.

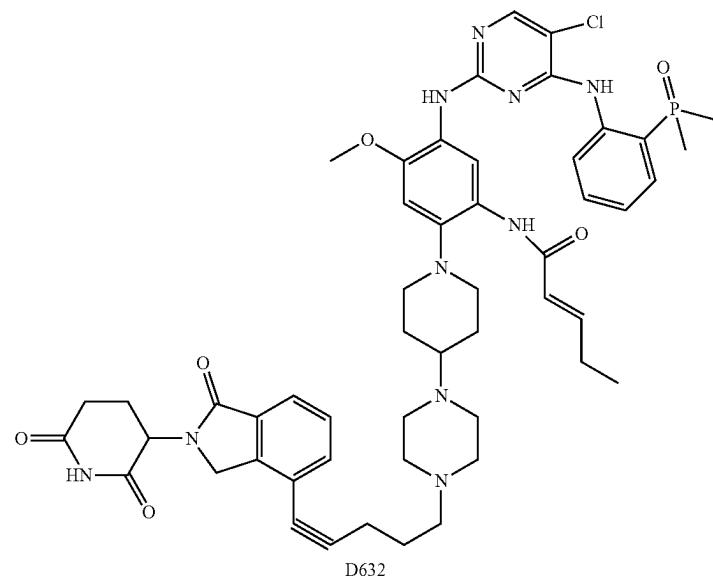
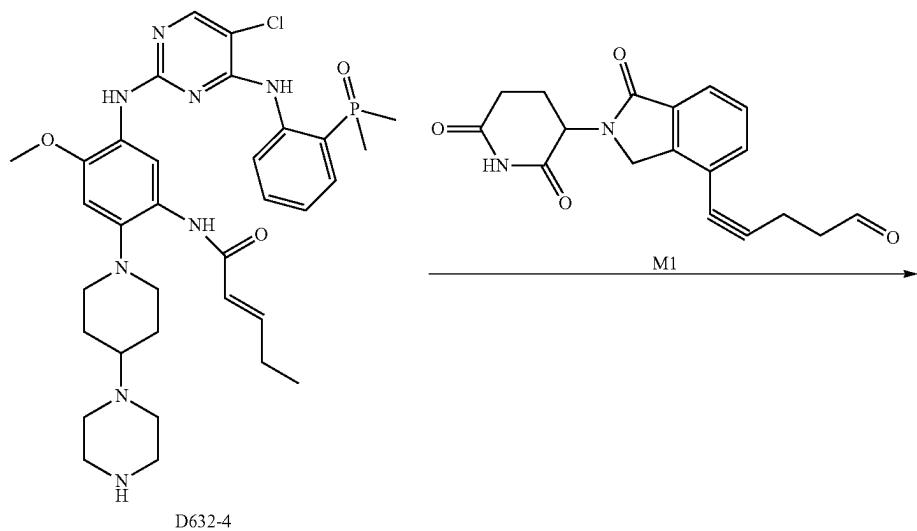
Step 3

[0645] D631-4 (56 mg, 0.083 mmol), M1 (29 mg, 0.091 mmol) and acetic acid (5.9 mg, 0.099 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (7.8 mg, 0.124 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D631 (26 mg, yield 32.1%), LCMS: $[M+H]^+=987$.

Preparation of N-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenylpent-2-enamide (D632)



-continued



Step 1

[0646] D632-1 (100 mg, 0.146 mmol), D632-2 (17.5 mg, 0.175 mmol), T3P (372 mg, 0.585 mmol) and TEA (59 mg, 0.585 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D632-3 (77 mg, yield 68.8%), Mass: 767.

Step 2

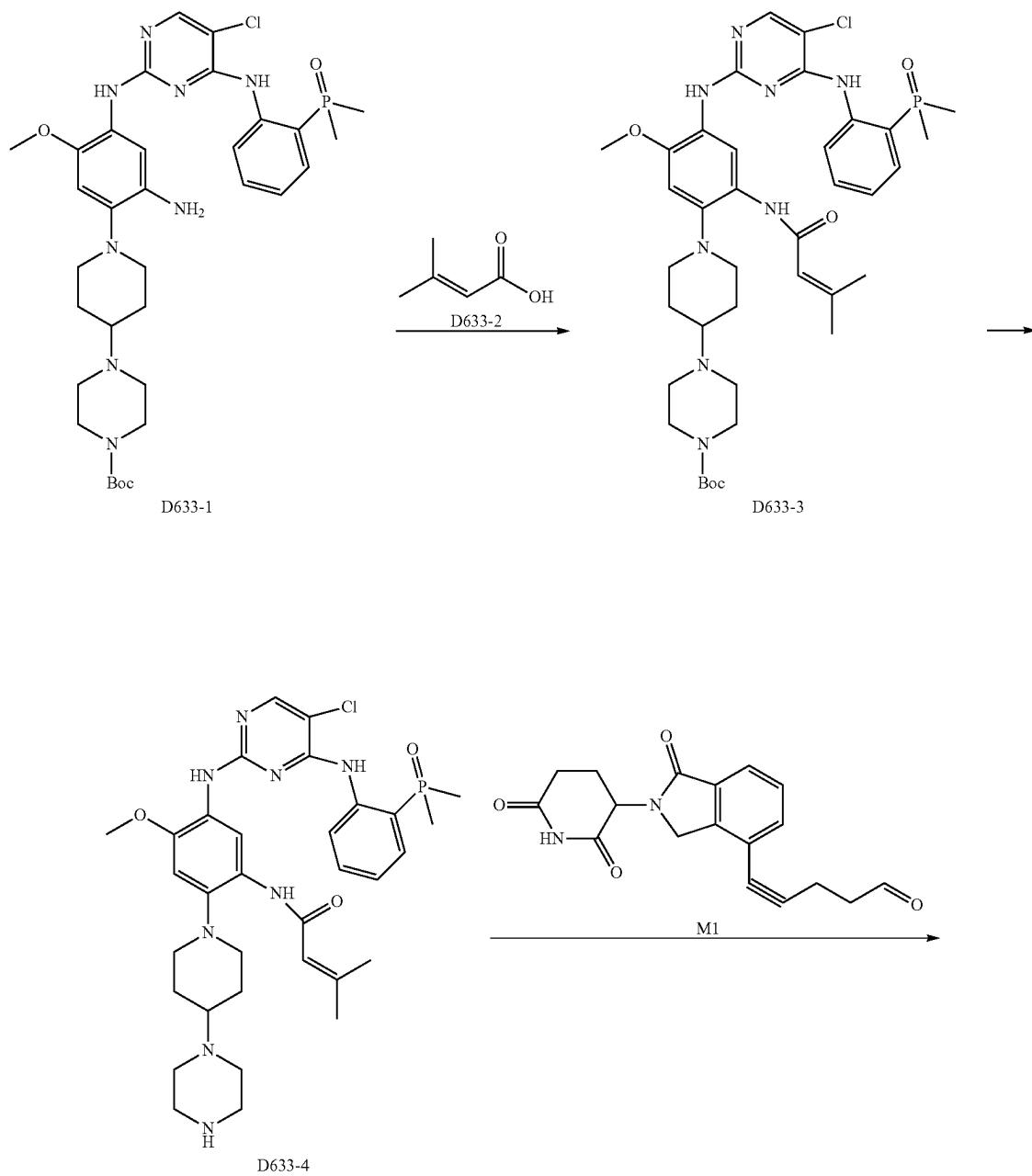
[0647] D632-3 (77 mg) was dissolved in 4 mL of dichloromethane, and trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D632-4 (62 mg, yield 92.5%), LCMS: $[M+H]^+$ =667.

Step 3

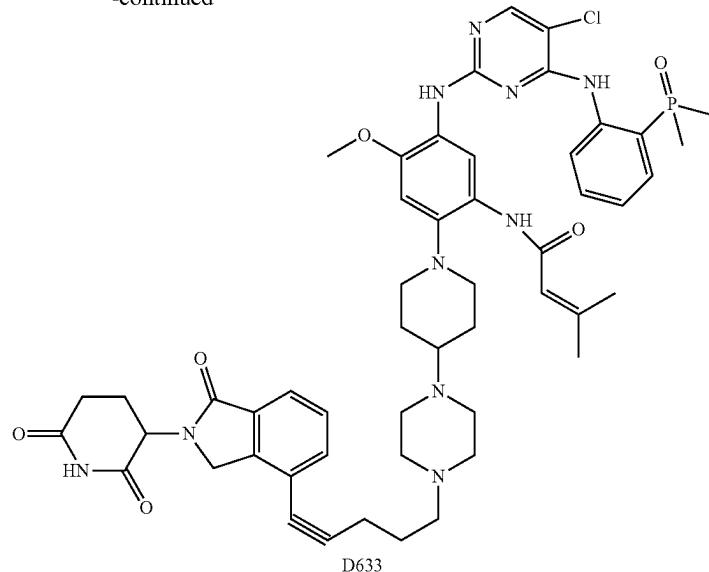
[0648] D632-4 (62 mg, 0.093 mmol), M1 (33 mg, 0.102 mmol) and acetic acid (6.7 mg, 0.112 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (8.8 mg, 0.140 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to obtain D632 (28 mg, yield 30.8%), LCMS: $[M+H]^+=975$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-3-methylbut-2-enamide (D633)



-continued

**Step 1**

[0649] D633-1 (100 mg, 0.146 mmol), D633-2 (17.5 mg, 0.175 mmol), T3P (372 mg, 0.585 mmol) and TEA (59 mg, 0.585 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D633-3 (75 mg, yield 67.0%), LCMS: $[M+H]^+=767$.

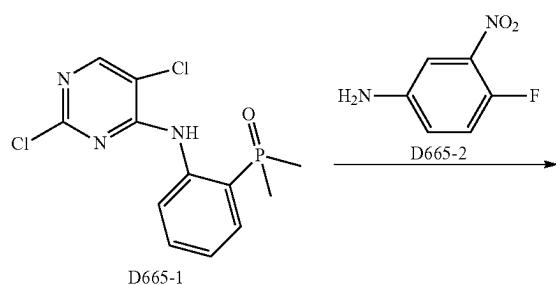
Step 2

[0650] D633-3 (75 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D633-4 (50 mg, yield 76.9%), LCMS: $[M+H]^+=667$.

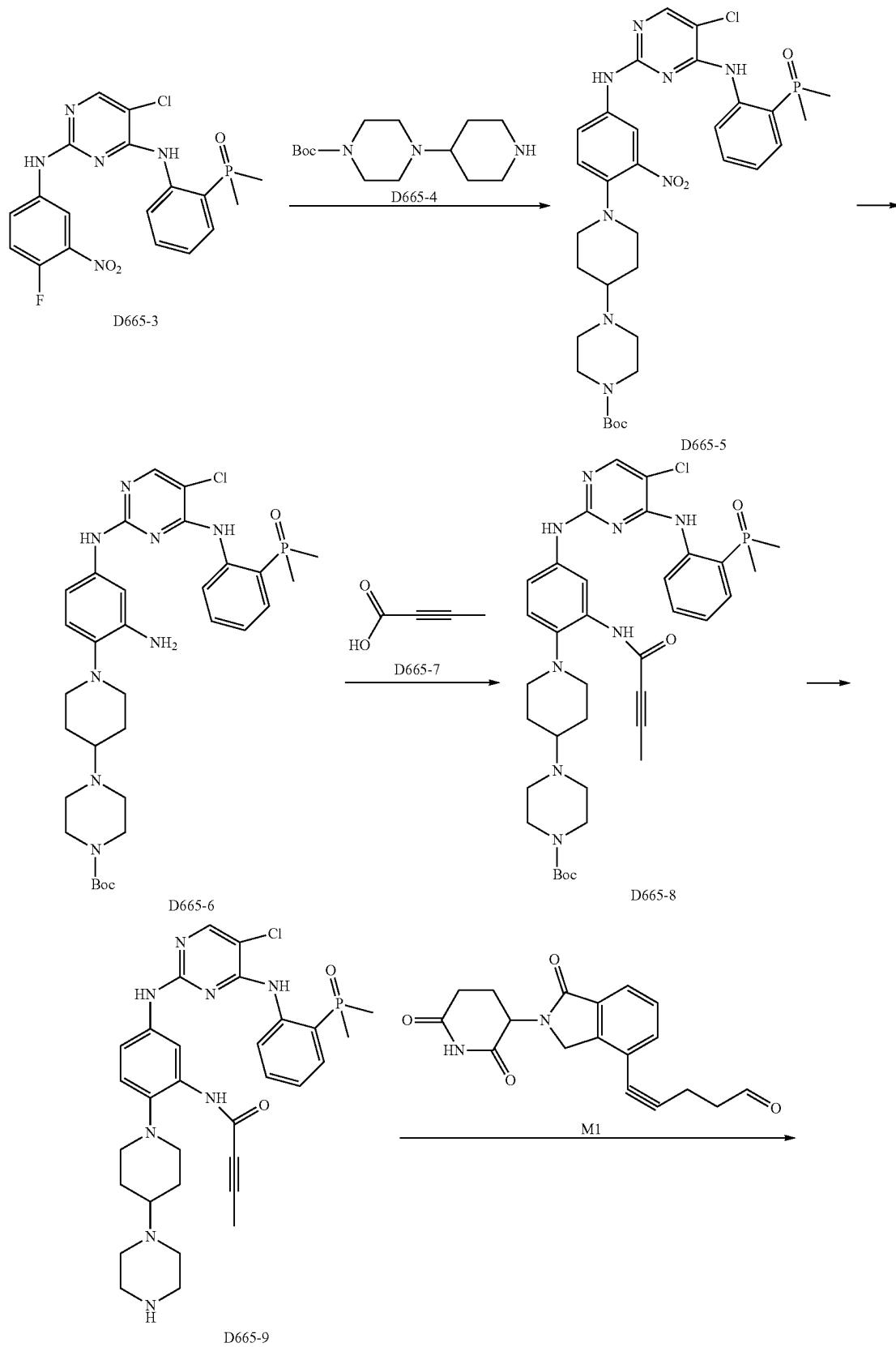
Step 3

[0651] D633-4 (50 mg, 0.075 mmol), M1 (27 mg, 0.083 mmol) and acetic acid (5.4 mg, 0.090 mmol) were dissolved in 2 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (7.1 mg, 0.113 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D633 (6 mg, yield 8.2%), LCMS: $[M+H]^+=975$.

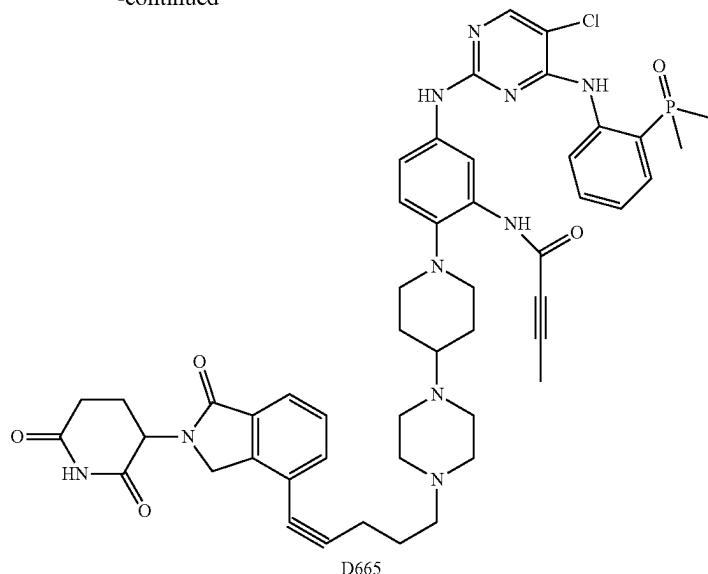
Preparation of N-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenylbut-2-ynameide (D665)



-continued



-continued



Step 1

[0652] D665-1 (200 mg, 0.635 mmol), D665-2 (99 mg, 0.635 mmol), and methanesulfonic acid (244 mg, 2.540 mmol) were dissolved in 5 mL of tert-butanol. Under nitrogen protection, the mixture was stirred at 90° C. overnight. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D665-3 (248 mg, yield 89.9%), LCMS: [M+H]⁺=436.

Step 2

[0653] D665-3 (496 mg, 1.14 mmol), D665-4 (368 mg) and cesium carbonate (1.115 g, 3.42 mmol) were added to 10 mL of DMF. The mixture was stirred at 70° C. overnight under nitrogen protection. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by Flash to give D665-5 (613 mg, yield 78.6%), LCMS: [M+H]⁺=685.

Step 3

[0654] D665-5 (613 mg, 0.896 mmol), iron powder (500 mg, 8.958 mmol) and ammonium chloride (288 mg, 5.375 mmol) were added to 8 mL of a mixed solvent of ethanol/water (3/1). The mixture was stirred at 100° C. for 1 hour. The reaction was cooled to room temperature. The solid was

filtered out. The solid residue was washed twice with a mixed solvent of ethanol and water. The solvent was evaporated under reduced pressure, and the crude product was purified by Flash to obtain D665-6 (425 mg). LCMS: [M+H]⁺=655.

Step 4

[0655] D665-6 (80 mg, 0.122 mmol), D665-7 (12 mg, 0.147 mmol), T3P (50% EA, 311 mg, 0.489 mmol) and TEA (49 mg, 0.489 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D665-8 (64 mg, yield 76.0%), LCMS: [M+H]⁺=721.

Step 5

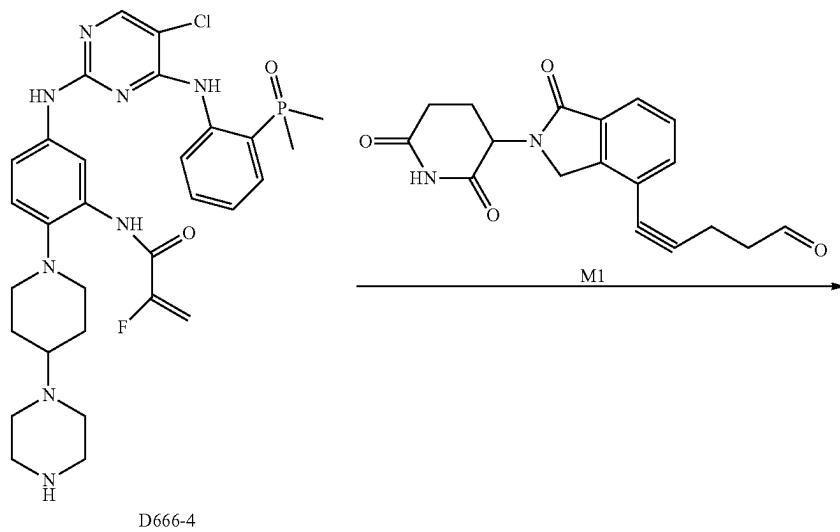
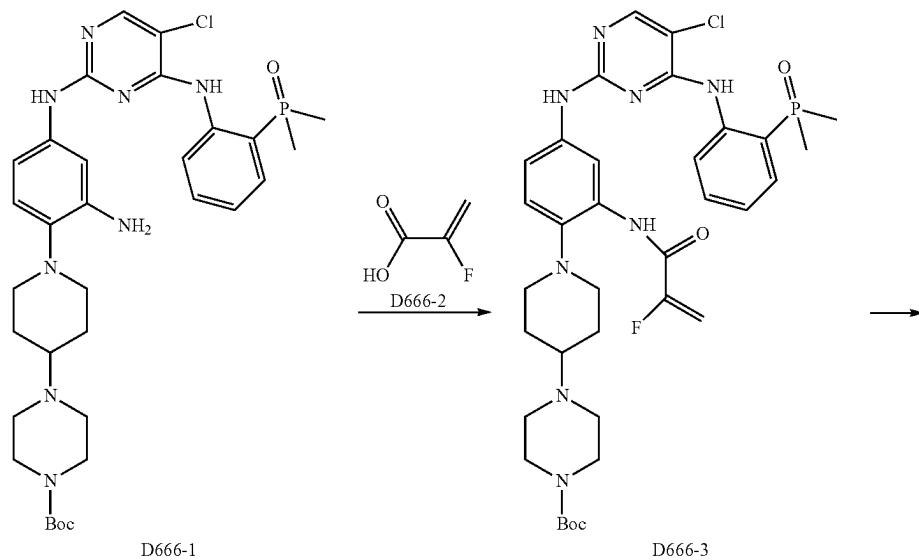
[0656] D665-8 (64 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D665-9 (41 mg, yield 74.5%), LCMS: [M+H]⁺=621.

Step 6

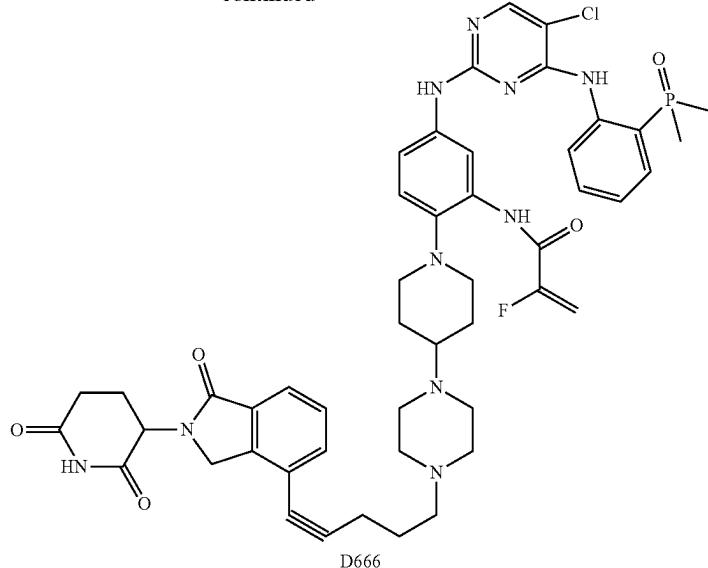
[0657] D665-9 (41 mg, 0.066 mmol), M1 (26 mg, 0.079 mmol) and acetic acid (4.8 mg, 0.080 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.2 mg, 0.099 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give compound D665 (20 mg, yield 32.8%), LCMS: $[M+H]^+=929$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisocindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenyl)-2-fluoroacrylamide (D666)



-continued



Step 1

[0658] D666-1 (80 mg, 0.122 mmol), D666-2 (13 mg, 0.147 mmol), T3P (311 mg, 0.489 mmol) and TEA (49 mg, 0.489 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D666-3 (56 mg, yield 63.1%), LCMS: $[\text{M}+\text{H}]^+ = 727$.

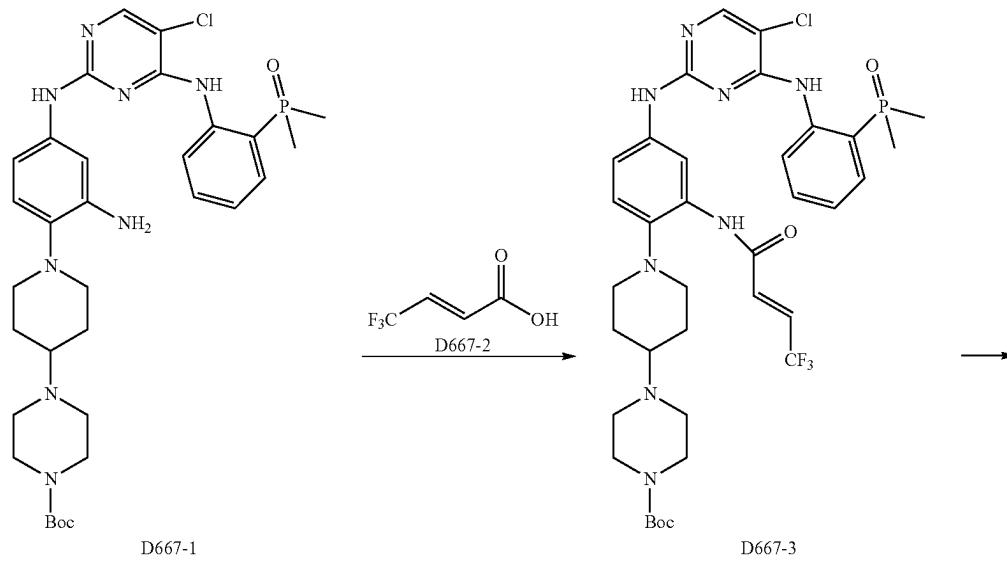
Step 2

[0659] D666-3 (56 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D666-4 (48 mg, yield 100%), LCMS: $[\text{M}+\text{H}]^+ = 627$.

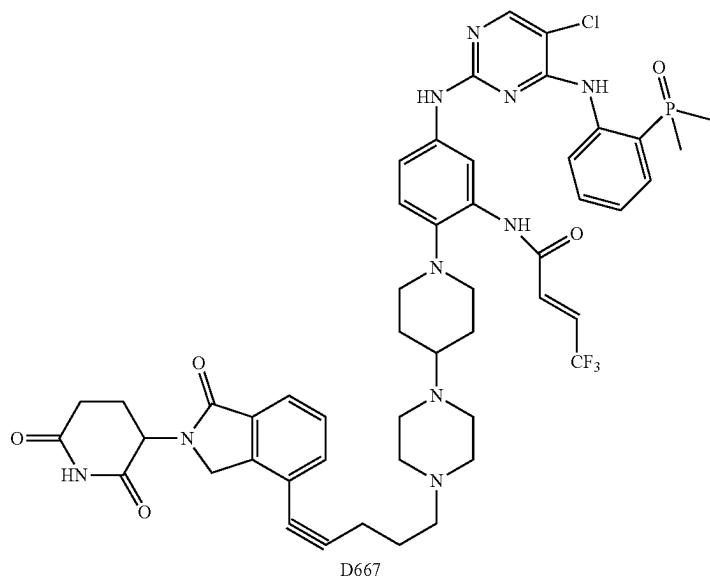
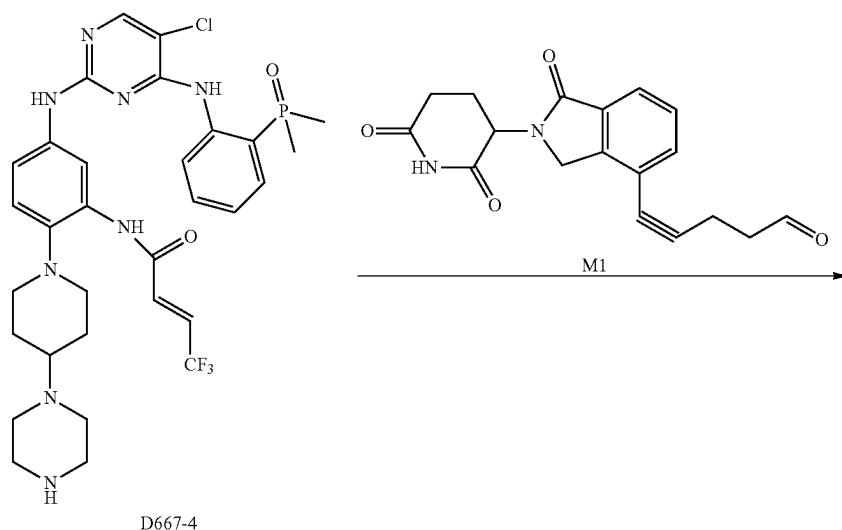
Step 3

[0660] D666-4 (55 mg, 0.088 mmol), M1 (34 mg, 0.105 mmol) and acetic acid (6.3 mg, 0.105 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (8.3 mg, 0.132 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D666 (35.6 mg, yield 43.4%), LCMS: $[\text{M}+\text{H}]^+ = 935$.

Preparation of (E)-N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenyl)-4,4,4-trifluorobut-2-enamide (D667)



-continued

**Step 1**

[0661] D667-1 (80 mg, 0.122 mmol), D667-2 (20 mg, 0.147 mmol), T3P (311 mg, 0.489 mmol) and TEA (49 mg, 0.489 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D667-3 (47 mg, yield 49.5%), LCMS: $[M+H]^+=777$.

Step 2

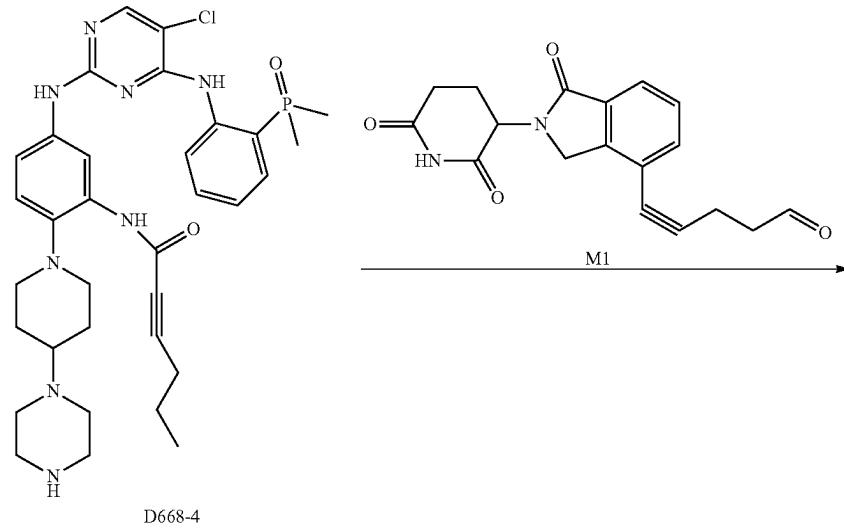
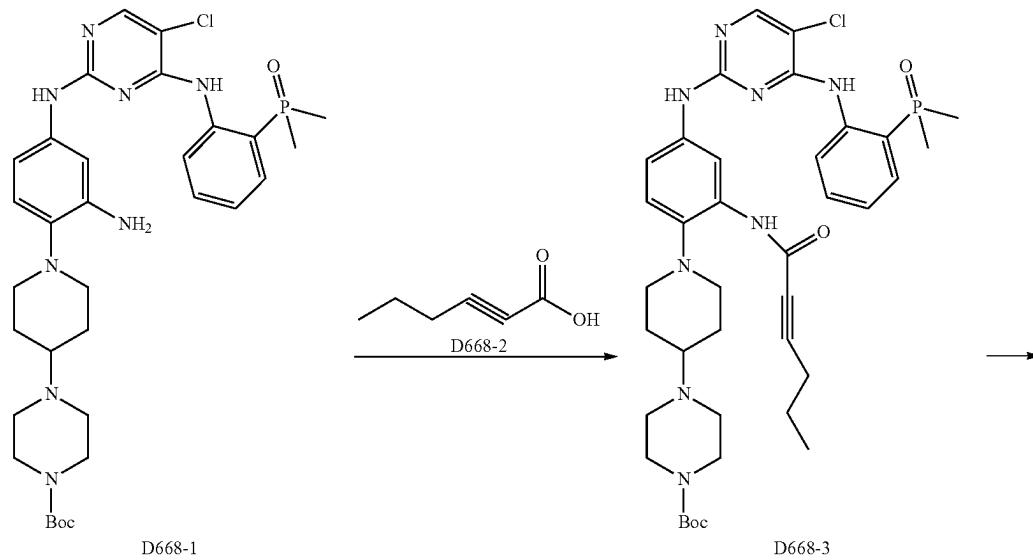
[0662] D667-3 (47 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D667-4 (40 mg, yield 97.8%), LCMS: $[M+H]^+=677$.

Step 3

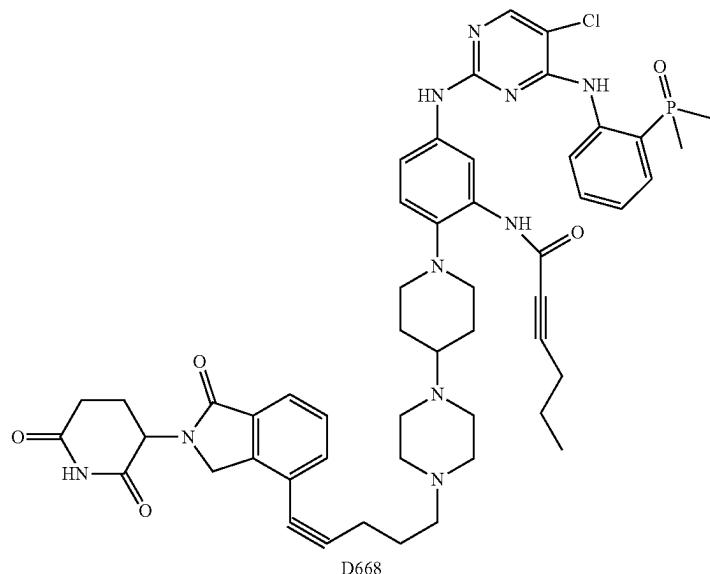
[0663] D667-4 (46 mg, 0.068 mmol), M1 (26 mg, 0.082 mmol) and acetic acid (4.9 mg, 0.082 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.4 mg, 0.102 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give compound D667 (30 mg, yield 44.8%), LCMS: $[M+H]^+=985$.

Preparation of N-(5-((5-chloro-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)phenyl)hex-2-ynamide (D668)



-continued

**Step 1**

[0664] D668-1 (80 mg, 0.122 mmol), D668-2 (16 mg, 0.147 mmol), T3P (311 mg, 0.489 mmol) and TEA (49 mg, 0.489 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D668-3 (36 mg, yield 39.6%), LCMS: $[M+H]^+=749$.

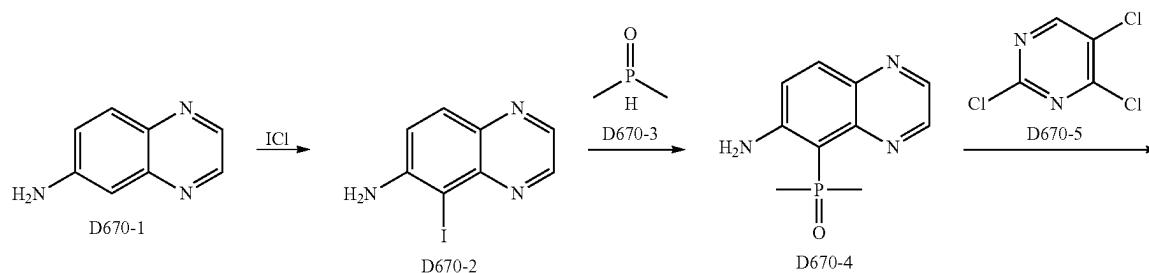
Step 2

[0665] D668-3 (36 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D668-4 (31 mg, yield 100%), LCMS: $[M+H]^+=649$.

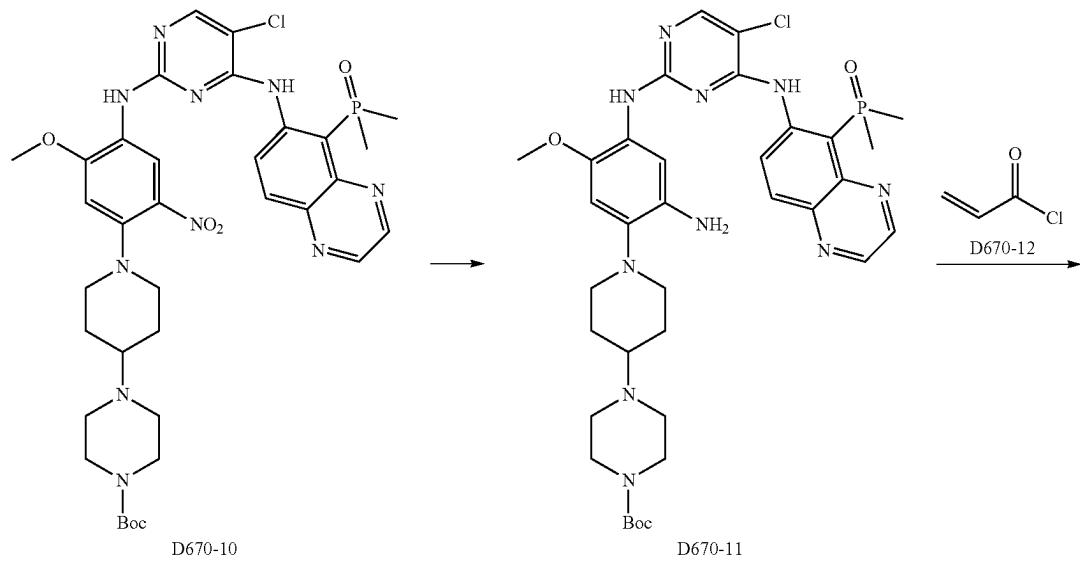
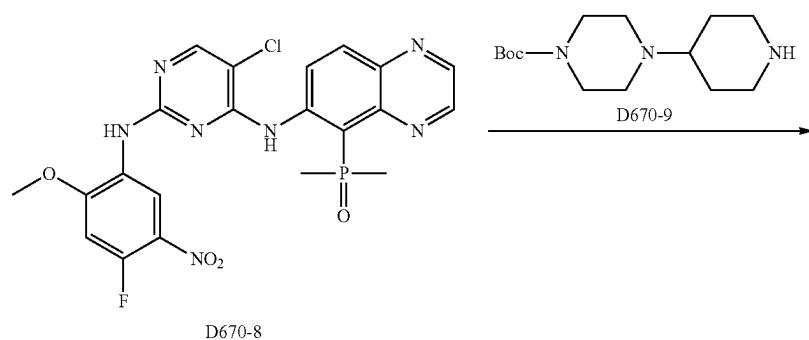
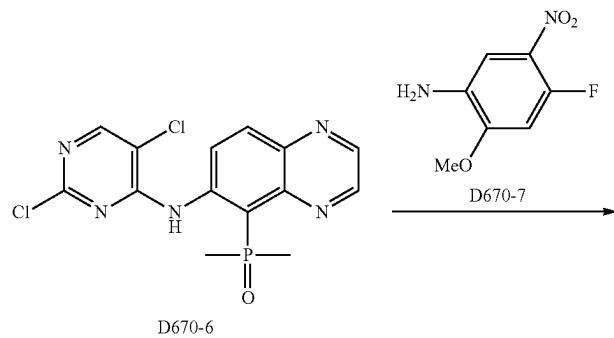
Step 3

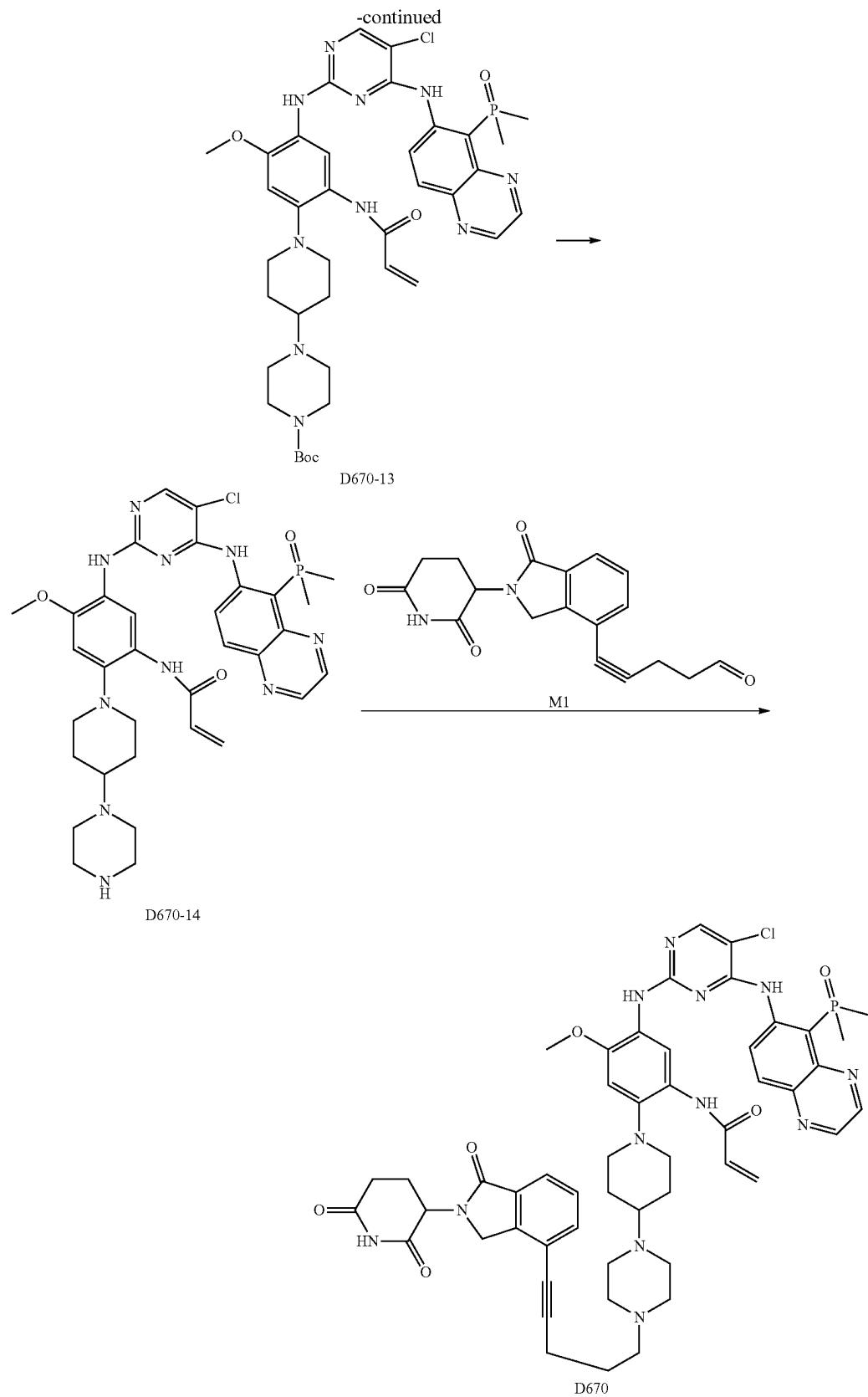
[0666] D668-4 (44 mg, 0.068 mmol), M1 (26 mg, 0.082 mmol) and acetic acid (4.9 mg, 0.082 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (6.4 mg, 0.102 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D668 (24 mg, yield 37.0%), LCMS: $[M+H]^+=957$.

Preparation of N-(5-((5-chloro-4-((5-(dimethylphosphoryl)quinoxalin-6-yl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)acrylamide (D670)



-continued





Step 1

[0667] D670-1 (6.87 g, 47.36 mmol) was dissolved in 210 mL of glacial acetic acid. To the mixture was added a solution of iodine monochloride (8.43 g, 60.66 mmol) in glacial acetic acid (75 mL) dropwise under stirring at room temperature. After the addition was completed, the mixture was stirred for another 1 hour. The solvent was removed by concentration under reduced pressure, and the mixture was added to 300 mL of ethyl acetate. The pH was adjusted to about 9 with saturated aqueous sodium bicarbonate solution. The organic phase was washed twice with saturated aqueous sodium thiosulfate solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D670-2 (8.43 g, yield 65.6%), LCMS: $[M+H]^+=272$.

Step 2

[0668] D670-2 (8.32 g, 30.71 mmol), dimethylphosphine oxide (D670-3, 3.59 g, 46.06 mmol), potassium phosphate (15.21 g, 70.00 mmol), palladium acetate (1.38 g, 6.14 mmol) and Xantphos (3.55 g, 6.14 mmol) were added to 80 mL of 1,4-dioxane. Under nitrogen protection, the mixture was stirred at 100° C. overnight. The reaction solution was cooled to room temperature. Water was added. The mixture was then extracted three times with dichloromethane, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D670-4 (5.1 g, yield 75.1%), LCMS: $[M+H]^+=222$.

Step 3

[0669] D670-4 (4.83 g, 21.85 mmol) was dissolved in 100 mL of N,N-dimethylformamide and the temperature was lowered to 0° C. Sodium hydride (60%, 1.92 g, 48.08 mmol) was added in batches with stirring. Under nitrogen protection, the mixture was stirred at this temperature for another 30 minutes. Then D670-5 (4.77 g, 26.22 mmol) was slowly added dropwise. After the addition was completed, the reaction was warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride was added to quench the reaction. The mixture was diluted with water. The mixture was extracted with ethyl acetate three times, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D670-6 (7.52 g, yield 93.8%), LCMS: $[M+H]^+=368$.

Step 4

[0670] D670-6 (7.32 g, 19.94 mmol), D670-7 (3.71 g, 19.94 mmol) and methanesulfonic acid (7.67 g, 79.78 mmol) were dissolved in 300 mL of tert-butanol. The mixture was stirred at 90° C. overnight under nitrogen. The reaction was cooled down. The solvent was removed. The residue was dissolved in dichloromethane and washed once with aqueous sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated. The crude product was purified by Flash to give D670-8 (8.0 g, yield 77.7%), LCMS: $[M+H]^+=518$.

Step 5

[0671] D670-8 (4.0 g, 0.097 mmol), D670-9 (2.5 g, 9.28 mmol) and cesium carbonate (7.57 g, 23.21 mmol) were

added to 60 mL of N,N-dimethylformamide. The mixture was stirred at 70° C. overnight under nitrogen. The solvent was removed under reduced pressure and the residue was purified by Flash to give D670-10 (3.9 g, yield 66.1%), LCMS: $[M+H]^+=767$.

Step 6

[0672] D670-10 (3.9 g, 5.09 mmol), iron powder (2.8 g, 50.89 mmol) and ammonium chloride (1.6 g, 30.54 mmol) were added to a mixed solvent of 120 mL ethanol/water (3/1). The mixture was stirred at 100° C. for 4.5 hours. The reaction was cooled to room temperature. The solid was filtered out. The solid residue was rinsed twice with a large amount of dichloromethane, and the filtrate was allowed to stand for stratification. The aqueous phase was washed once with dichloromethane. The organic phases were combined, washed once with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by Flash to obtain D670-11 (3.2 g, yield 85.3%). LCMS: $[M+H]^+=737$.

Step 7

[0673] D670-11 (150 mg, 0.204 mmol) and TEA (62 mg, 0.611 mmol) were dissolved in 20 mL of dichloromethane. A solution of D670-12 (18 mg, 0.204 mmol) in 1 mL of dichloromethane was added dropwise at -12° C. under nitrogen protection. The temperature was maintained and the mixture was stirred for 1.5 hours. Methanol was added to quench the reaction. The solvent was evaporated and the crude product was purified by thin layer chromatography (dichloromethane/methanol=10/1) to give D670-13 (123 mg, yield 76.4%), LCMS: $[M+H]^+=791$.

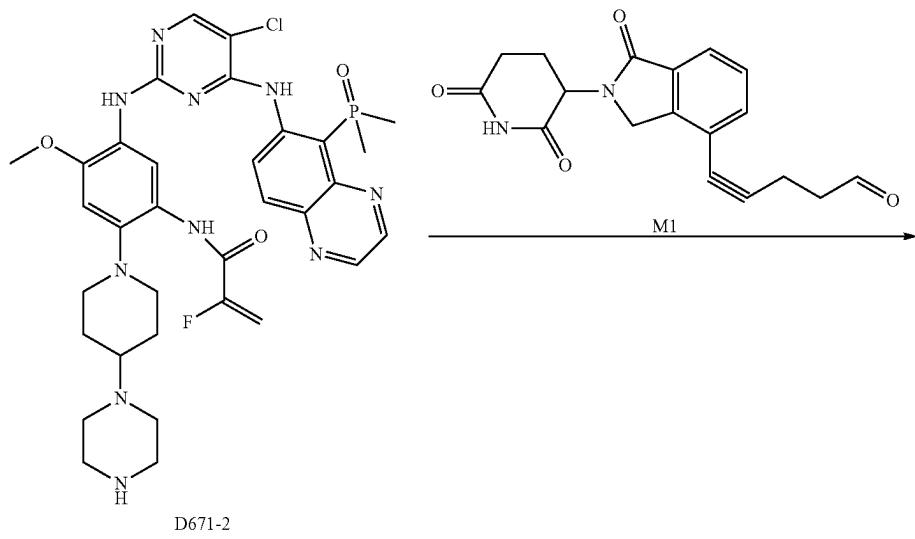
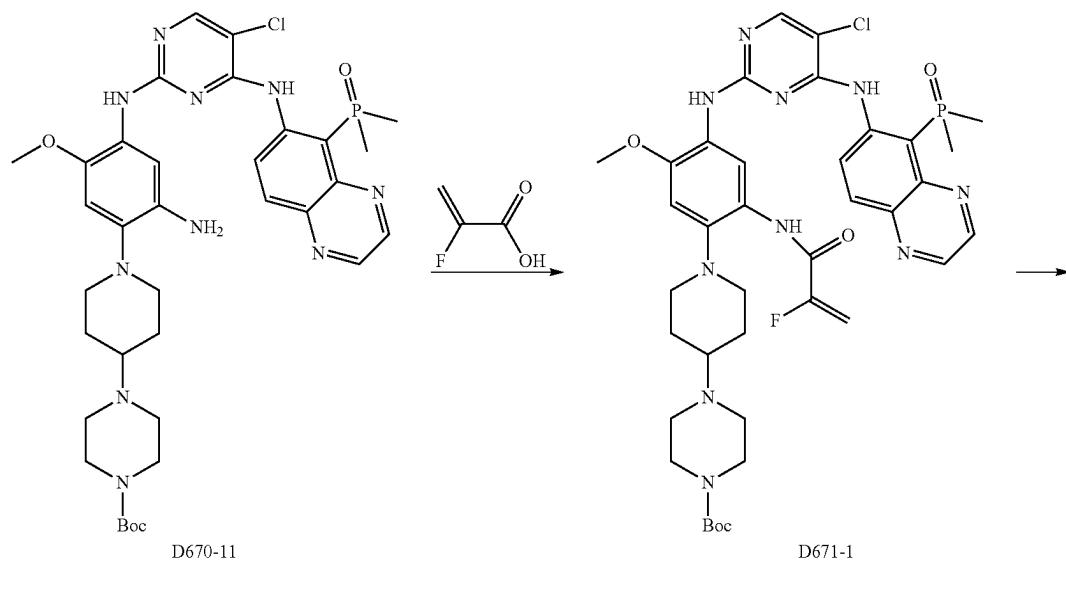
Step 8

[0674] D670-13 (123 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D670-14 (72 mg, yield 67.3%), LCMS: $[M+H]^+=691$.

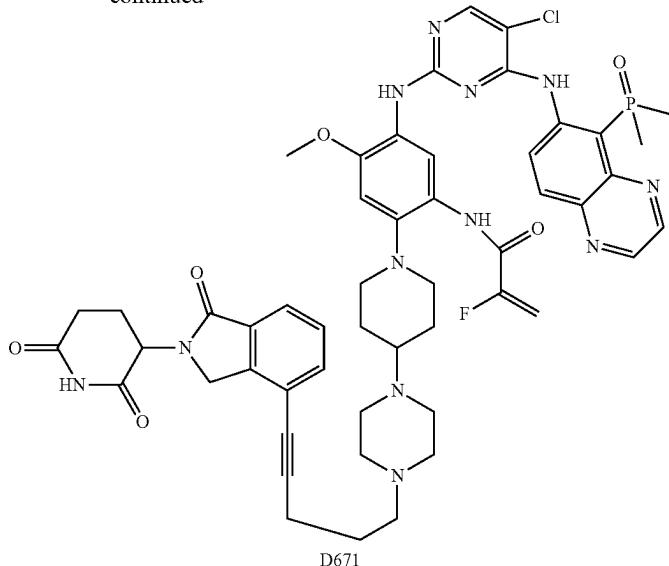
Step 9

[0675] D670-14 (40 mg, 0.058 mmol), M1 (23 mg, 0.070 mmol) and acetic acid (4.2 mg, 0.070 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.5 mg, 0.087 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D670 (29 mg, yield 50.0%), LCMS: $[M+H]^+=999$.

Preparation of N-(5-((5-chloro-4-((5-(dimethylphosphoryl)quinoxalin-6-yl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D671)



-continued



Step 1

[0676] D670-11 (150 mg, 0.20 mmol), 2-fluoroacrylic acid (18.3 mg, 0.20 mmol), T3P (518 mg, 0.81 mmol) and TEA (82 mg, 0.81 mmol) were dissolved in 3 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The mixture was purified by Flash to give compound D671-1 (83 mg, yield 50.6%), LCMS: $[M+H]^+$ =809.

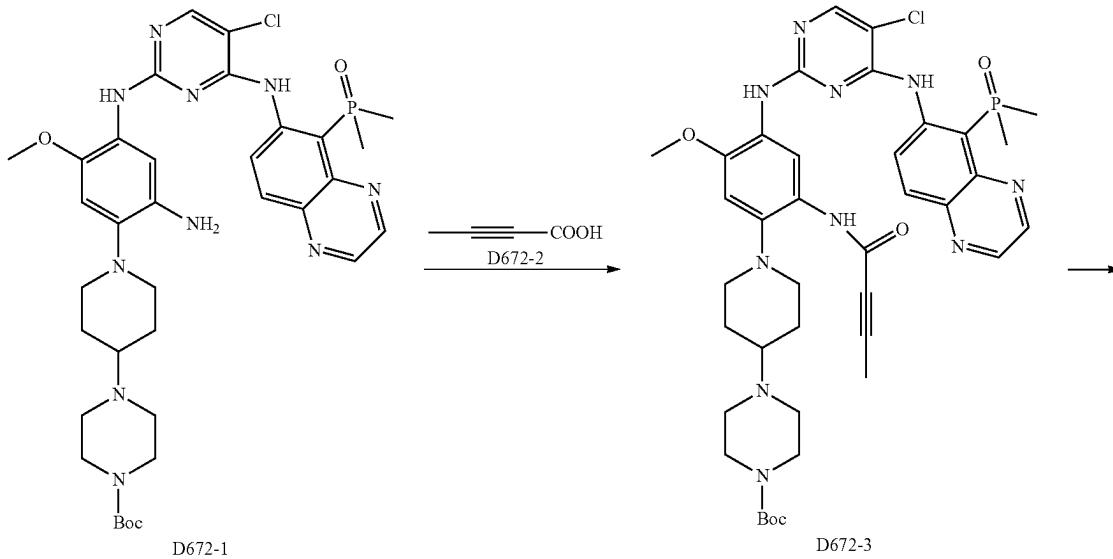
Step 2

[0677] D671-1 (83 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D671-2 (68 mg, yield 93.2%), LCMS: $[M+H]^+$ = 709.

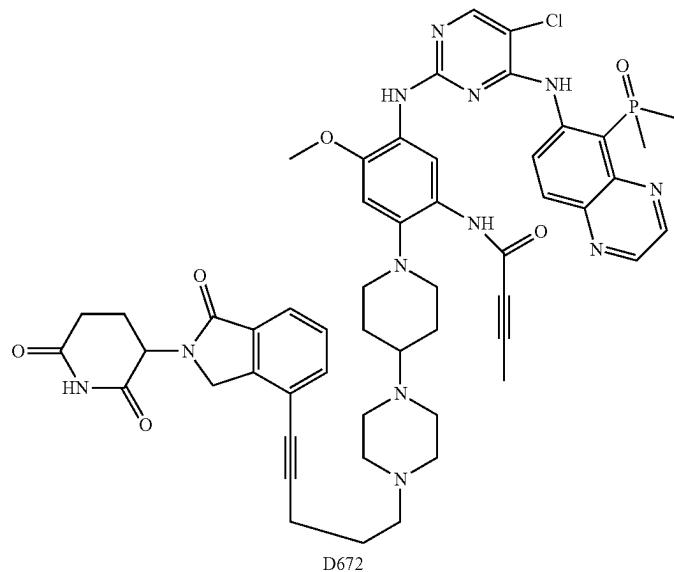
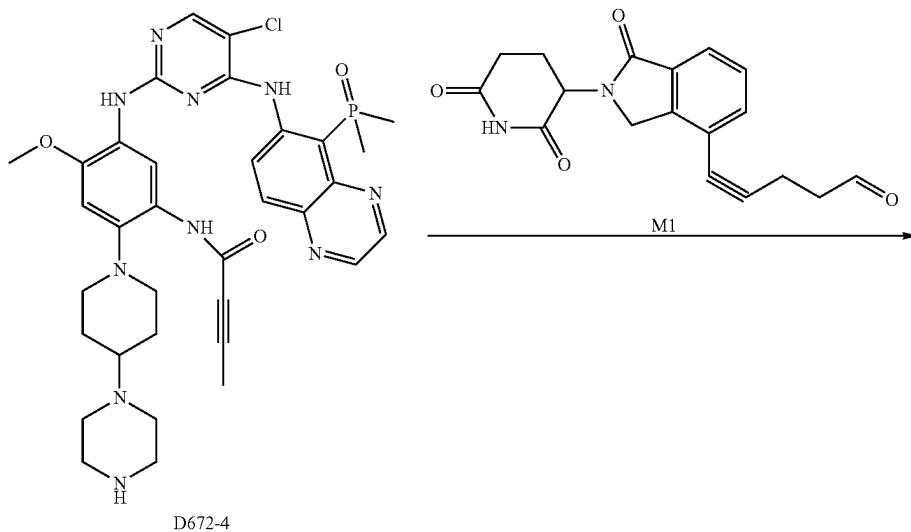
Step 3

[0678] D671-2 (34 mg, 0.048 mmol), M1 (19 mg, 0.058 mmol) and acetic acid (3.4 mg, 0.058 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (4.5 mg, 0.072 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D671 (21 mg, yield 43.0%), LCMS: $[\text{M}+\text{H}]^+ = 1017$.

Preparation of N-(5-((5-chloro-4-(((dimethylphosphoryl)quinoxalin-6-yl)amino)pyrimidin-2-yl)amino)-2-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide (D672)



-continued



Step 1

[0679] D672-1 (150 mg, 0.20 mmol), D672-2 (17.1 mg, 0.20 mmol), T3P (518 mg, 0.81 mmol) and TEA (82 mg, 0.81 mmol) were dissolved in 3 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The mixture was purified by Flash to give D672-3 (76 mg, yield 46.6%), LCMS: $[M+H]^+$ =803.

Step 2

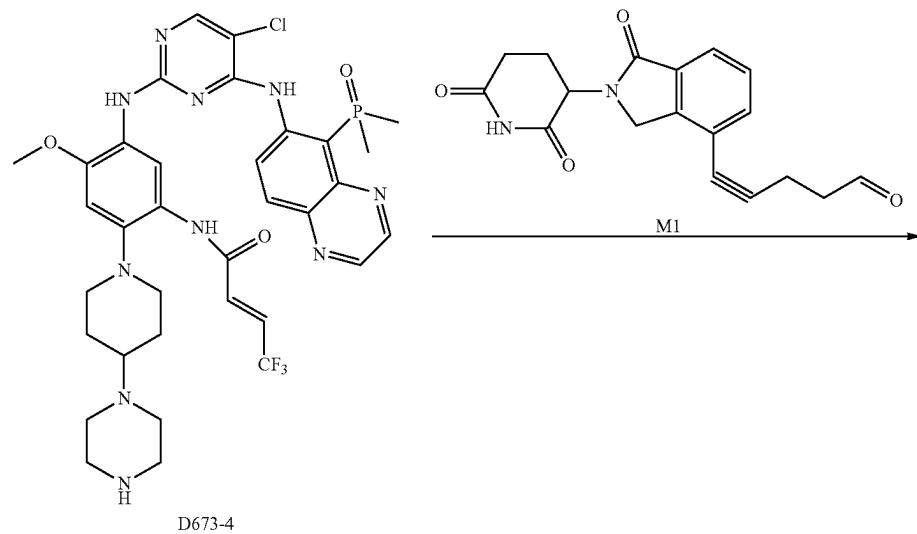
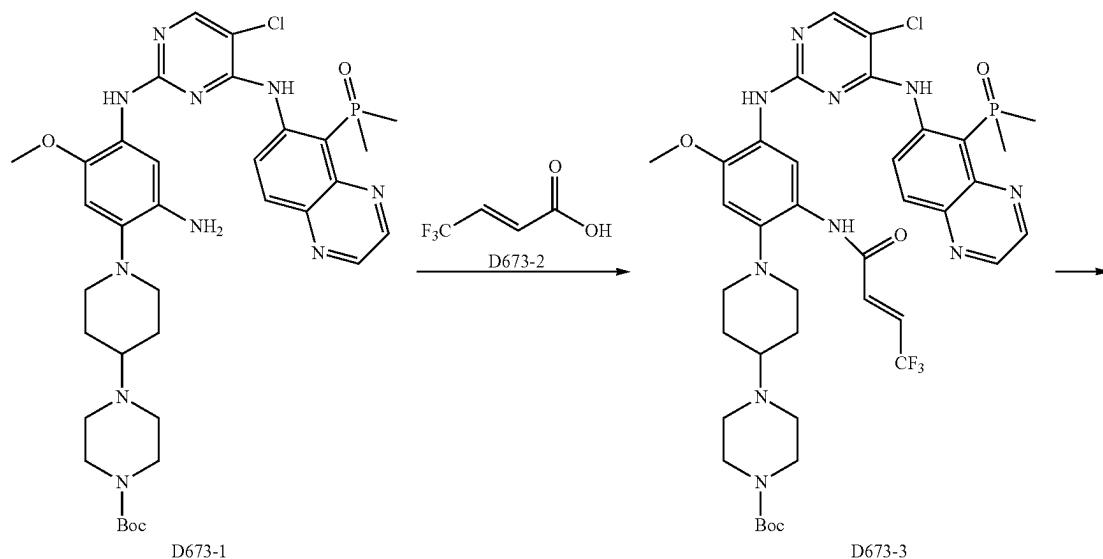
[0680] D672-3 (76 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D672-4 (66 mg, yield 100%), LCMS: $[M+H]^+$ =703.

Step 3

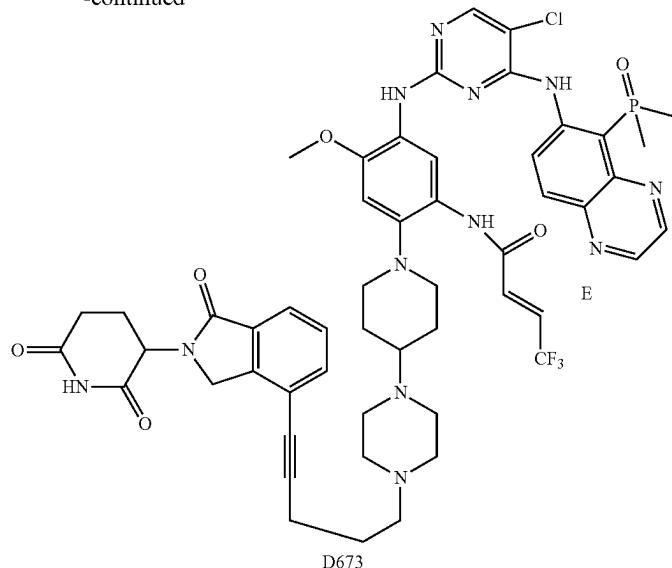
[0681] D672-4 (34 mg, 0.048 mmol), M1 (19 mg, 0.058 mmol) and glacial acetic acid (3.5 mg, 0.058 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (4.6 mg, 0.073 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced

pressure below 40° C., and the crude product was purified by HPLC to give D672 (4 mg, yield 8.2%), LCMS: $[M+H]^+$ =1011.

Preparation of (E)-N-(5-((5-chloro-4-((5-(dimethylphosphoryl)quinoxalin-6-yl)amino)pyrimidin-2-yl)amino)-2-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide (D673)



-continued



Step 1

[0682] D673-1 (150 mg, 0.20 mmol), D673-2 (28.5 mg, 0.20 mmol), T3P (518 mg, 0.81 mmol) and TEA (82 mg, 0.81 mmol) were dissolved in 3 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature for 4 hours. The residue was purified by Flash to give D673-3 (116 mg, yield 66.3%), LCMS: $[M+H]^+$ = 859.

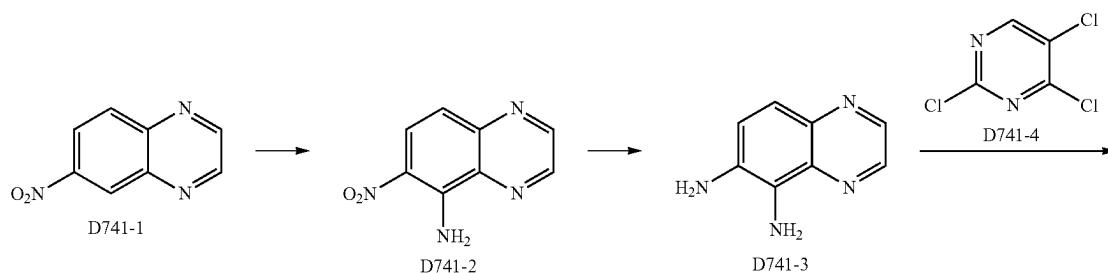
Step 2

[0683] D673-3 (116 mg) was dissolved in 4 mL of dichloromethane. Trifluoroacetic acid (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by Flash to obtain D673-4 (86 mg, yield 84.3%), LCMS: $[M+H]^+$ = 759.

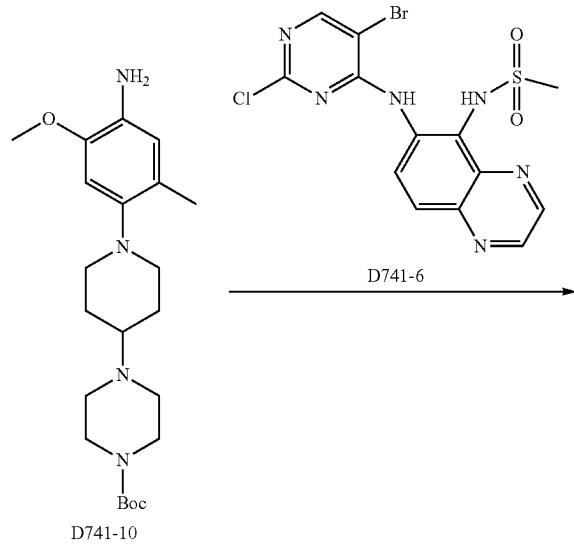
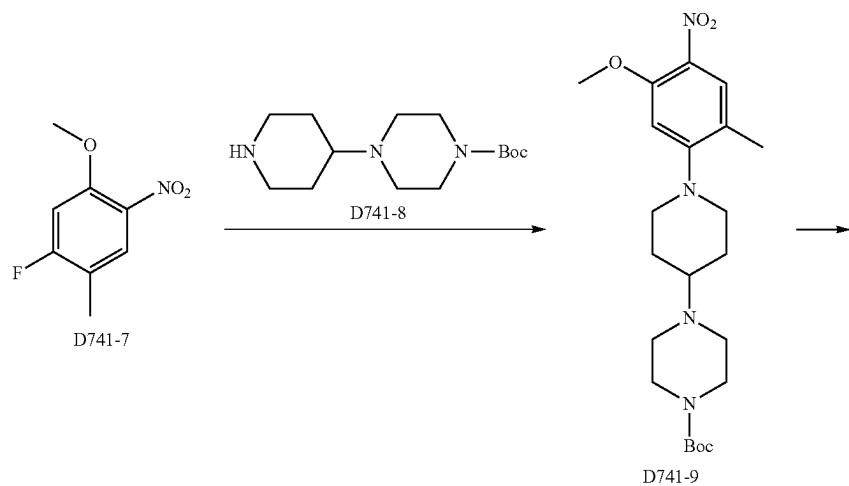
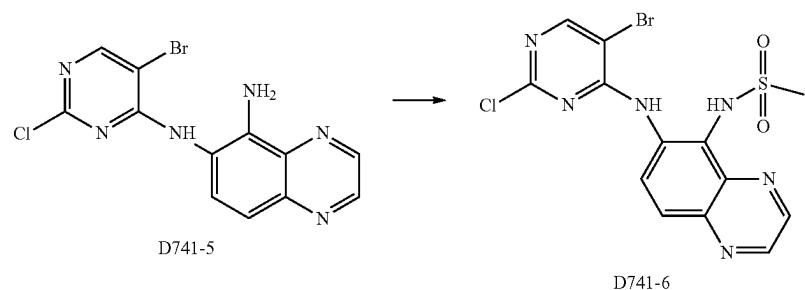
Step 3

[0684] D673-4 (43 mg, 0.057 mmol), M1 (22 mg, 0.068 mmol) and glacial acetic acid (4.1 mg, 0.068 mmol) were dissolved in 3 mL of a mixed solvent of dichloromethane/methanol (2/1). Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (5.3 mg, 0.085 mmol) was added and the mixture was stirred for another 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D673 (26 mg, yield 43.3%), LCMS: $[M+H]^+$ = 1067.

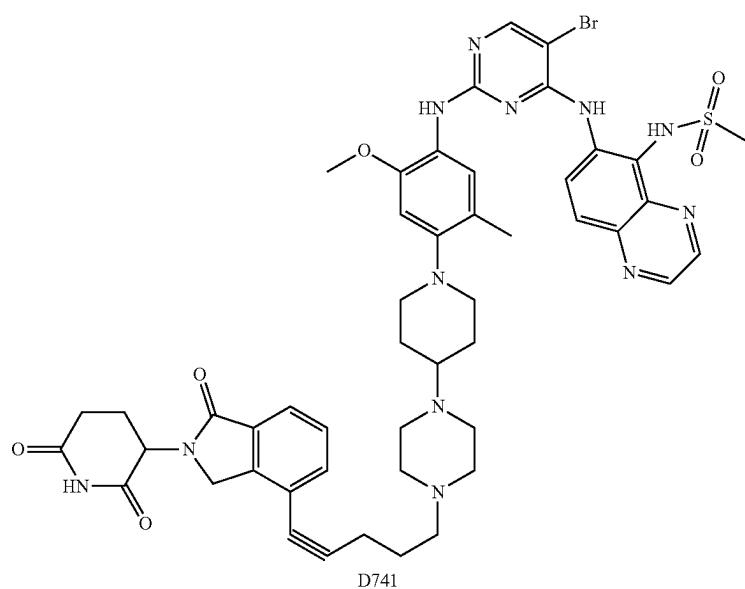
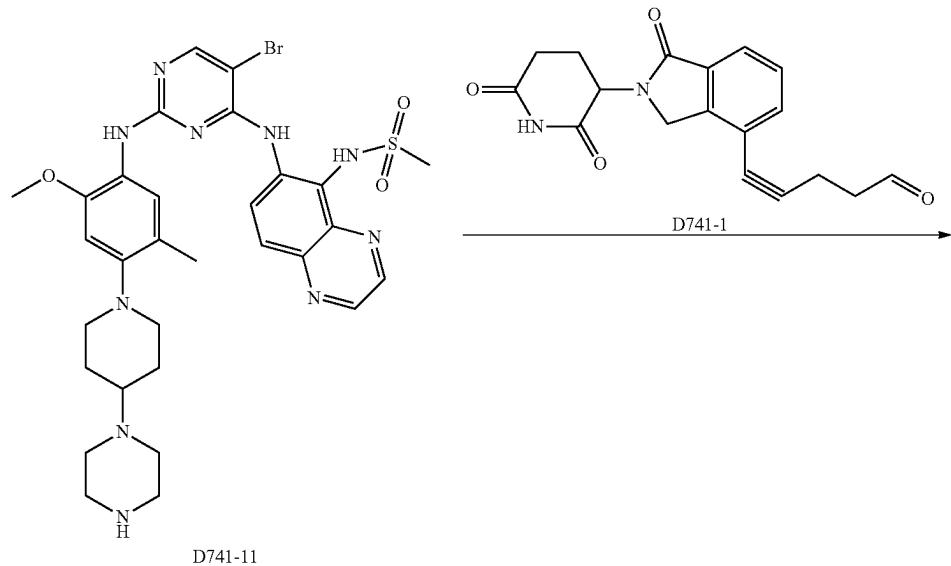
Preparation of N-((5-bromo-2-((4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-2-methoxy-5-methylphenyl)amino)pyrimidin-4-yl)amino)quinoxalin-5-yl)methanesulfonamide (D741)



-continued



-continued

**Step 1**

[0685] D741-1 (5.00 g, 28.6 mmol) was added to methanol (240 mL). The reaction was heated to 80° C. with continuous stirring. Hydroxylamine hydrochloride (2.98 g, 42.9 mmol) was dissolved in methanol (150 mL). Sodium methoxide (5.09 g, 94.3 mmol) was added under stirring at 0° C., and the mixture was allowed to stand. The supernatant was added dropwise to the above solution. The mixture was

stirred at 80° C. for 1.5 hours. The reaction was allowed to stand. The reaction was cooled to 0° C., and filtered. The mother liquor was concentrated. The reaction was cooled to room temperature, and filtered. The solid was added to 8 mL of acetic acid/water (3/1). The mixture was stirred at 100° C. for ten minutes. The reaction was cooled down, and filtered. The residue was dried and collected to give D741-2 (2.445 g, yield 45.0%), LCMS: [M+H]⁺=191.

Step 2

[0686] D741-2 (100 mg, 0.53 mmol) and Pd/C (10%, 11 mg) were added to 5 mL of anhydrous ethanol. The mixture was heated and stirred at 78° C. for 1 hour. Hydrazine hydrate (527 mg, 10.53 mmol) was added and the mixture was stirred for another 1 hour. The mixture was cooled to room temperature. The solid was filtered out. The mother liquor was concentrated, and the crude product was used directly in the next step. LCMS: [M+H]⁺=161.

Step 3

[0687] D741-3 (76 mg, 0.475 mmol), D741-4 (107 mg, 0.475 mmol) and DIEA (122 mg, 0.946 mmol) were added to 6 mL of n-butanol. The mixture was reacted in a microwave oven at 110° C. for 1 hour under nitrogen protection. The solvent was removed under reduced pressure. The residue was purified by thin layer chromatography to obtain D741-5 (55 mg, 33.1%), LCMS: [M+H]⁺=351.

Step 4

[0688] D741-5 (55 mg, 0.157 mmol) was dissolved in 3 mL of pyridine. Methanesulfonyl chloride (125 mg, 1.100 mmol) was added dropwise under nitrogen protection at 0° C. with stirring. After the addition was completed, the mixture was stirred at room temperature overnight. The reaction solution was added to 0° C. ice water. The mixture was extracted three times with ethyl acetate. The organic phases were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure. The residue was purified by thin layer chromatography to obtain D741-6 (18 mg, 26.9%), LCMS: [M+H]⁺=429.

Step 5

[0689] D741-7 (500 mg, 2.70 mmol), D741-8 (1.09 g, 4.05 mmol), and potassium carbonate (745 mg, 5.40 mmol) were added to 15 mL of DMF. The mixture was stirred at 80° C. overnight under nitrogen protection. The reaction was

cooled, and filtered. The residue was purified by flash to give D741-9 (660 mg, yield 56.3%), LCMS: [M+H]⁺=435.

Step 6

[0690] D741-9 (660 mg, 1.52 mmol) and Pd/C (10%, 132 mg) were added to 20 mL of methanol. Hydrogen was introduced, and the mixture was stirred at room temperature for 3 hours. The mixture was filtered and concentrated to give a crude product D741-10 (600 mg, 97.7%), which was used directly in the next step. LCMS: [M+H]⁺=405.

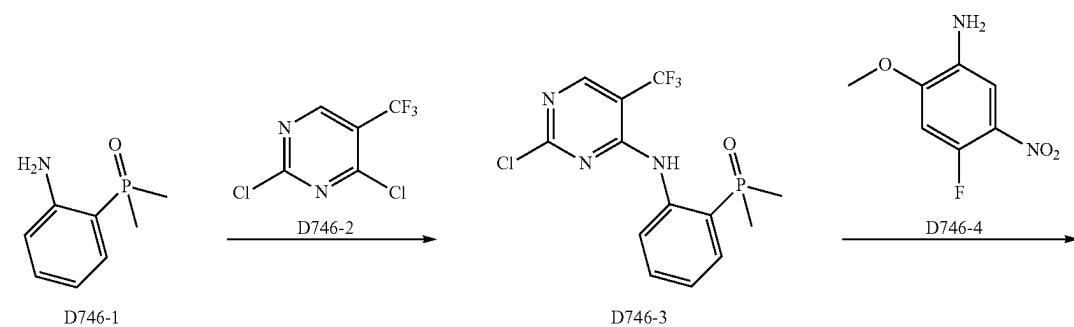
Step 7

[0691] D741-10 (11.8 mg, 0.028 mmol), D741-6 (22 mg, 0.055 mmol) and methanesulfonic acid (11 mg, 0.110 mmol) were dissolved in 2 mL of n-butanol. The mixture was stirred at 90° C. for 20 hours under nitrogen protection. The residue was purified by Flash to give D741-11 (7.5 mg, yield 39.5%), LCMS: [M+H]⁺=697.

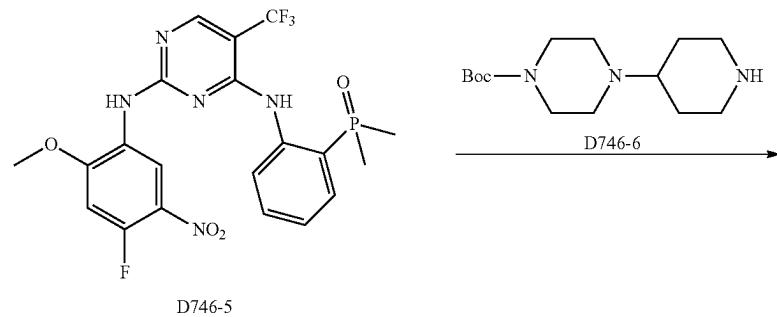
Step 8

[0692] D741-11 (12 mg, 0.017 mmol) was dissolved in 3 mL of dichloromethane/methanol (2/1). D741-12 (6.7 mg, 0.021 mmol) and acetic acid (1.2 mg, 0.021 mmol) were added. Under nitrogen, the mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (4.8 mg, 0.076 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D741 (8 mg, yield 47.1%), LCMS: [M+H]⁺=1005.

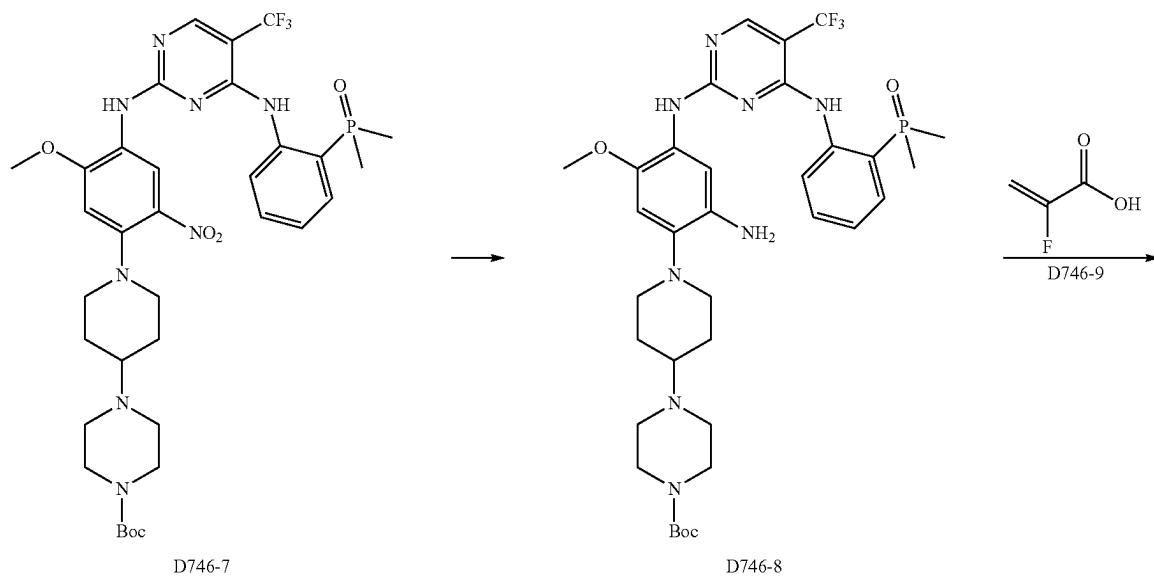
Preparation of N-(5-((4-((2-(dimethylphosphoryl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D746)



-continued

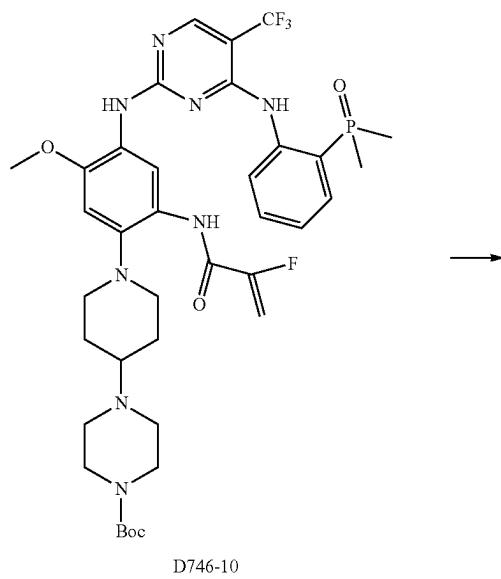


D746-5



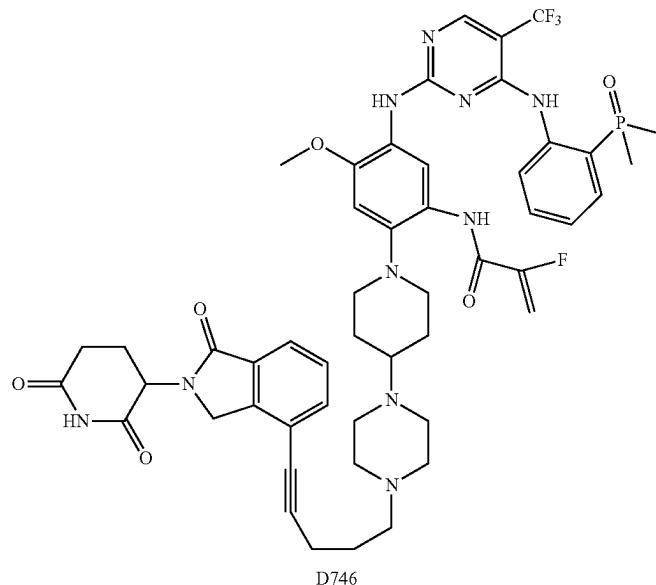
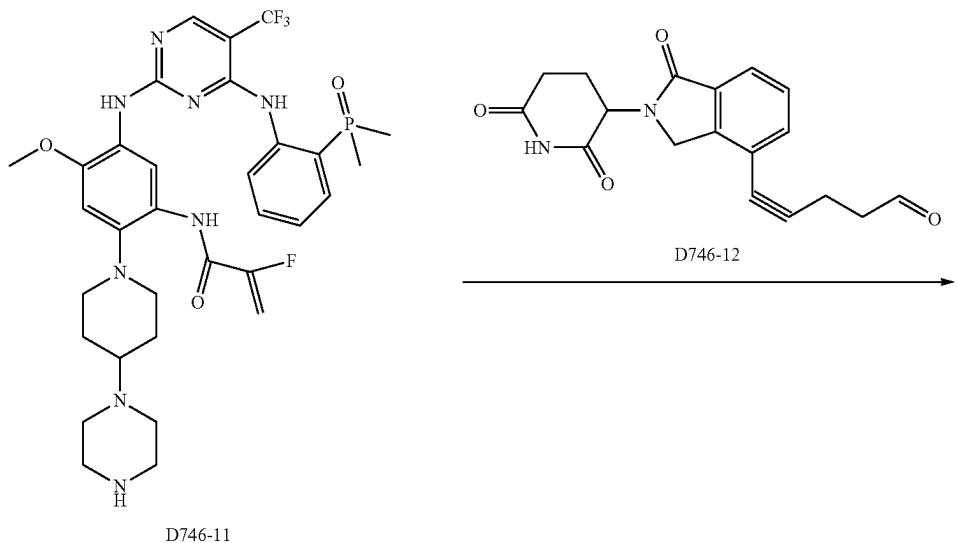
D746-7

D746-8



D746-10

-continued



Step 1

[0693] Compound D746-1 (5 g, 29.6 mmol) was dissolved in n-butanol (50 mL). Compound D746-2 (6.45 g, 29.9 mmol) was added dropwise under stirring at 0° C., followed by DIEA (4.59 g, 35.5 mmol). The mixture was stirred at 0-5° C. for 1 hour. The mixture was heated to room temperature and stirred for 4 hours. The solvent was removed under reduced pressure. The residue was purified by Flash to give compound D746-3 (2.68 g, 26.0%). LCMS: $[\text{M}+\text{H}]^+ = 350$.

Step 2

[0694] D746-3 (2.68 g, 7.68 mmol), D746-4 (1.57 g, 8.45 mmol) and methanesulfonic acid (2.95 g, 30.71 mmol) were

dissolved in 70 mL of tert-butanol. The mixture was stirred at 90° C. overnight under nitrogen protection. The mixture was cooled to room temperature. The solvent was evaporated under reduced pressure. The pH was adjusted to 7 with aqueous sodium bicarbonate solution. The mixture was extracted three times with dichloromethane, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product. The crude product was purified by Flash to obtain D746-5 (2.48 g, 64.8%). LCMS: $[M+H]^+$ =500.

Step 3

[0695] D746-5 (2.48 g, 4.97 mmol), D746-6 (1.61 g, 5.96 mmol) and cesium carbonate (4.86 g, 14.91 mmol) were

dissolved in 30 mL of DMF. The mixture was stirred at 70° C. overnight under nitrogen protection. The mixture was cooled to room temperature. The solid was filtered out. The solvent was evaporated under reduced pressure, and the crude product was purified by Flash to obtain D746-7 (3.7 g, yield 99.5%). LCMS: [M+H]⁺=749.

Step 4

[0696] Under stirring at room temperature, a solution of sodium hydrosulfite (3.64 g, 24.7 mmol) in water (100 mL) was added to a solution of D746-7 (3.70 g, 4.94 mmol) in ethanol (100 mL). The mixture was stirred for 10 minutes. Dichloromethane was added, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product D746-8 (3.5 g, yield 98.6%), which was used directly in the next step. LCMS: [M+H]⁺=719.

Step 5

[0697] D746-8 (3.50 g, 4.87 mmol), D746-9 (351 mg, 3.390 mmol), T3P (12.40 g, 19.49 mmol) and TEA (1.97 g, 19.49 mmol) were dissolved in 140 mL of dichloromethane. The mixture was stirred overnight at room temperature under nitrogen protection. The mixture was washed once with aqueous ammonium chloride solution, and the organic phase was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D746-10 (3.67 g, yield 95.3%), LCMS: [M+H]⁺=791.

Step 6

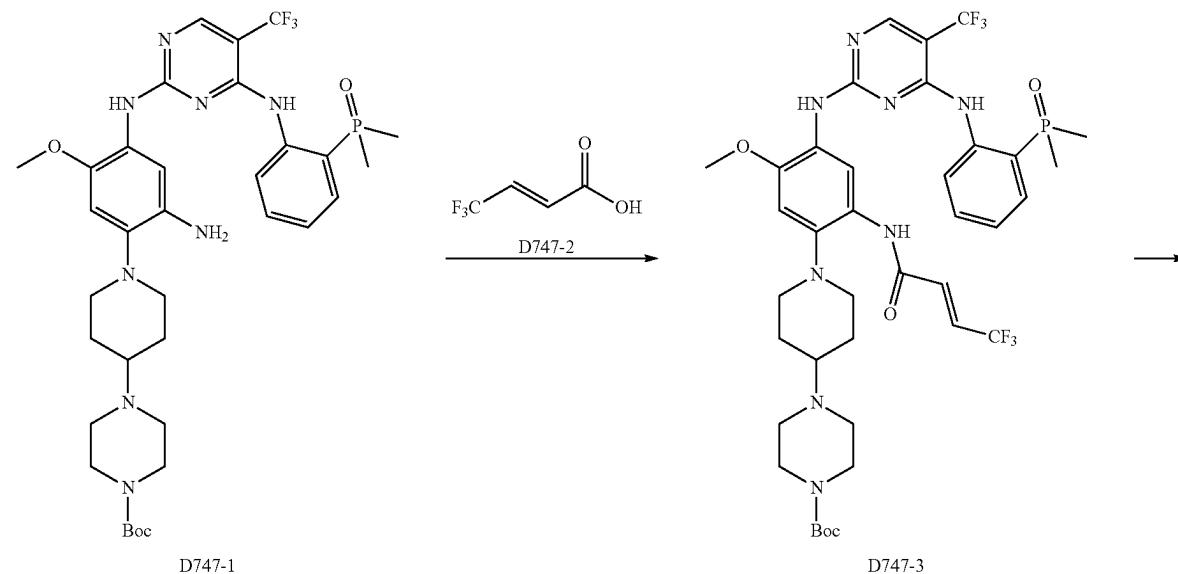
[0698] D746-10 (3.67 g) was dissolved in 24 mL of dichloromethane. TFA (6 mL) was added under stirring.

Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and an aqueous sodium bicarbonate solution was added dropwise under stirring to adjust the pH to 7.5. The mixture was extracted three times with a large amount of dichloromethane. The organic phase was dried over anhydrous sodium sulfate, allowed to stand, and filtered. The solvent was removed under reduced pressure to obtain D746-11 (3.06 g, yield 95.3%), which was used directly in the next step. LCMS: [M+H]⁺=691.

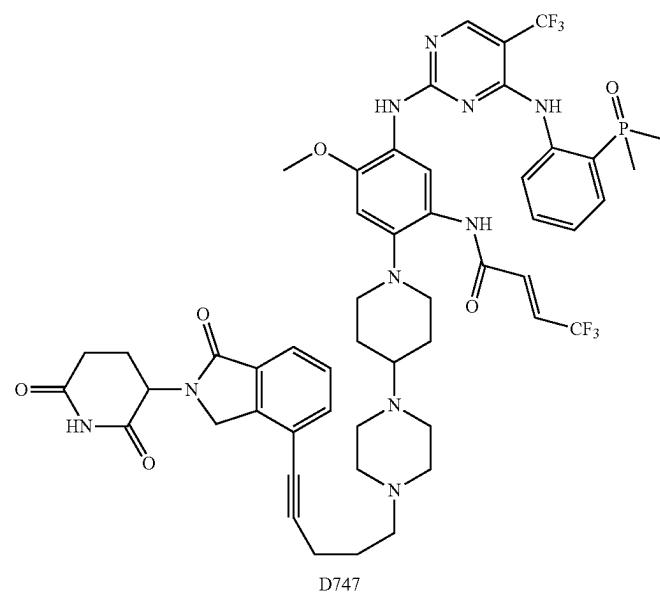
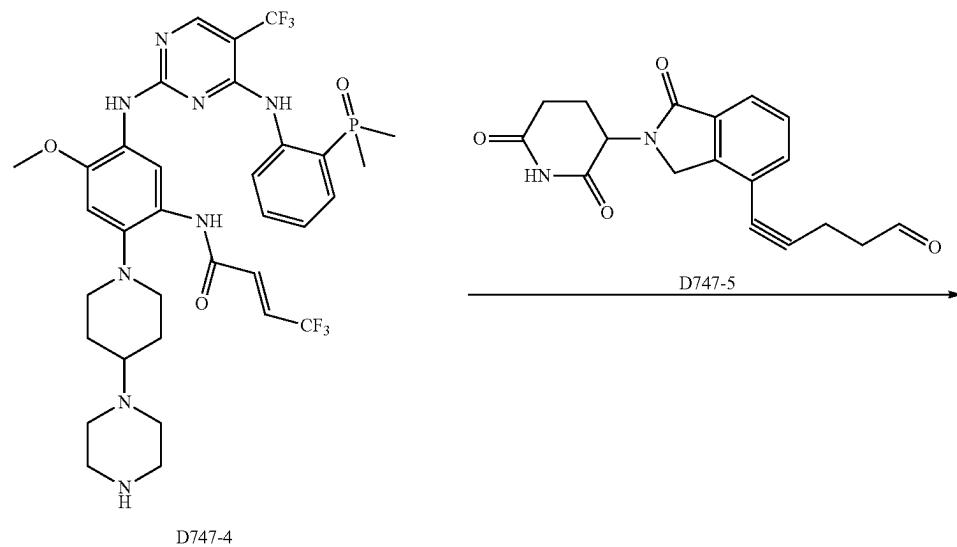
Step 7

[0699] D746-11 (3.06 g, 4.43 mmol), D746-12 (1.87 g, 5.76 mmol) and acetic acid (0.32 g, 5.32 mmol) were dissolved in 60 mL of dichloromethane/methanol (2/1, v/v). The mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (1.26 g, 20.05 mmol) was added in batches over two hours. The solvent was removed under reduced pressure below 40° C., and the crude product was flash purified to give an off-white solid compound D746 (2.4 g, yield 54.2%), LCMS: [M+H]⁺=999.

Preparation of (E)-N-(5-((4-((2-(dimethylphosphoryl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-(4-(5-(2,(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-4,4,4-trifluorobut-2-enamide (D747)



-continued



Step 1

[0700] D747-1 (50 mg, 0.070 mmol), D747-2 (7.8 mg, 0.056 mmol), T3P (50% EA, 177 mg, 0.278 mmol) and TEA (28 mg, 0.278 mmol) were dissolved in 3 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D747-3 (39 mg, yield 67.2%), LCMS: $[M+H]^+=841$.

Step 2

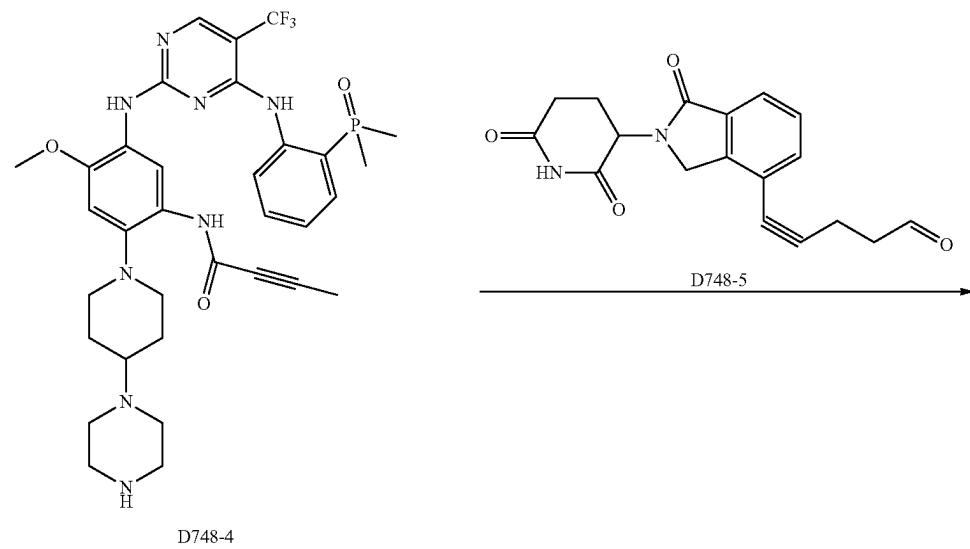
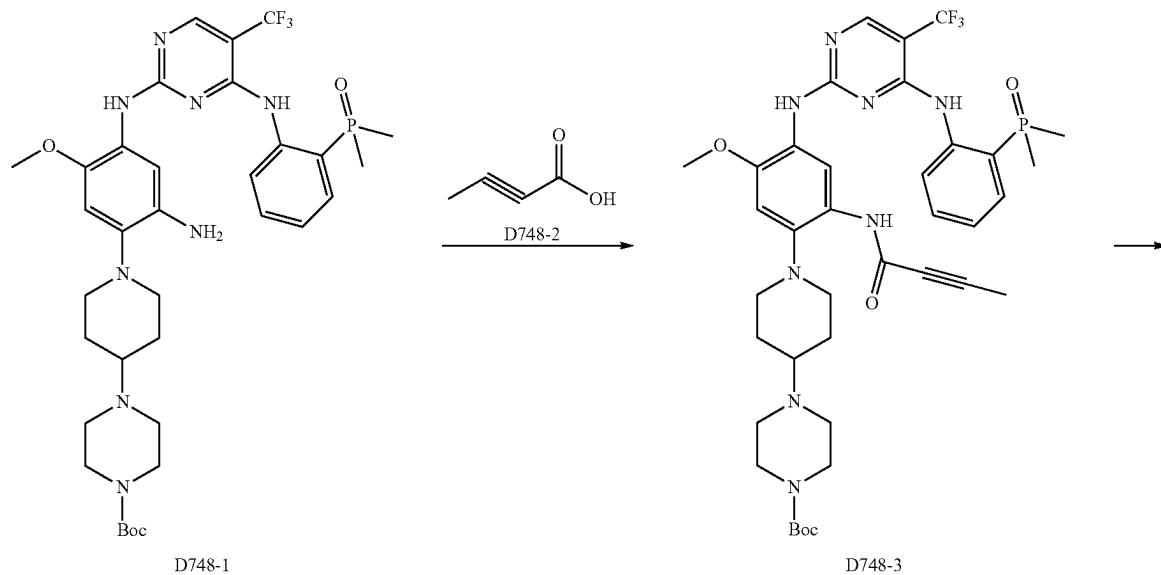
[0701] D747-3 (39 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and the crude product was used directly in the next step, LCMS: $[M+H]^+=741$.

Step 3

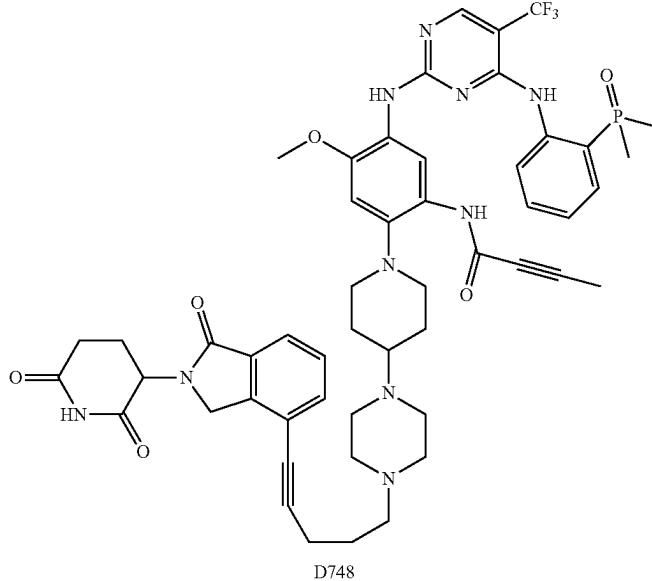
[0702] D747-4 (34.4 mg, 0.046 mmol) and D747-5 (19.6 mg, 0.060 mmol) were dissolved in 3 mL of dichloromethane/methanol (2/1). TEA was added dropwise, and the pH was adjusted to 7.5. Acetic acid (3.3 mg, 0.056 mmol) was added. The mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (13.2 mg, 0.210 mmol) was added in batches over 2 hours. The solvent

was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D747 (23 mg, yield 47.2%), LCMS: $[M+H]^+=1049$.

Preparation of N-(5-((4-((2-(dimethylphosphoryl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)but-2-ynamide
(D748)



-continued



Step 1

[0703] D748-1 (50 mg, 0.070 mmol), D748-2 (4.7 mg, 0.056 mmol), T3P (50% EA, 177 mg, 0.278 mmol) and TEA (28 mg, 0.278 mmol) were dissolved in 3 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D748-3 (27 mg, yield 49.1%), LCMS: $[M+H]^+=785$.

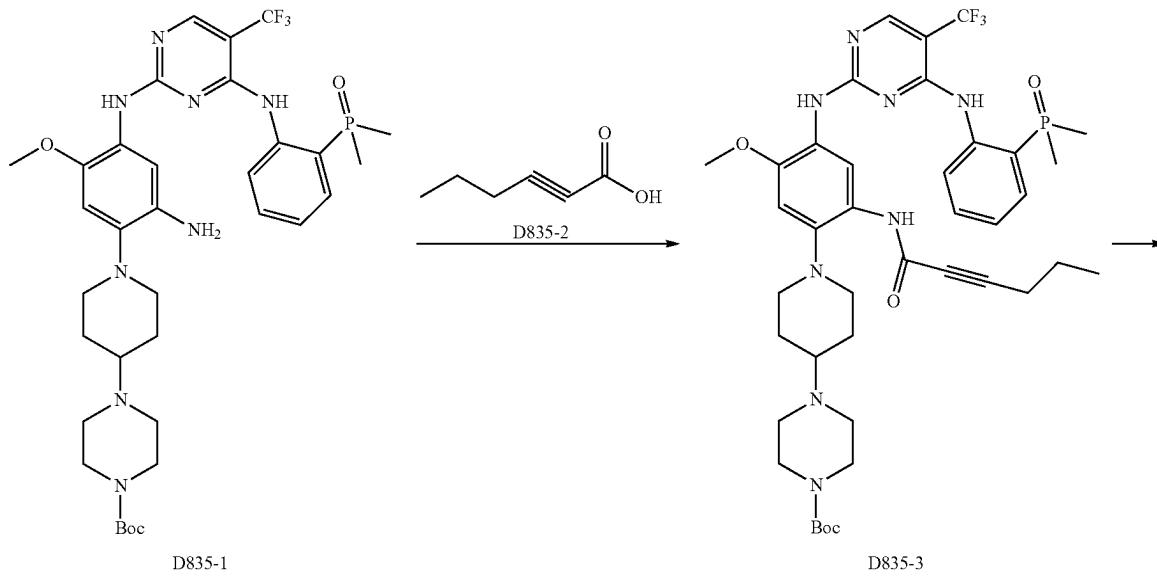
Step 2

[0704] D748-3 (27 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and the crude product was used directly in the next step, LCMS: $[M+H]^+=685$.

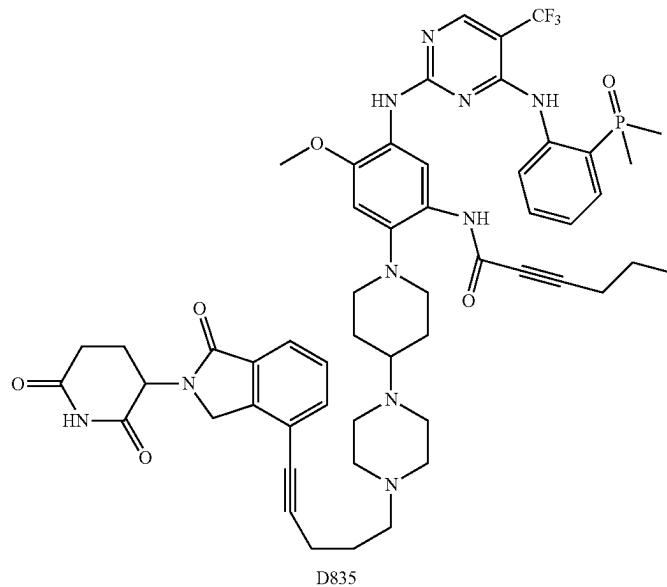
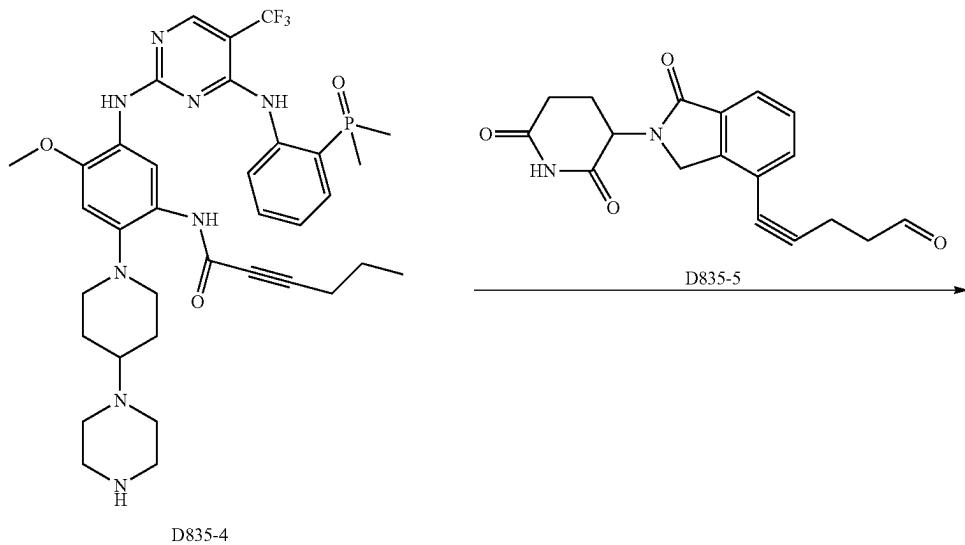
Step 3

[0705] D748-4 (23.6 mg, 0.034 mmol) and D748-5 (14.5 mg, 0.045 mmol) were dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise, and the pH was adjusted to 7.5. Acetic acid (2.5 mg, 0.041 mmol) was added, and the mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (9.9 mg, 0.156 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D748 (12 mg, yield 35.3%), LCMS: $[M+H]^+=993$.

Preparation of N-(5-((4-((2-(dimethylphosphoryl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)hex-2-ynamide (D835)



-continued

**Step 1**

[0706] D835-1 (100 mg, 0.139 mmol), D835-2 (12.5 mg, 0.111 mmol), T3P (50% EA, 354 mg, 0.557 mmol) and TEA (56 mg, 0.557 mmol) were dissolved in 3 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D835-3 (65.6 mg, yield 58.1%), LCMS: $[M+H]^+$ =813.

Step 2

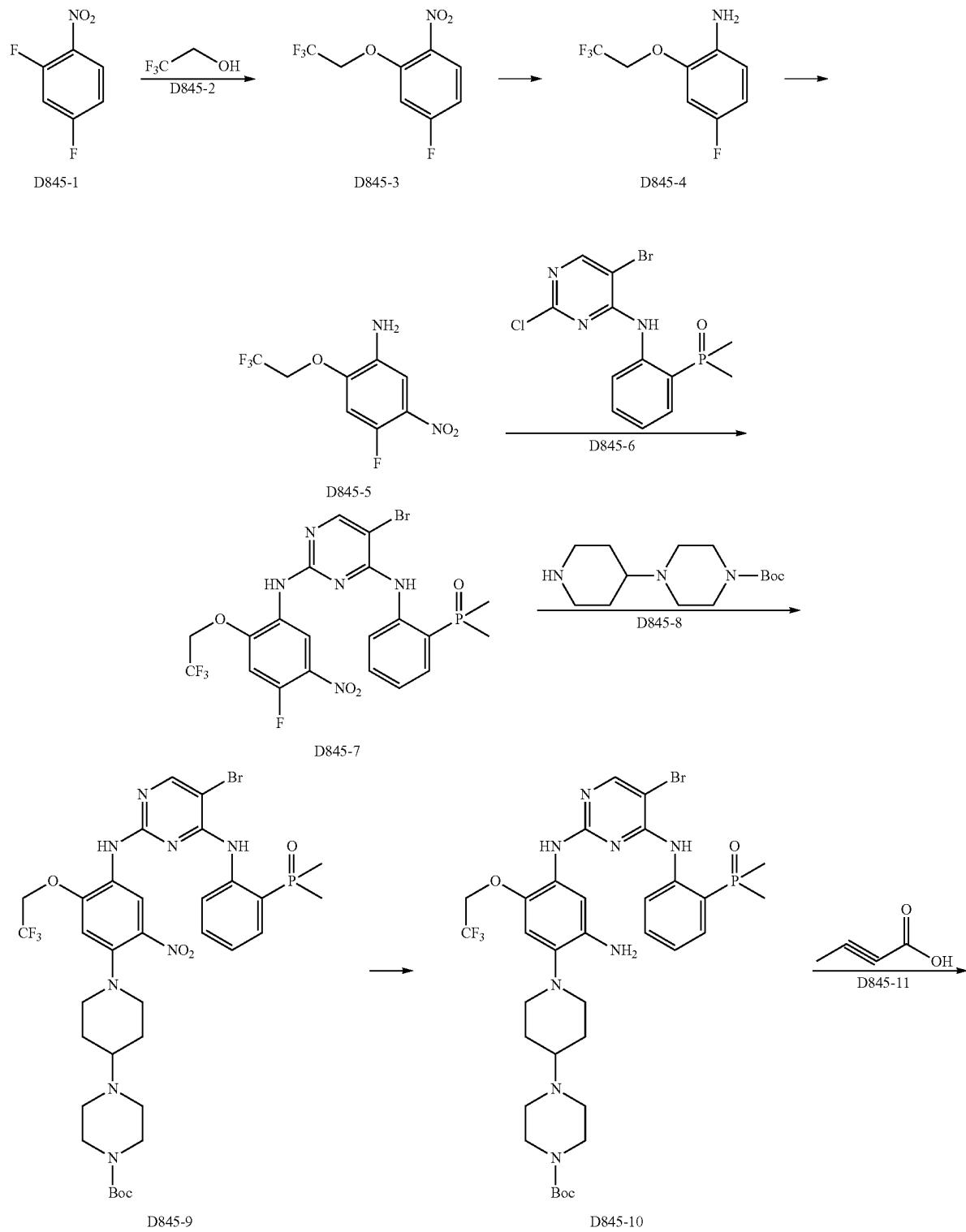
[0707] D835-3 (44.4 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under

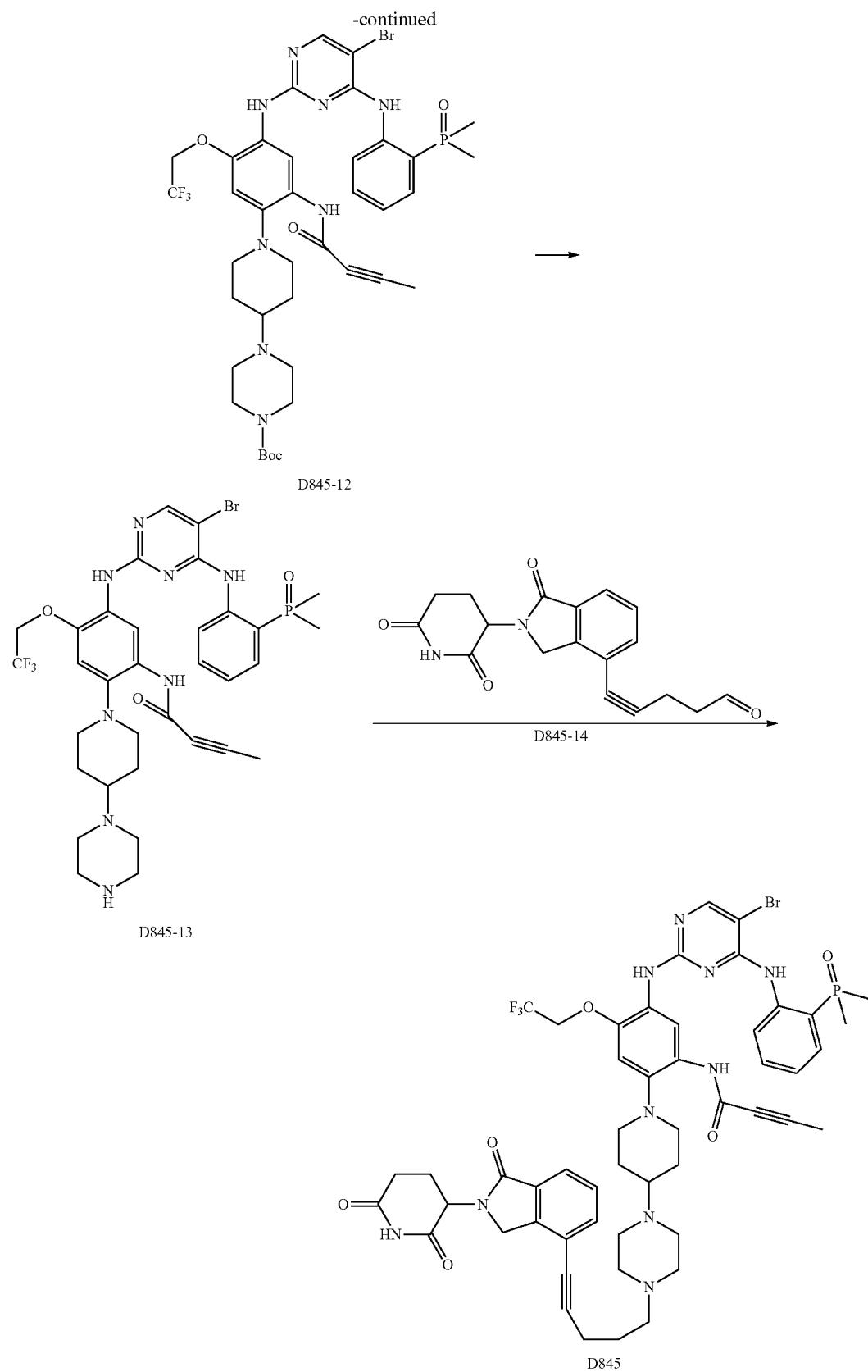
reduced pressure, and the crude product was used directly in the next step, LCMS: $[M+H]^+$ =713.

Step 3

[0708] D835-4 (38.9 mg, 0.055 mmol) and D835-5 (23 mg, 0.071 mmol) were dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise, and the pH was adjusted to 7.5. Acetic acid (3.9 mg, 0.066 mmol) was added, and the mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (15.3 mg, 0.246 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D835 (26 mg, yield 46.7%), LCMS: $[M+H]^+$ =1021.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-(2,2,2-trifluoroethoxy)phenyl)but-2-ynamide (D845)





Step 1

[0709] D845-1 (10 g, 62.9 mmol) and cesium carbonate (20.5 g, 62.9 mmol) were added to tetrahydrofuran (100 mL). D845-2 (6.29 g, 62.9 mmol) was added dropwise under stirring. The mixture was stirred at room temperature overnight, and filtered. The solvent was removed under reduced pressure. The residue was purified by Flash to obtain D845-3 (14.35 g, yield 95.7%). LCMS: $[M+H]^+=240$.

Step 2

[0710] D845-3 (14.35 g, 60 mmol), iron powder (20.12 g, 360 mmol) and ammonium chloride (9.63 g, 180 mmol) were added to 100 mL of water/ethanol (1/4, V/V). The mixture was heated and stirred at 100° C. for 1 hour. The mixture was filtered while hot and the filtrate was cooled. The filtrate was extracted with ethyl acetate three times. The organic phases were combined. The solvent was evaporated under reduced pressure. The residue was purified by Flash to obtain D845-4 (9.76 g, yield 78.1%). LCMS: $[M+H]^+=210$.

Step 3

[0711] D845-4 (9.76 g, 47 mmol) was added to 40 mL of concentrated sulfuric acid under stirring at 0° C. Potassium nitrate (5.66 g, 56 mmol) was added in batches. The temperature was maintained and the mixture was stirred for 1 hour. The reaction solution was poured into ice water and extracted twice with ethyl acetate. The aqueous phase was adjusted to pH=7 with dilute hydrochloric acid, and then extracted twice with ethyl acetate. The organic phases were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product. The crude product was purified by Flash to obtain D845-5 (8.58 g, 72.3%). LCMS: $[M+H]^+=255$.

Step 4

[0712] Compound D845-5 (1 g, 2.79 mmol), D845-6 (708 mg, 2.79 mmol) and methanesulfonic acid (803 mg, 8.36 mmol) were dissolved in 20 mL of tert butanol. The mixture was stirred at 90° C. for 24 hours under nitrogen protection. The temperature was cooled to room temperature. The solvent was evaporated under reduced pressure. The pH was

adjusted to 7 with sodium bicarbonate aqueous solution. The mixture was extracted with dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product. The crude product was purified by Flash to give compound D845-7 (1.30 g, yield 80.7%). LCMS: $[M+H]^+=578$.

Step 5

[0713] D845-7 (900 mg, 1.56 mmol), D845-8 (504 mg, 1.87 mmol), and cesium carbonate (1.53 g, 4.68 mmol) were added to 10 mL of DMF. The mixture was stirred at 70° C. overnight under nitrogen protection. The mixture was cooled, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D845-9 (1.055 g, yield 81.4%), LCMS: $[M+H]^+=827$.

Step 6

[0714] Under stirring at room temperature, a solution of sodium hydrosulfite (1.05 g, 6.05 mmol) in water (40 mL) was added to a solution of D845-9 (1.0 g, 1.21 mmol) in ethanol (40 mL). The mixture was stirred and reacted for 10 minutes. Dichloromethane was added, and the layers were separated. The mixture was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product D845-10 (0.7 g, 72.9%), which was directly used in the next step. LCMS: $[M+H]^+=797$.

Step 7

[0715] D845-10 (50 mg, 0.063 mmol), D845-11 (4.2 mg, 0.050 mmol), T3P (50% EA, 160 mg, 0.251 mmol) and TEA (25 mg, 0.251 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D845-12 (36.3 mg, yield 67.1%), LCMS: $[M+H]^+=863$.

Step 8

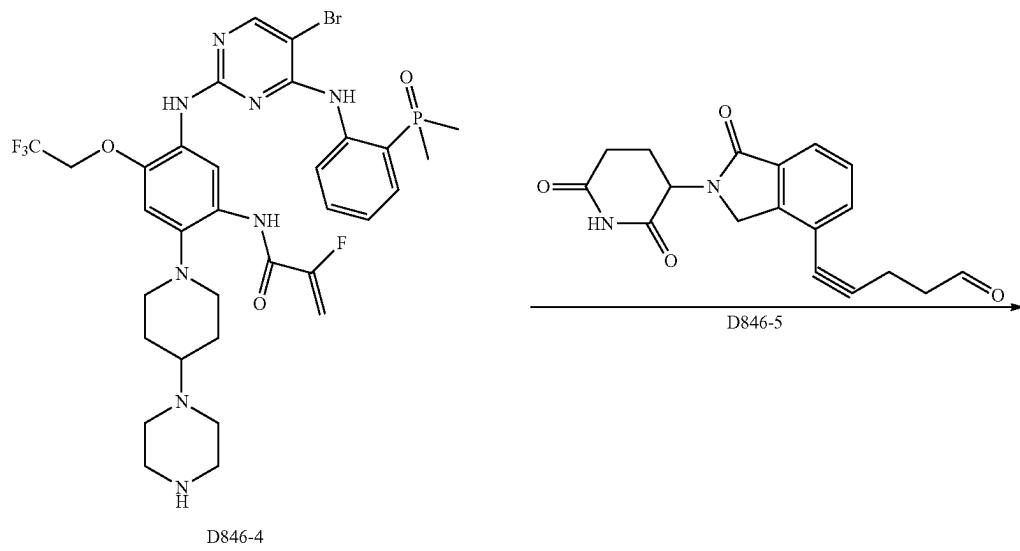
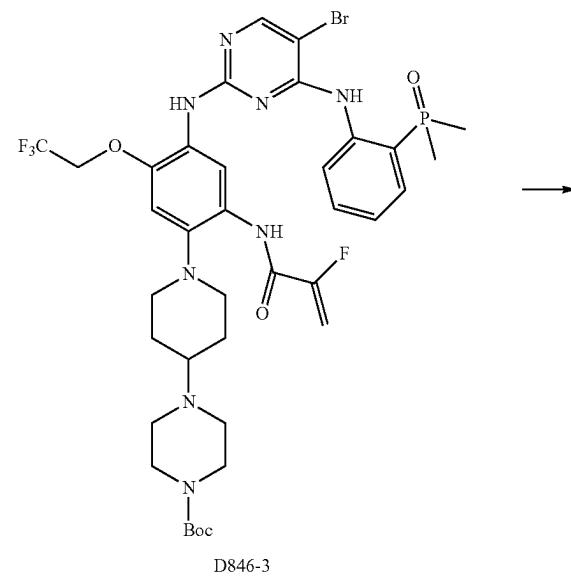
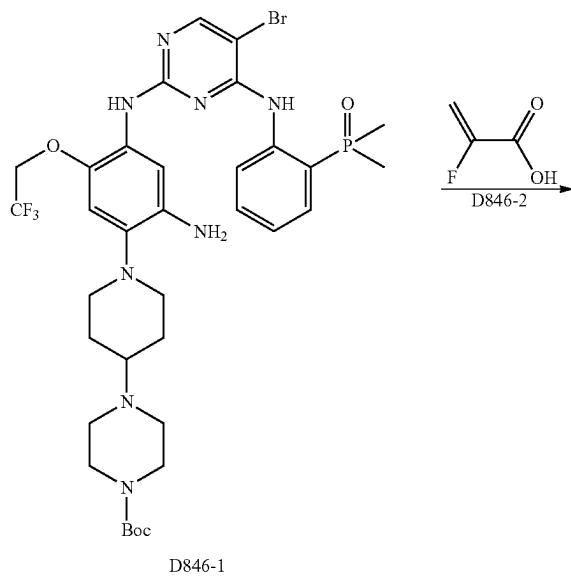
[0716] D845-12 (36.3 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and the crude product was used directly in the next step. LCMS: $[M+H]^+=763$.

Step 9

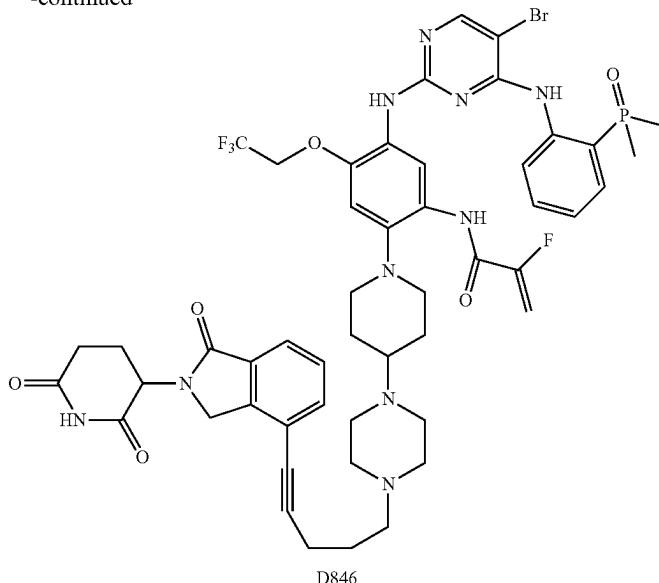
[0717] D845-13 (32 mg, 0.042 mmol) was dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise. The pH was adjusted to 7.5. Compound D845-14 (17.7 mg, 0.055 mmol) and acetic acid (3.0 mg, 0.050 mmol) were added. The mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (12.0 mg, 0.189 mmol) was added in batches over 2 hours. The

solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D845 (15 mg, yield 33.4%), LCMS: [M+H]⁺ =1071.

Preparation of N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-(2,2,2-trifluoroethoxy)phenyl)-2-fluoroacrylamide (D846)



-continued



Step 1

[0718] D846-1 (50 mg, 0.063 mmol), D846-2 (4.5 mg, 0.050 mmol), T3P (50% EA, 160 mg, 0.251 mmol) and TEA (25 mg, 0.251 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D846-3 (41.5 mg, yield 76.1%), LCMS: $[M+H]^+$ =869.

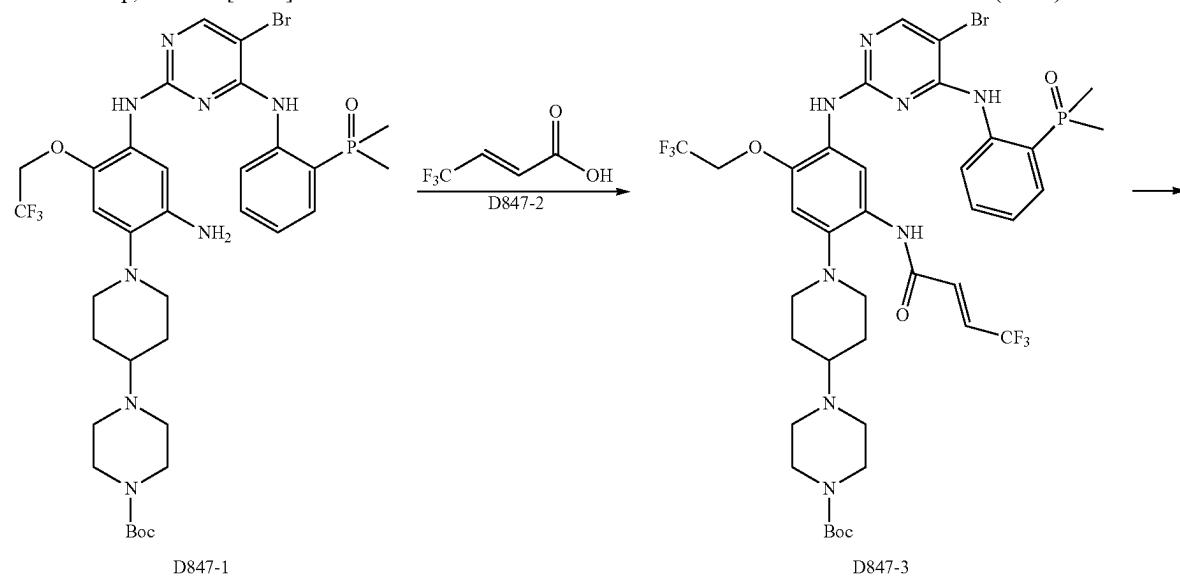
Step 2

[0719] D846-3 (41.5 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and the crude product was used directly in the next step. LCMS: $[\text{M}+\text{H}]^+ = 769$.

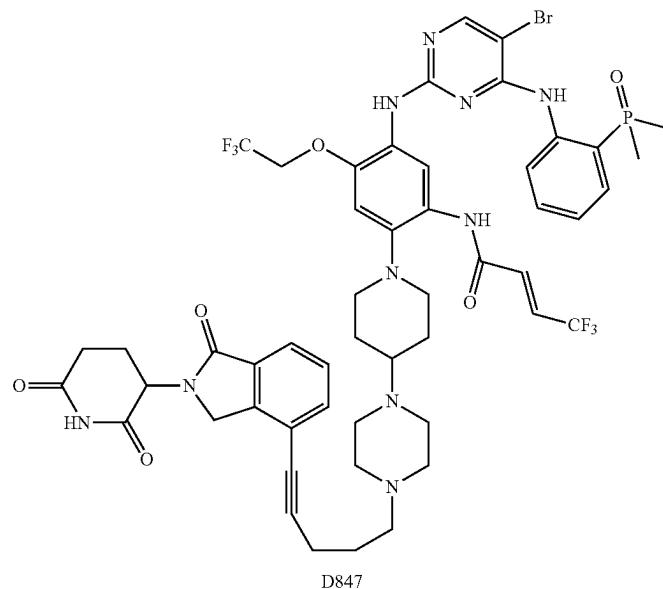
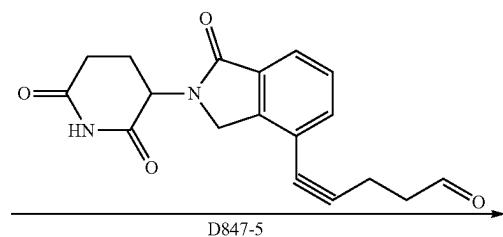
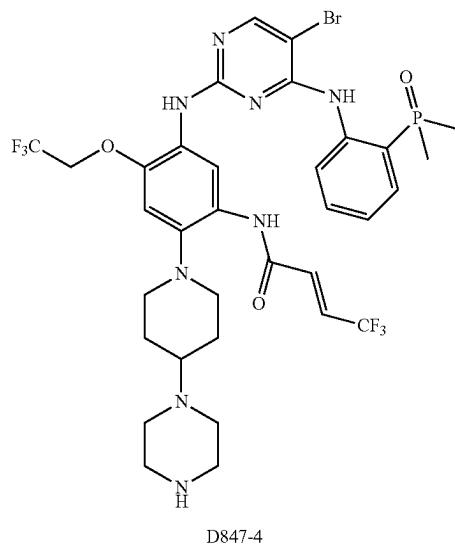
Step 3

[0720] D846-4 (36.7 mg, 0.048 mmol) was dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise. The pH was adjusted to 7.5. D846-5 (20.1 mg, 0.062 mmol) and acetic acid (3.4 mg, 0.057 mmol) were added, and the mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (13.5 mg, 0.216 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D846 (17 mg, yield 33.3%), LCMS: $[M+H]^+$ =1077.

Preparation of (E)-N-(5-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-(2,2,2-trifluoroethoxy)phenyl)-4,4,4-trifluorobut-2-enamide (D847)



-continued



Step 1

[0721] D847-1 (50 mg, 0.063 mmol), D847-2 (7.0 mg, 0.050 mmol), T3P (50% EA, 160 mg, 0.251 mmol) and TEA (25 mg, 0.251 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D847-3 (53.6 mg, yield 93.1%), LCMS: $[M+H]^+=919$.

Step 2

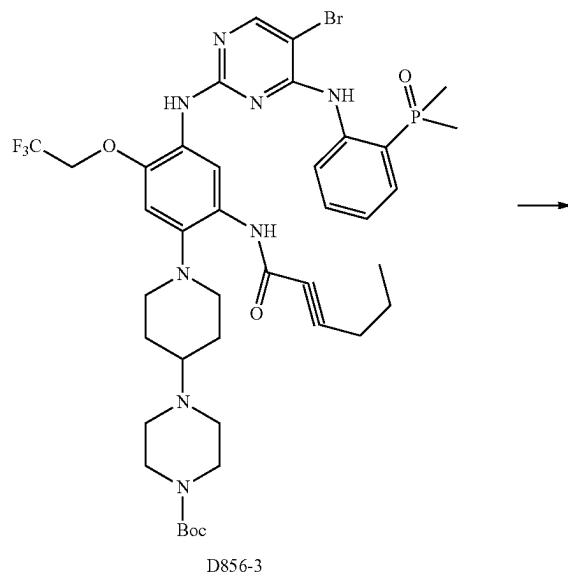
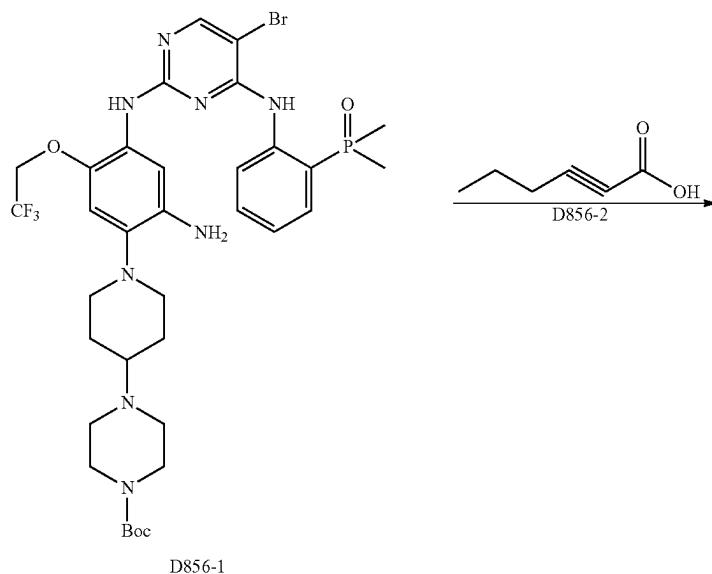
[0722] D847-3 (53.6 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and the crude product was used directly in the next step, LCMS: $[M+H]^+=819$.

Step 3

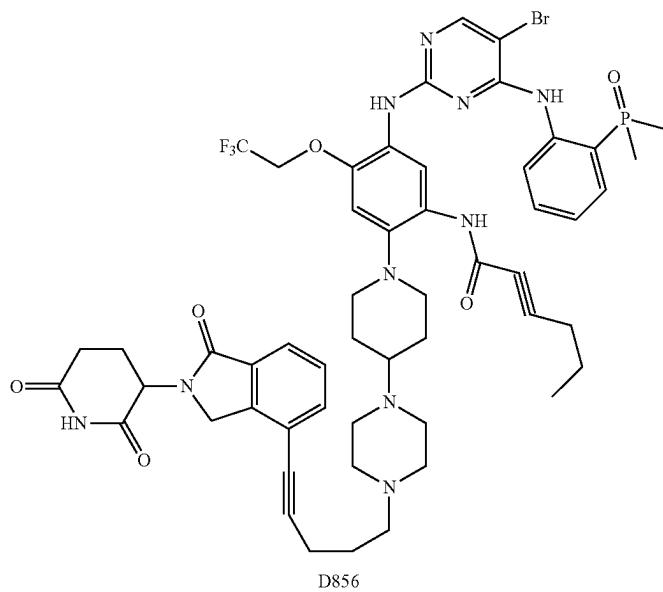
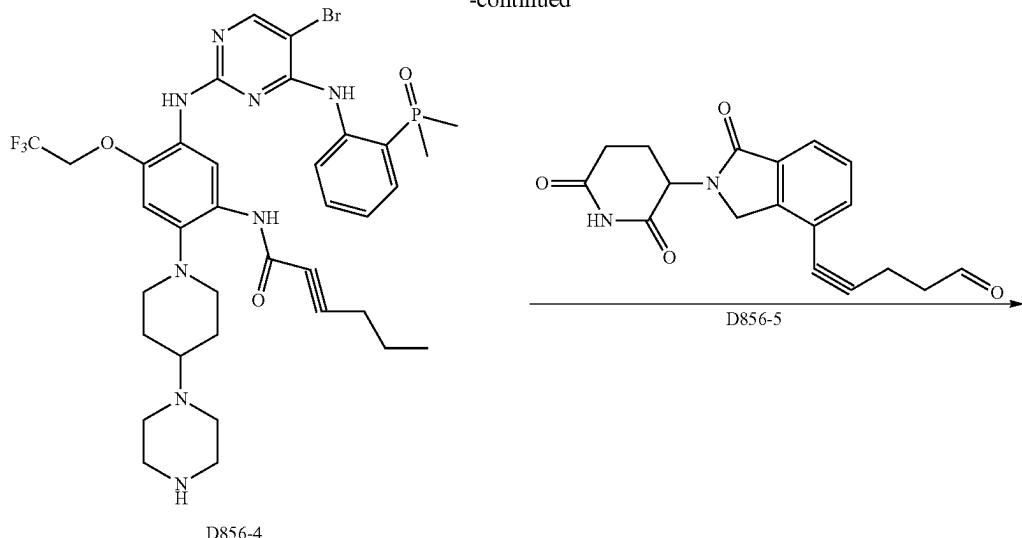
[0723] D847-4 (51.8 mg, 0.063 mmol) was dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise. The pH was adjusted to 7.5. D847-5 (26.7 mg, 0.082 mmol) and acetic acid (4.6 mg, 0.076 mmol) were added, and the mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (18.0 mg, 0.285 mmol) was added in batches over 2 hours. The

solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D847 (28 mg, yield 36.4%), LCMS: $[M+H]^+=1127$.

Preparation of N-((5-bromo-4-((2-(dimethylphosphoryl)phenyl)amino)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-(2,2,2-trifluoroethoxy)phenyl)hex-2-ynamide (D856)



-continued



Step 1

[0724] D856-1 (50 mg, 0.063 mmol), D856-2 (5.6 mg, 0.050 mmol), T3P (50% EA, 160 mg, 0.251 mmol) and TEA (25 mg, 0.251 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D856-3 (39.4 mg, yield 70.5%), LCMS: $[\text{M}+\text{H}]^+ = 891$.

Step 2

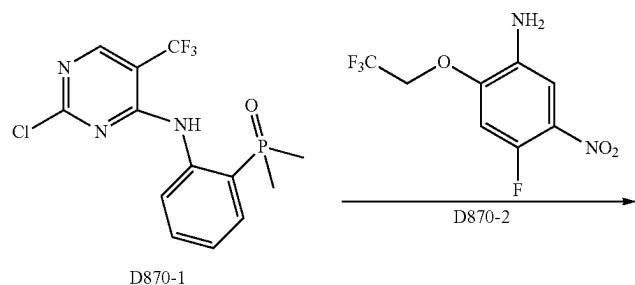
[0725] D856-3 (39.4 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under

reduced pressure, and the crude product was used directly in the next step, LCMS: $[M+H]^+=791$.

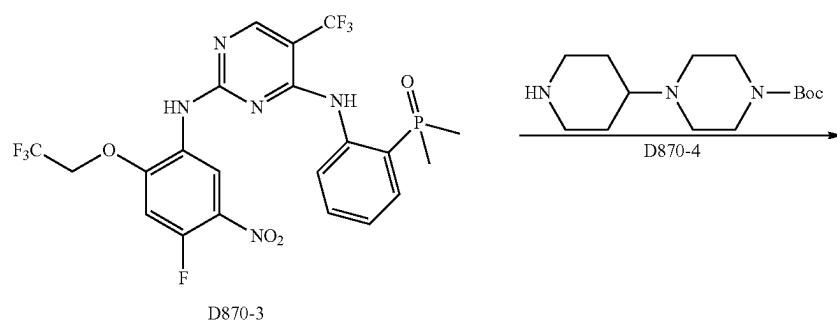
Step 3

[0726] D856-4 (34.9 mg, 0.044 mmol) was dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise. The pH was adjusted to 7.5. D856-5 (18.6 mg, 0.057 mmol) and acetic acid (3.2 mg, 0.053 mmol) were added, and the mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (12.6 mg, 0.198 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D856 (16 mg, yield 33.3%), LCMS: [M+H]⁺ =1099.

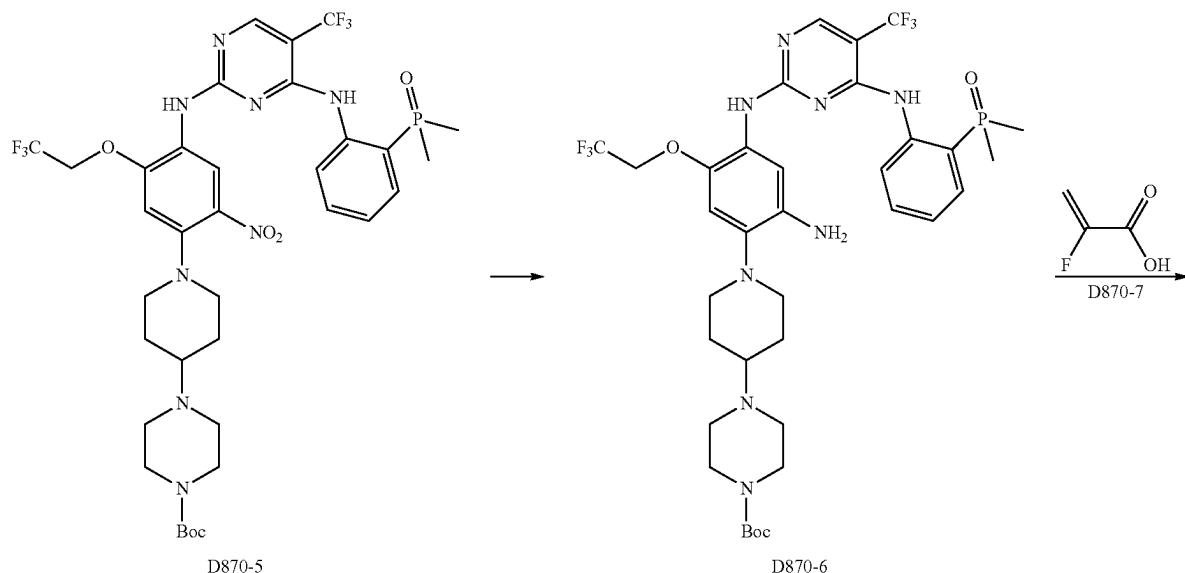
Preparation of N-(5-((4-((2-(dimethylphosphoryl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-(2,2,2-trifluoroethoxy)phenyl)-2-fluoroacrylamide (D870)



D870-1

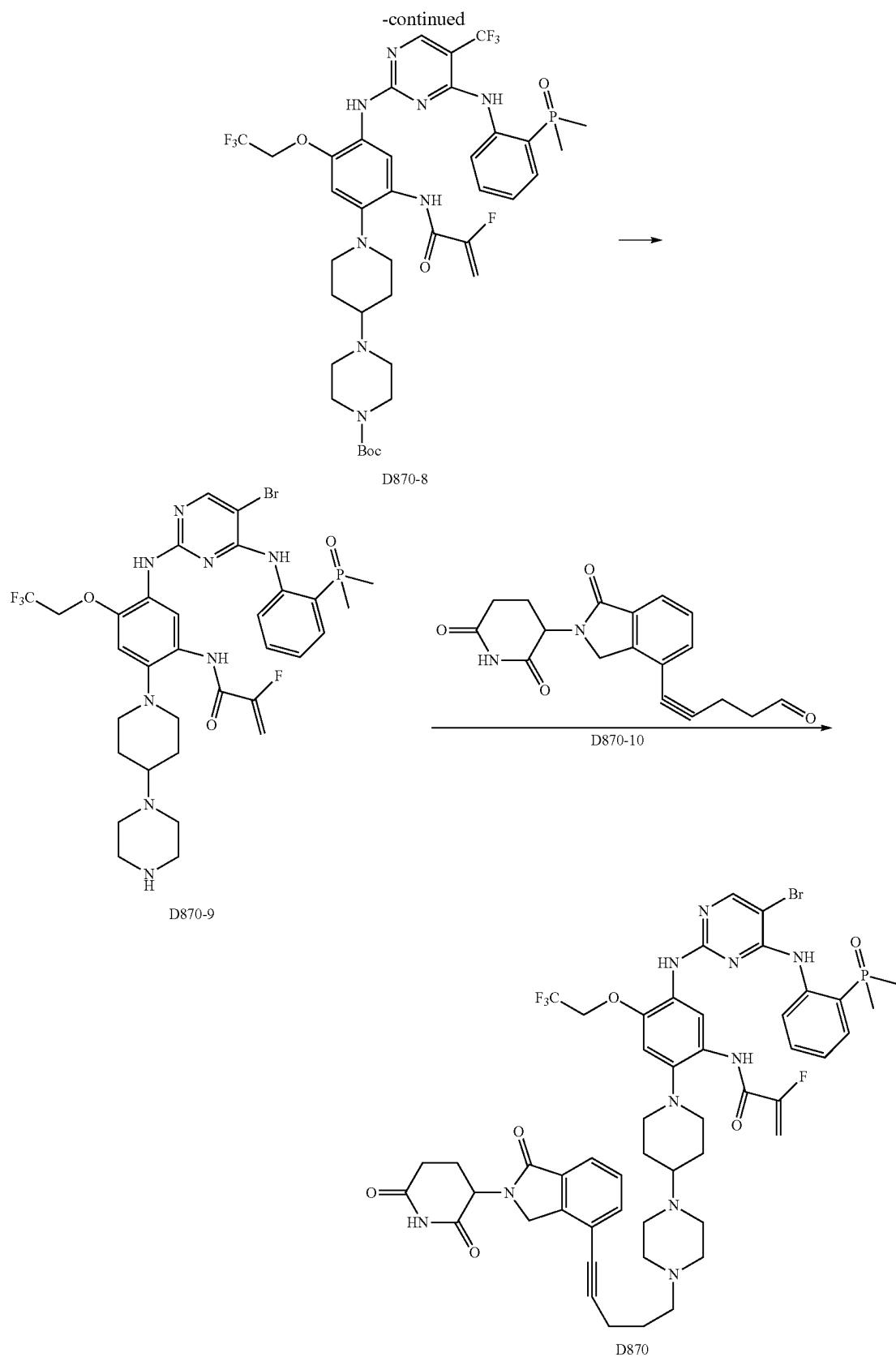


D870-3



D870-5

D870-6



Step 1

[0727] D870-1 (401 mg, 1.15 mmol), D870-2 (321 mg, 1.26 mmol) and methanesulfonic acid (442 mg, 4.60 mmol) were dissolved in 20 mL of tert butanol. The mixture was stirred at 90° C. for 24 hours under nitrogen protection. The temperature was cooled to room temperature, the solvent was evaporated under reduced pressure, and the crude product was purified by Flash to obtain D870-3 (505 mg, 77.0%). LCMS: [M+H]⁺=568.

Step 2

[0728] D870-3 (300 mg, 0.529 mmol), D870-4 (171 mg, 0.635 mmol), and cesium carbonate (517 mg, 1.587 mmol) were added to 5 mL of DMF. The mixture was stirred at 70° C. overnight under nitrogen protection. The mixture was cooled, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D870-5 (416 mg, yield 96.5%), LCMS: [M+H]⁺=817.

Step 3

[0729] Under stirring at room temperature, a solution of sodium hydrosulfite (444 g, 2.55 mmol) in water (20 mL) was added to a solution of D870-5 (416 mg, 0.51 mmol) in ethanol (20 mL). The mixture was stirred and reacted for 10 minutes. Dichloromethane was added, and the layers were separated. The mixture was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product D870-6 which was directly used in the next step. LCMS: [M+H]⁺=787.

Step 4

[0730] D870-6 (60 mg, 0.076 mmol), D870-7 (5.5 mg, 0.061 mmol), T3P (50% EA, 194 mg, 0.305 mmol) and TEA

(31 mg, 0.305 mmol) were dissolved in 2 mL of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D870-8 (30 mg, yield 46.2%), LCMS: [M+H]⁺=859.

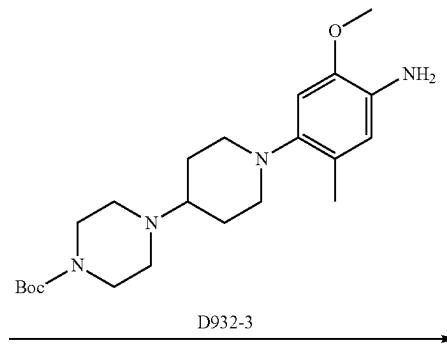
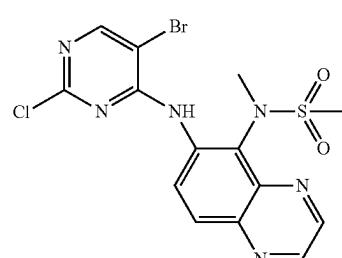
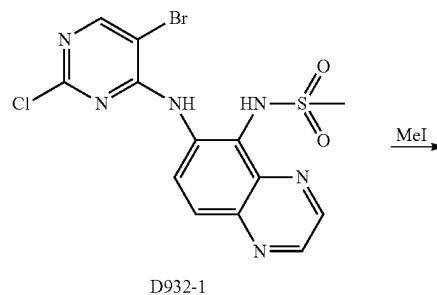
Step 5

[0731] D870-8 (30 mg) was dissolved in 4 mL of dichloromethane. TFA (1 mL) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure, and the crude product was used directly in the next step, LCMS: [M+H]⁺=759.

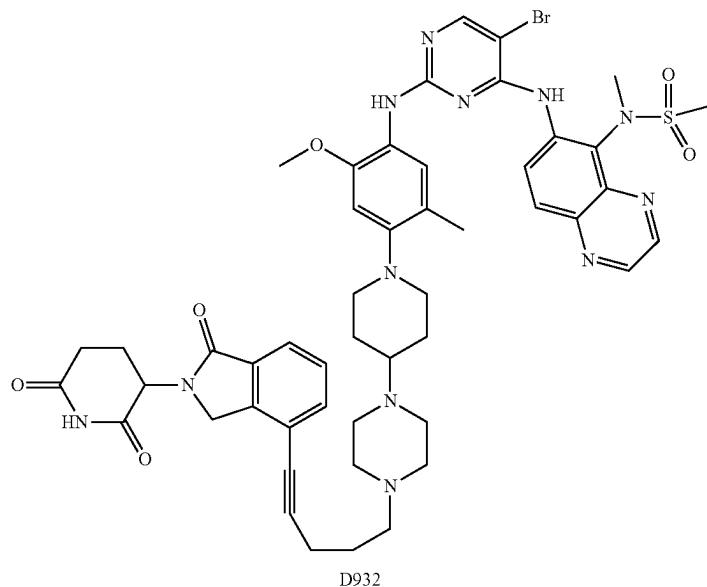
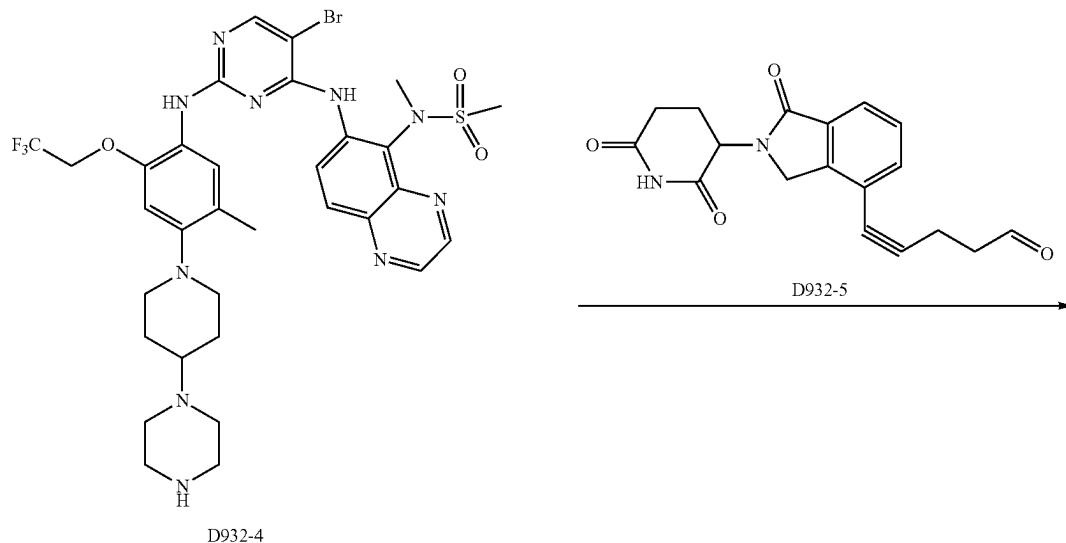
Step 6

[0732] D870-9 (27 mg, 0.036 mmol) was dissolved in 3 mL of dichloromethane/methanol (2/1, v/v). TEA was added dropwise. The pH was adjusted to 7.5. D870-10 (15 mg, 0.046 mmol) and acetic acid (2.6 mg, 0.043 mmol) were added, and the mixture was stirred at room temperature under nitrogen for 1 hour. Sodium cyanoborohydride (10.2 mg, 0.159 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D870 (16 mg, yield 42.1%), LCMS: [M+H]⁺=1067.

Preparation of N-(6-((5-bromo-2-((4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-2-methoxy-5-methylphenyl)amino)pyrimidin-4-yl)amino)quinoxalin-5-yl)-N-methylmethanesulfonamide
(D932)



-continued



Step 1:

[0733] Compound D932-1 (or D741-6, 120 mg, 0.280 mmol), iodomethane (60 mg, 0.421 mmol), and potassium carbonate (58 mg, 0.421 mmol) were added to 2 ml of acetonitrile. The mixture was stirred at 50° C. overnight under nitrogen protection. The residue was purified by Flash to give D932-2 (29 mg, yield 23.6%), LCMS: $[M+H]^+=443$.

Step 2:

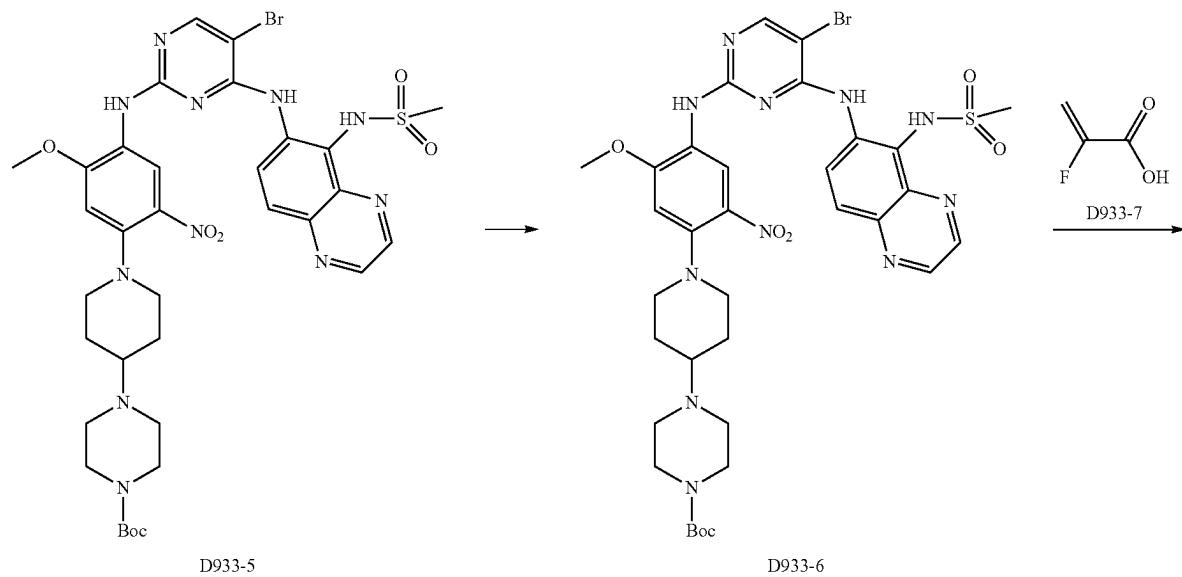
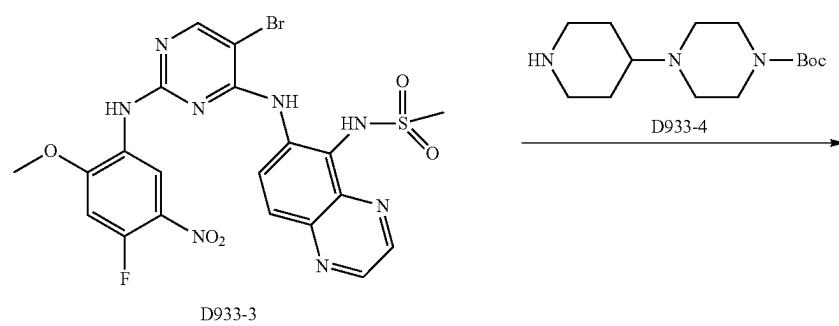
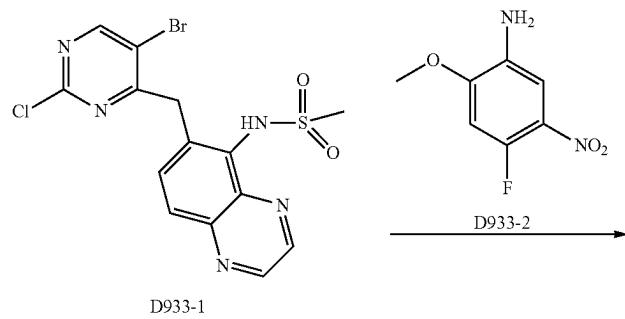
[0734] D932-2 (10 mg, 0.0226 mmol), D932-3 (18 mg, 0.0453 mmol) and methanesulfonic acid (8.7 mg, 0.0905 mmol) were dissolved in 2 ml of n-butanol. The mixture was

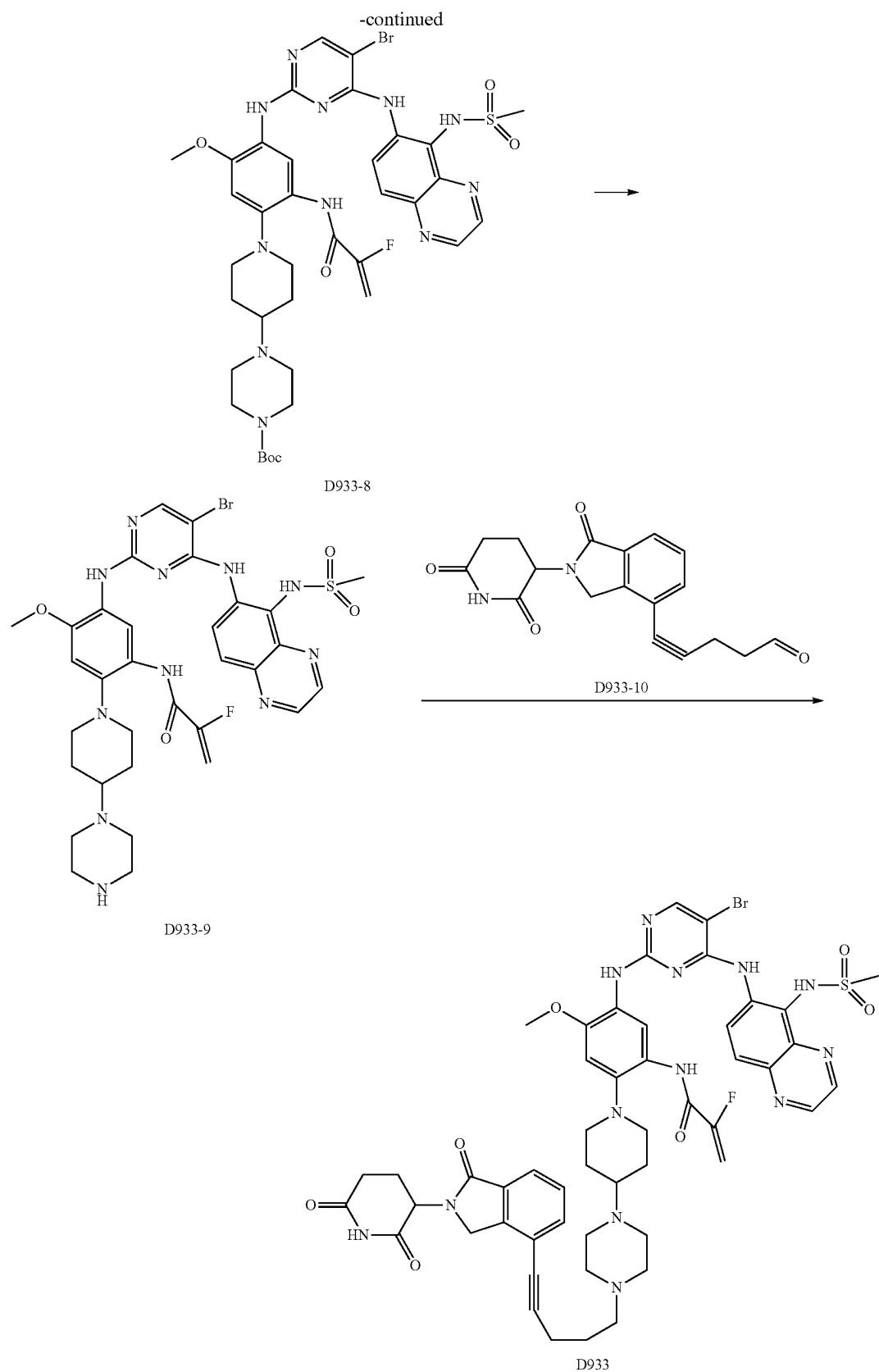
stirred at 90° C. overnight under nitrogen protection. The residue was purified by Flash to give D932-4 (12 mg, yield 75%), LCMS: $[M+H]^+=711$.

Step 3:

[0735] D932-4 (26 mg, 0.037 mmol), D932-5 (14 mg, 0.044 mmol) and acetic acid (2.6 mg, 0.04 mmol) were dissolved in 2 ml of dichloromethane/methanol (2/1, v/v). The mixture was stirred at room temperature for 1 hour under nitrogen. Sodium cyanoborohydride (10.5 mg, 0.156 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D932 (3.7 mg, yield 10.0%), LCMS: $[M+H]^+=1019$.

Preparation of N-(5-((5-bromo-4-((5-(methylsulfo-namido)quinoxalin-6-yl)amino)pyrimidin-2-yl)amino-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D933)





Step 1

[0736] Compound D933-1 (or D741-6, 50 mg, 0.117 mmol), D933-2 (23 mg, 0.123 mmol) and methanesulfonic acid (45 mg, 0.467 mmol) were dissolved in 2 ml of n-butanol. The mixture was stirred at 90° C. overnight under nitrogen protection. The mixture was cooled to room temperature. The solvent was evaporated under reduced pressure, and the crude product was purified by Flash to obtain D933-3 (27 mg, 40.0%). LCMS: [M+H]⁺=579.

Step 2

[0737] D933-3 (27 mg, 0.047 mmol), D933-4 (15 mg, 0.056 mmol), and cesium carbonate (46 mg, 0.140 mmol) were added to 2 ml of DMF. The mixture was stirred at 70° C. overnight under nitrogen protection. The mixture was cooled, and filtered. The filtrate was concentrated. The crude product was purified by Flash to obtain D933-5 (28 mg, yield 72.5%), LCMS: [M+H]⁺=828.

Step 3

[0738] Under stirring at room temperature, a solution of sodium hydrosulfite (59 mg, 0.338 mmol) in water (10 ml) was added to a solution of D933-5 (28 mg, 0.34 mmol) in ethanol (10 ml). The mixture was stirred and reacted for 10 minutes. Dichloromethane was added, and the layers were separated. The mixture was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product D933-6 which was directly used in the next step. LCMS: [M+H]⁺=798.

Step 4

[0739] D933-6 (32.6 mg, 0.041 mmol), D933-7 (2.94 mg, 0.033 mmol), T3P (104 mg, 0.164 mmol) and TEA (16.5 mg, 0.164 mmol) were dissolved in 2 ml of dichloromethane. Under nitrogen protection, the mixture was stirred at room temperature overnight. The mixture was purified by Flash to give D933-8 (5 mg, yield 14.1%), LCMS: [M+H]⁺=870.

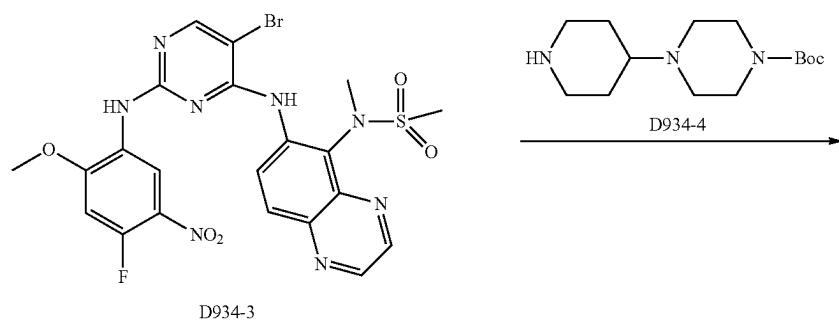
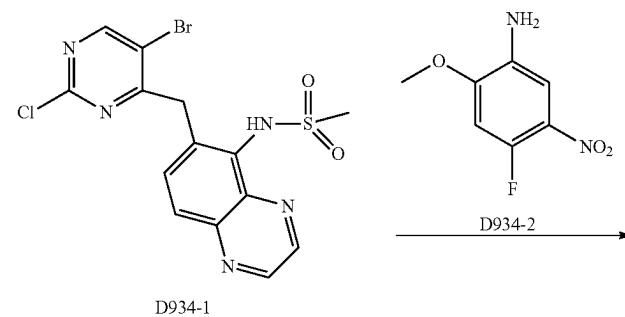
Step 5

[0740] D933-8 (5 mg) was dissolved in 4 ml of dichloromethane. TFA (1 ml) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, and the crude product was directly used in the next step. LCMS: [M+H]⁺=770.

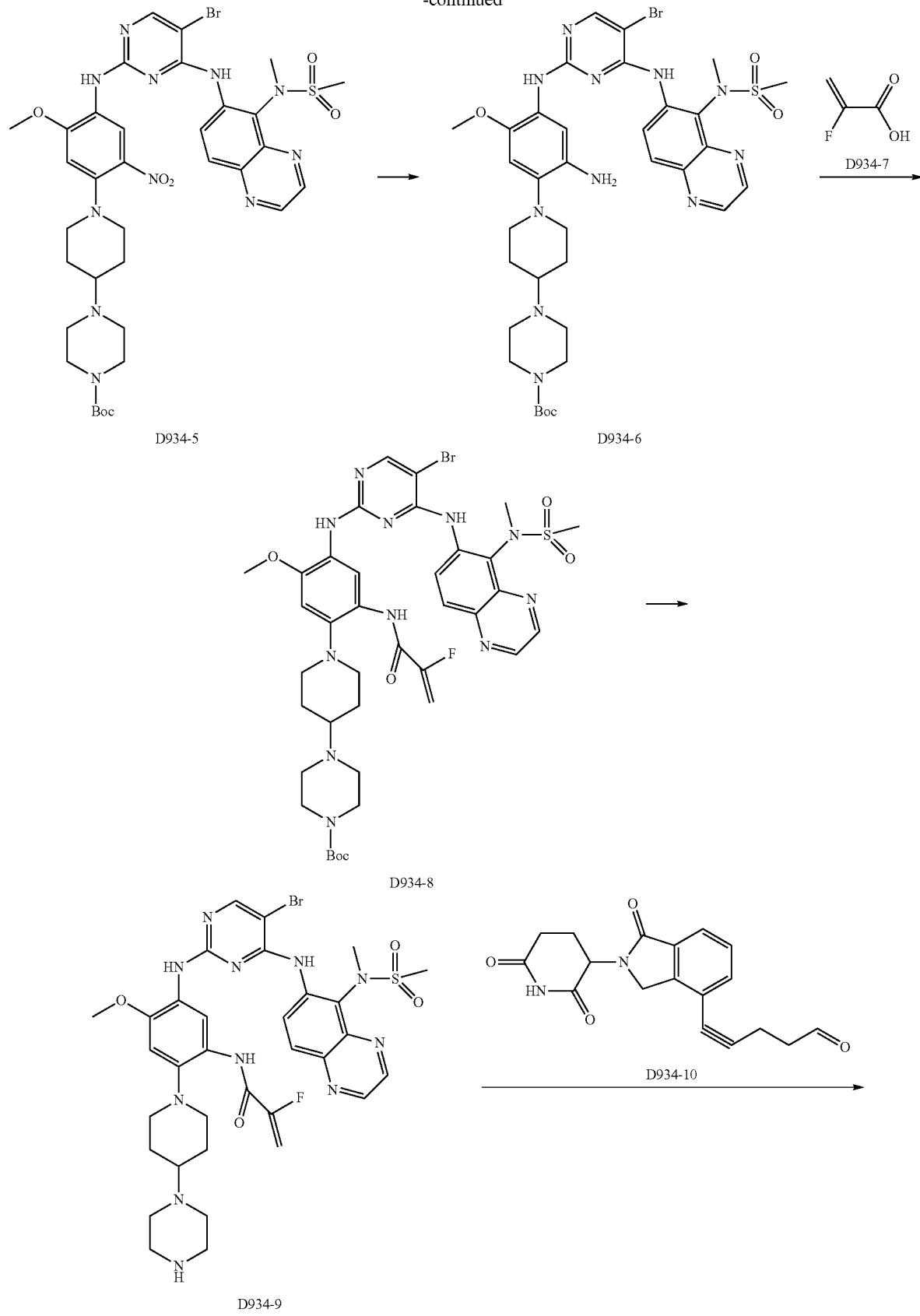
Step 6

[0741] D933-9 (4.4 mg, 0.006 mmol), D933-10 (2.2 mg, 0.007 mmol) and acetic acid (0.4 mg, 0.007 mmol) were dissolved in 3 ml of dichloromethane/methanol (2/1, v/v). The mixture was stirred at room temperature for 1 hour under nitrogen. Sodium cyanoborohydride (1.5 mg, 0.027 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to give compound D933 (2 mg, yield 32.5%), LCMS: [M+H]⁺=1078.

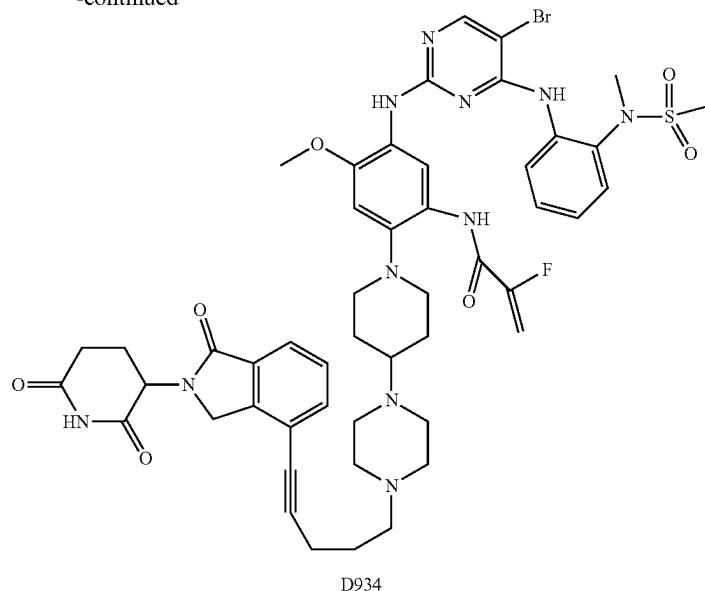
Preparation of N-((5-bromo-4-((5-(N-methylmethanesulfonamido)quinoxalin-6-yl)amino)pyrimidin-2-yl)amino-2-(4-(4-(5-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)piperidin-1-yl)-4-methoxyphenyl)-2-fluoroacrylamide (D934)



-continued



-continued



Step 1

[0742] D934-1 (or D932-2, 19 mg, 0.043 mmol), D934-2 (8.4 mg, 0.045 mmol) and methanesulfonic acid (16 mg, 0.172 mmol) were dissolved in 2 ml of n-butanol and the mixture was stirred overnight at 90° C. under nitrogen protection. The mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by thin layer chromatography to obtain D934-3 (14 mg, 56.0%). LCMS: [M+H]⁺=593.

Step 2

[0743] D934-3 (14 mg, 0.024 mmol), D934-4 (8 mg, 0.028 mmol), and cesium carbonate (23 mg, 0.071 mmol) were added to 2 ml of DMF. The mixture was stirred at 70° C. overnight under nitrogen protection. The mixture was cooled, and filtered. The filtrate was concentrated and purified by thin layer chromatography to obtain D934-5 (12 mg, yield 60.0%), LCMS: [M+H]⁺=842.

Step 3

[0744] Under stirring at room temperature, a solution of sodium hydrosulfite (25 mg, 0.143 mmol) in water (10 ml) was added to a solution of D934-5 (12 mg, 0.014 mmol) in ethanol (10 ml). The mixture was stirred and reacted for 10 minutes. Dichloromethane was added, and the layers were

separated. The mixture was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give a crude product D934-6 which was directly used in the next step. LCMS: [M+H]⁺=812.

Step 4

[0745] D934-6 (13.7 mg, 0.017 mmol), D934-7 (1.21 mg, 0.014 mmol), T3P (50% EA, 43 mg, 0.068 mmol) and TEA (6.8 mg, 0.068 mmol) were dissolved in 2 ml of dichloromethane. The mixture was stirred at room temperature overnight under nitrogen protection. The residue was purified by thin layer chromatography to obtain D934-8 (5 mg, yield 33.6%), LCMS: [M+H]⁺=884.

Step 5

[0746] D934-8 (5 mg) was dissolved in 4 ml of dichloromethane. TFA (1 ml) was added with stirring. Under nitrogen protection, the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, and the crude product was directly used in the next step. LCMS: [M+H]⁺=784.

Step 6

[0747] D934-9 (4.4 mg, 0.006 mmol), D934-10 (2.2 mg, 0.007 mmol) and acetic acid (0.4 mg, 0.007 mmol) were dissolved in 3 ml of dichloromethane/methanol (2/1, v/v). The mixture was stirred at room temperature for 1 hour under nitrogen. Sodium cyanoborohydride (1.5 mg, 0.024 mmol) was added in batches over 2 hours. The solvent was removed under reduced pressure below 40° C., and the crude product was purified by HPLC to obtain D934 (2 mg, yield 32.8%), LCMS: [M+H]⁺=1092.

Assay of Activity on Ba/F3 (EGFR^{L858R/T790M/C797S}) Cells

[0748] Osimertinib is a small molecule EGFR inhibitor used in the clinical treatment of non-small cell lung cancer. Due to the mutation of EGFR C797S, patients develop resistance to Osimertinib. In order to explore the potential of the compounds of the present disclosure to overcome Osimertinib resistance, Ba/F3 (EGFR^{L858R/T790M/C797S}) cells were used as the test cell line to test the anti-proliferative activity of the compounds of the present disclosure.

1. Assay Methods

[0749] 1) Ba/F3 (EGFR^{L858R/T790M/C797S}) cells were cultured according to the requirements of ATCC, incubated in an incubator at 37° C. and 5% CO₂, and analyzed by index; cells with viability of >90% can be used in the assay, and cells were seeded in a 384-well plate (PerkinElmer, 6007680) with 700 cells/well, 30 μL/well.

[0750] 2) A compound stock solution was prepared, and then diluted 3× to give a compound dilution. 30 nL of the compound dilution was added to a 384-well plate by Echo (Labcyte, Echo550). The cells were incubated in an incubator at 37° C. and 5% CO₂ for 72h.

[0751] 3) 30 μL of CTG was added to each well, and the 384-well plate was shaken on a Plate shaker (QILIN-BEIER, QB-9002). The 384-well plate was incubated at 37° C. and 5% CO₂ in the dark for 30 min, and the chemiluminescence value was read by Envision (PerkinElmer, EnVision 2104).

2. Data Analysis

[0752] The percent inhibition rate (% inhibition) was calculated by the following formula

$$\text{Inhibition}(\%) = \left[1 - \frac{\overline{LUM}_{\text{compd}} - \overline{LUM}_{\text{positive}}}{\overline{LUM}_{\text{vehicle}} - \overline{LUM}_{\text{positive}}} \right] \times 100$$

[0753] $\overline{LUM}_{\text{compd}}$: Luminescence value of assay compound.

[0754] $\overline{LUM}_{\text{positive}}$: Average LUM value of positive drug with a concentration of 10 μM.

[0755] $\overline{LUM}_{\text{vehicle}}$: Average LUM value of negative control group without drug treatment.

[0756] The nonlinear regression curve (dose response-variable slope) between the value of inhibition rate (%) and the logarithm of compound concentration was fitted with graphpad prism 8.0, the effect dose curve of compound was drawn, and the IC₅₀ value was calculated.

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{Log } IC_{50} - X) * \text{Hill-Slope})})$$

[0757] X-axis: logarithm of compound concentration; Y axis: inhibition rate (% inhibition).

3. Assay Result

[0758] IC₅₀ values of the antiproliferative activity of the compounds of the present disclosure on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells are shown in Table 1.

TABLE 1

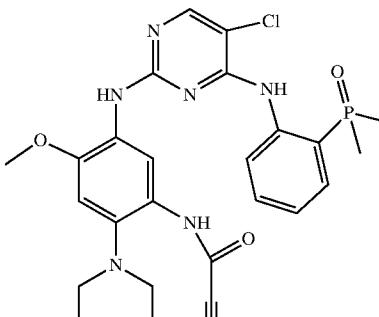
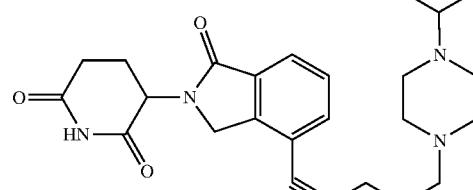
Antiproliferative activity of compounds on Ba/F3 (EGFR ^{L858R/T790M/C797S}) cells		
Compound No.	Structural formula	IC ₅₀ (nM)
D058	 	35.63

TABLE 1-continued

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

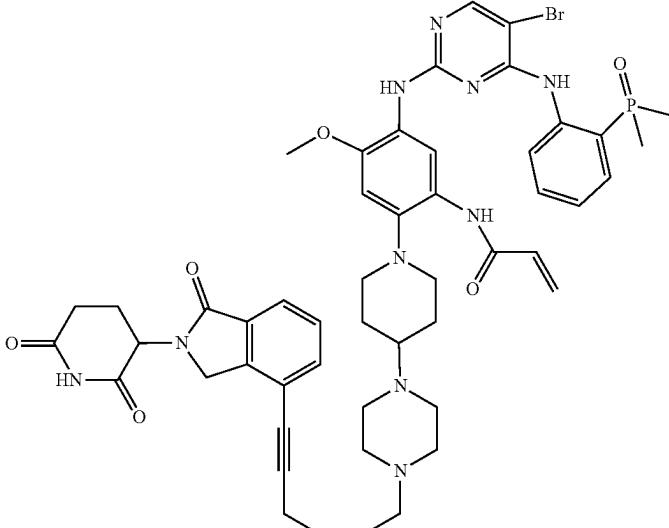
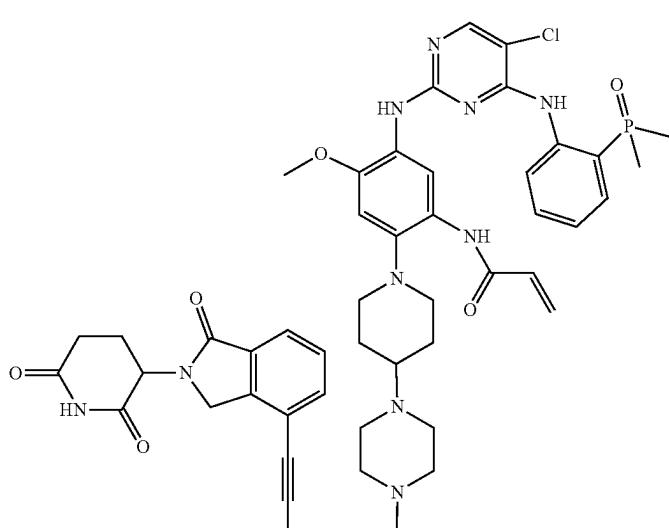
Compound No.	Structural formula	IC ₅₀ (nM)
D479		86.76
D481		68.73

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

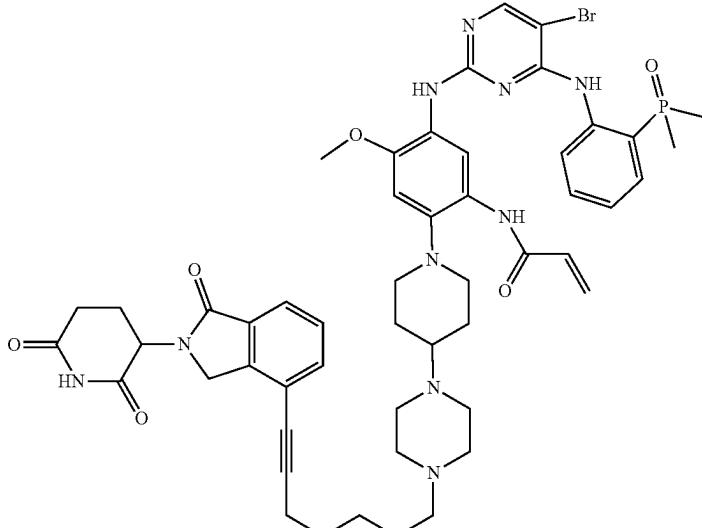
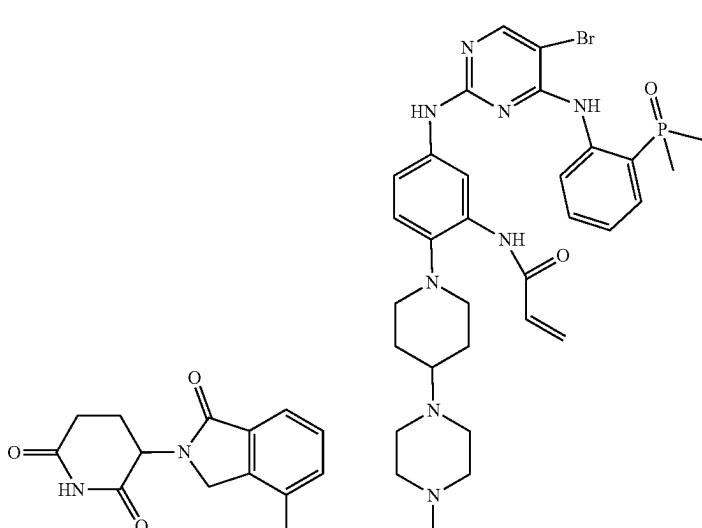
Compound No.	Structural formula	IC ₅₀ (nM)
D503		51.19
D549		7.409

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D550		14.36
D551		14.54

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D552		37.34
D553		49.45

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

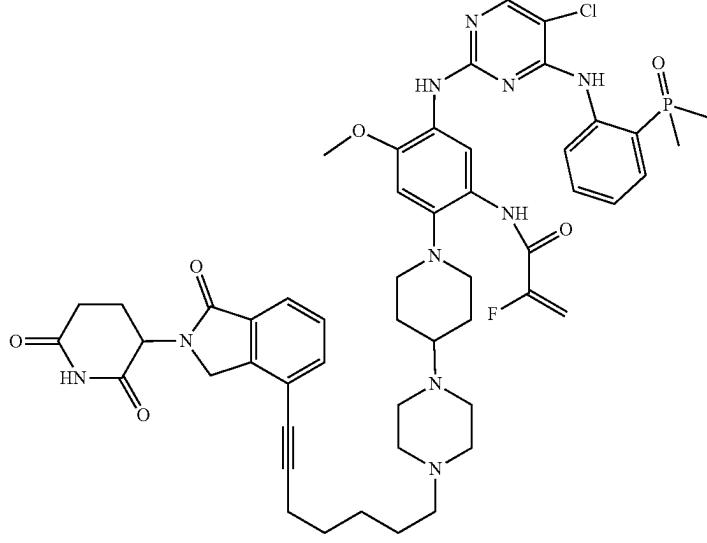
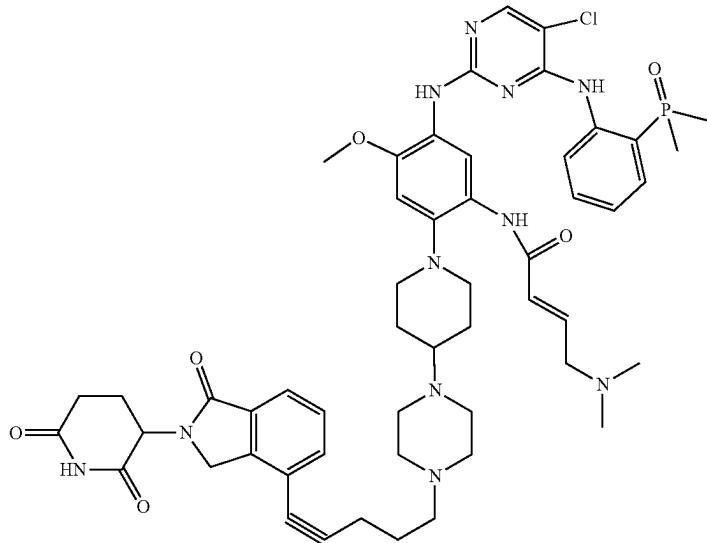
Compound No.	Structural formula	IC ₅₀ (nM)
D554		45.25
D555		67.60

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

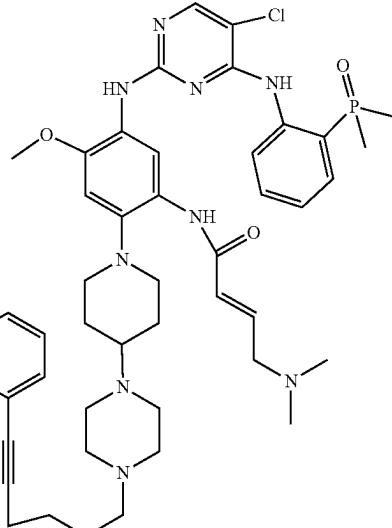
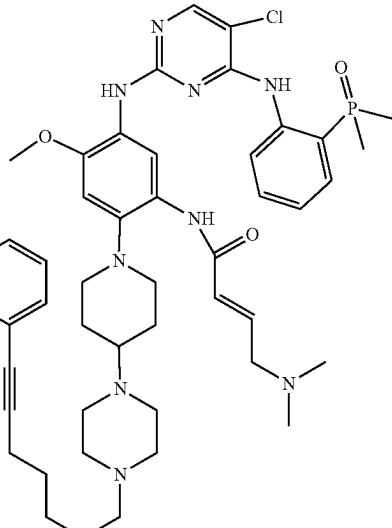
Compound No.	Structural formula	IC ₅₀ (nM)
D556		582.0
D557		382.6

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D559		50.45
D560		112.2

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

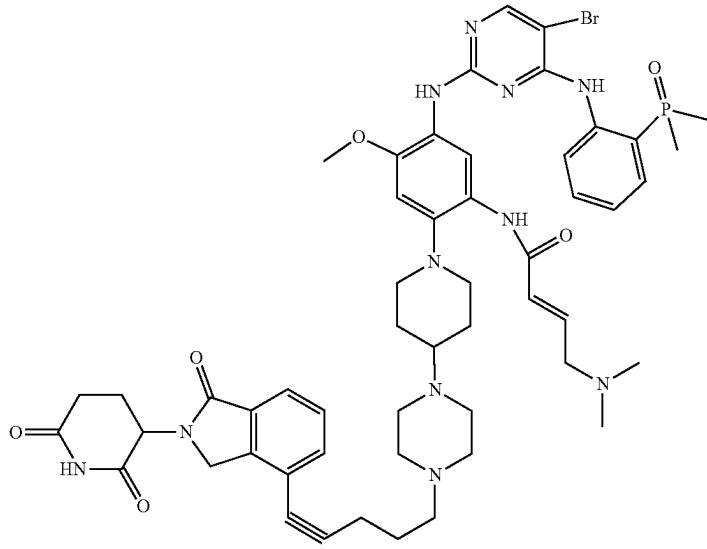
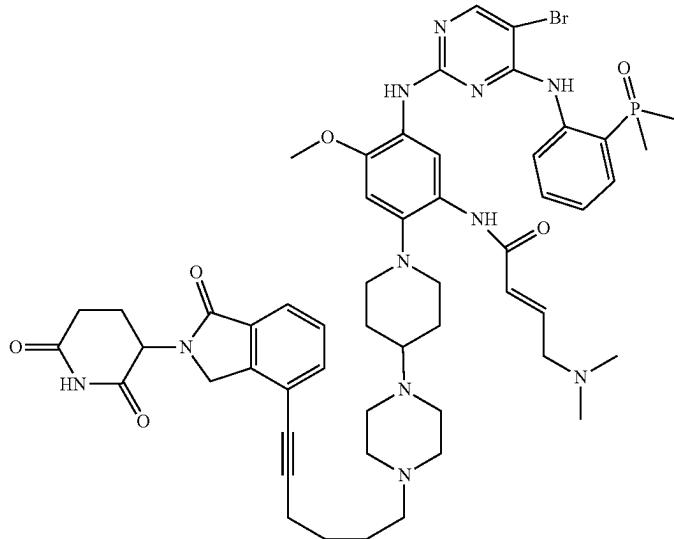
Compound No.	Structural formula	IC ₅₀ (nM)
D561		
D562		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

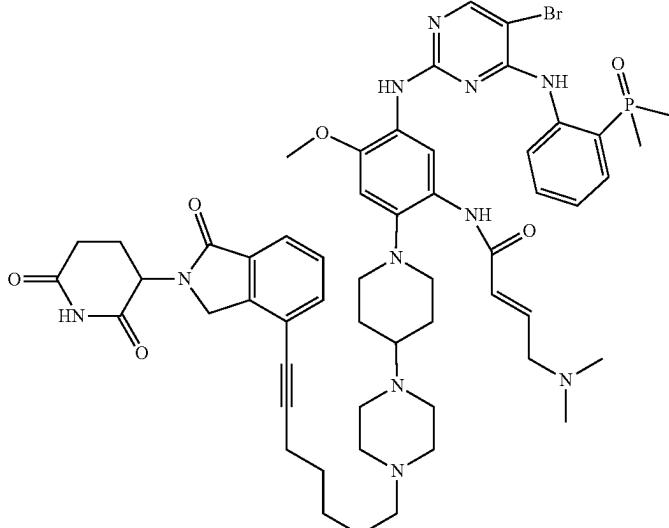
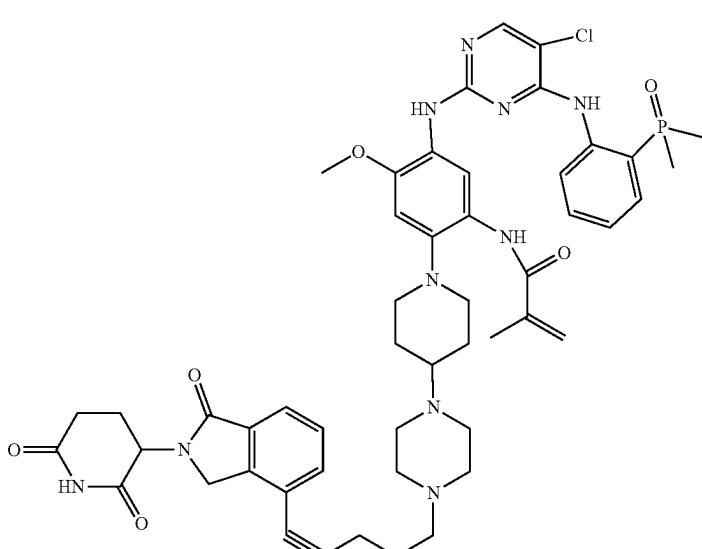
Compound No.	Structural formula	IC ₅₀ (nM)
D563		305.5
D579		41.38

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

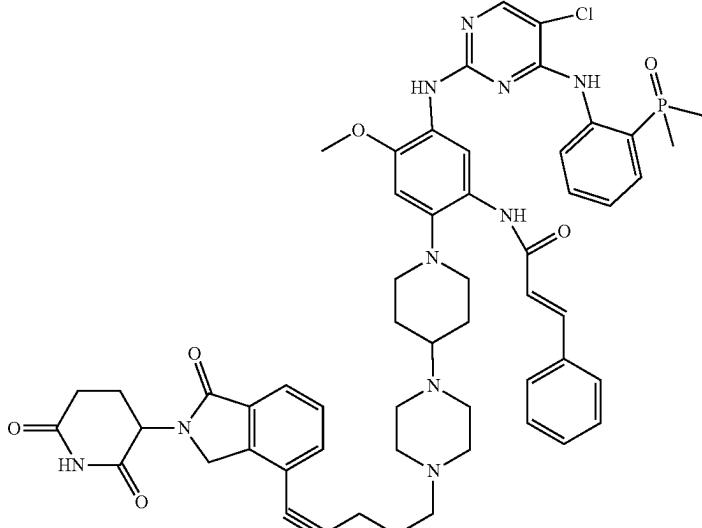
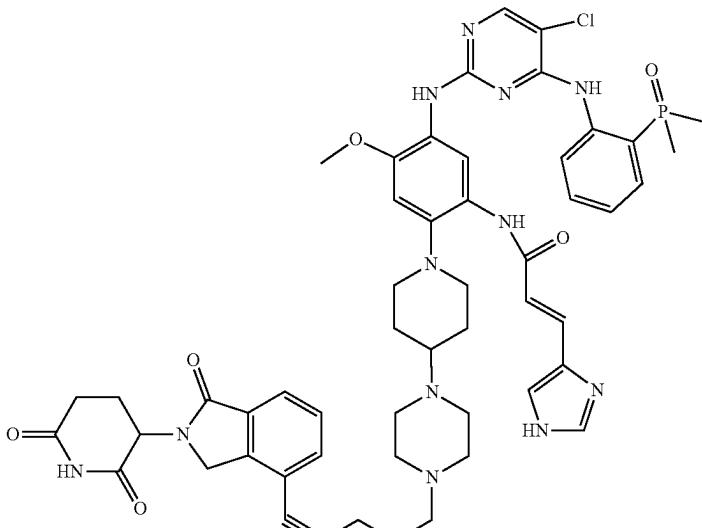
Compound No.	Structural formula	IC ₅₀ (nM)
D580		
D581		2598

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

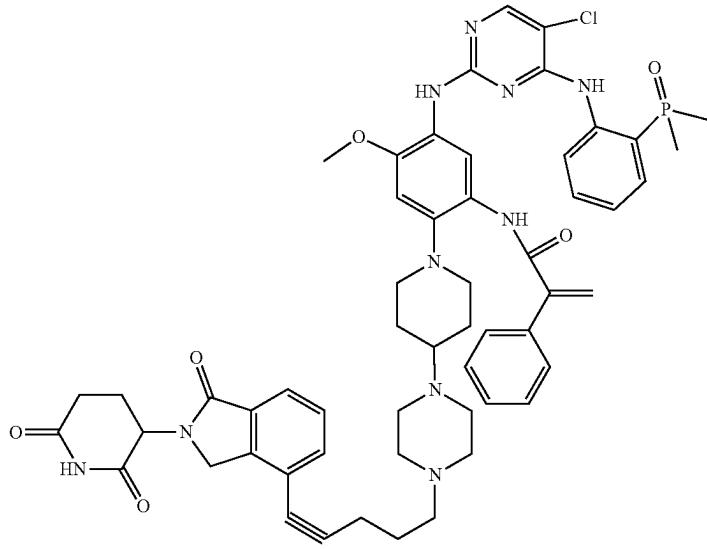
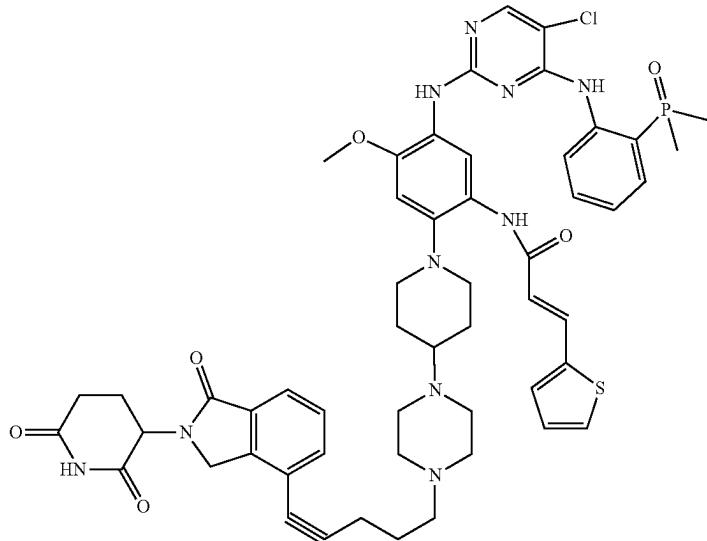
Compound No.	Structural formula	IC ₅₀ (nM)
D582		
D583		45.58

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D584		216.2
D596		31.74

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.

Structural formula

IC₅₀ (nM)

D597

The chemical structure of D597 consists of two main parts. The top part is a purine derivative with a chlorine atom at position 6 and a 4-methoxyphenyl group at position 2'. The bottom part is a piperazine derivative linked to the purine via its 2' nitrogen. It features a 4-(chloromethyl)piperazine ring, a 4-allylphenyl group, and a 4-(dimethylphosphoryl)phenyl group.

459.7

D600

The chemical structure of D600 is similar to D597 but with a fluorine atom instead of a chlorine atom at position 6 of the purine ring.

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D601	<p>Chemical structure of compound D601: 6-[4-(2-allylacetoxymethyl)-4-methoxyphenyl]-2-chloropyrimidine.</p>	144.4
D602	<p>Chemical structure of compound D602: 6-[4-(2-propynylacetoxymethyl)-4-methoxyphenyl]-2-chloropyrimidine.</p>	57.25

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D603		37.07
D604		44.41

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D620		46.68
D622		257.6

TABLE 1-continued

Compound No.	Structural formula	IC ₅₀ (nM)
D623		94.31
D628		325.3

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D630		
D631		48.15

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D632		
D633		56.48

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

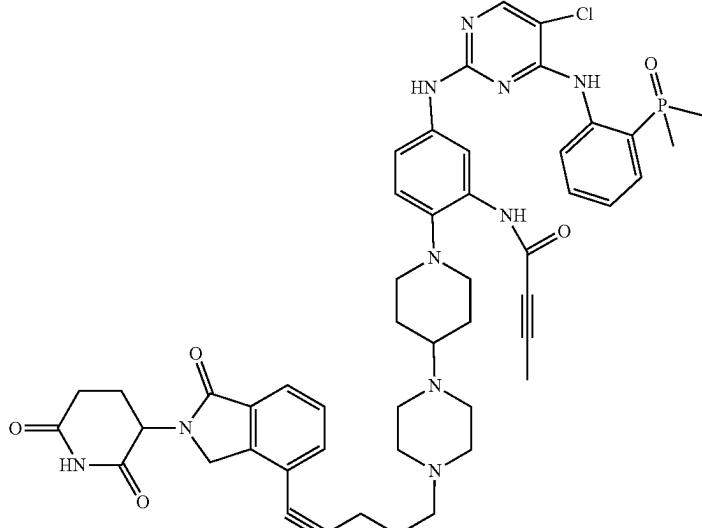
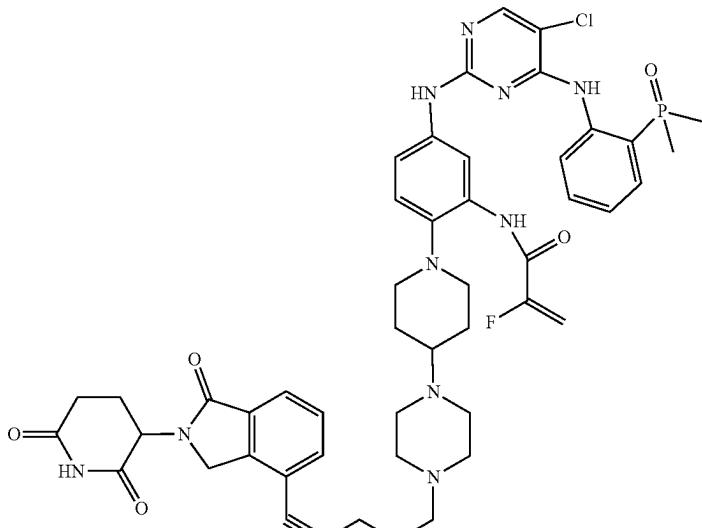
Compound No.	Structural formula	IC ₅₀ (nM)
D665		10.34
D666		13.74

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

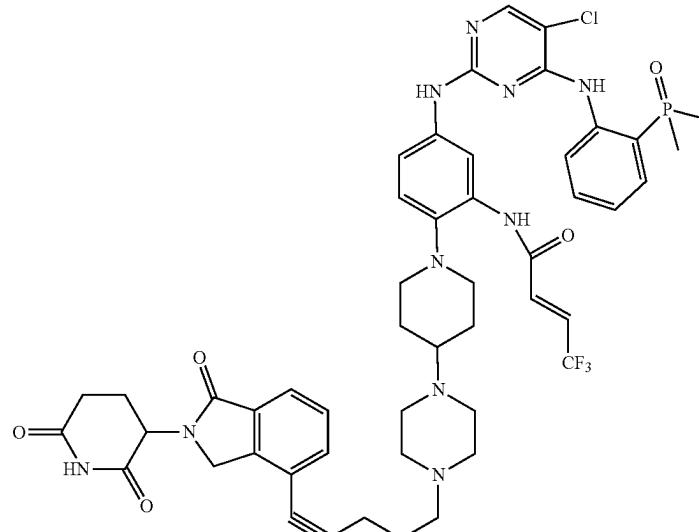
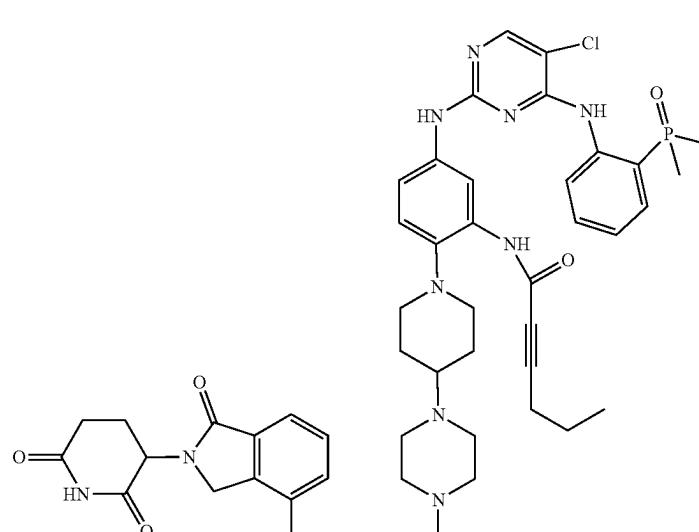
Compound No.	Structural formula	IC ₅₀ (nM)
D667		18.15
D668		21.16

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

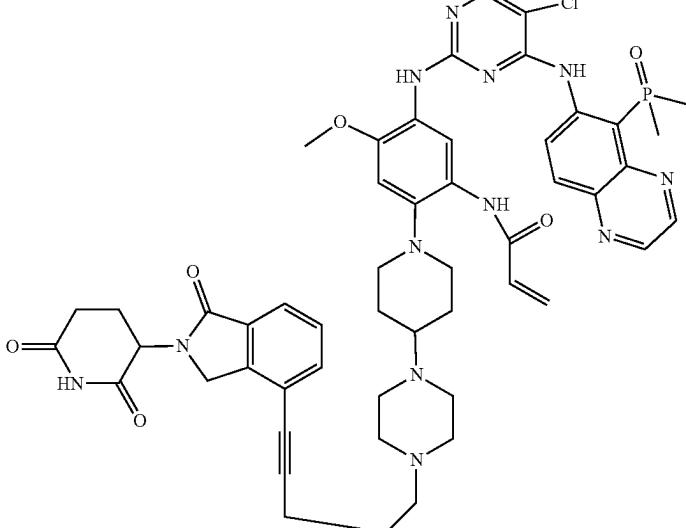
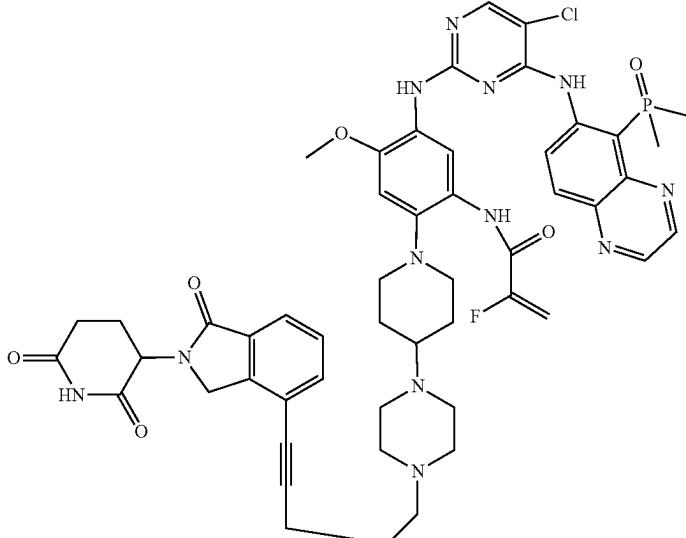
Compound No.	Structural formula	IC ₅₀ (nM)
D670		25.74
D671		14.51

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D672		15.05
D673		20.63

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

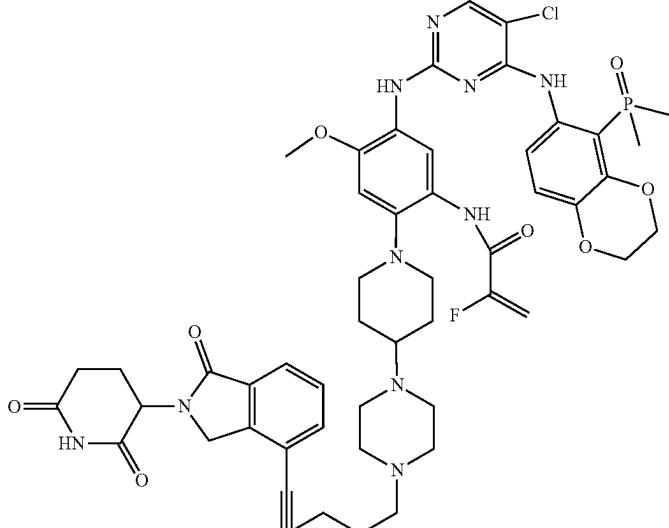
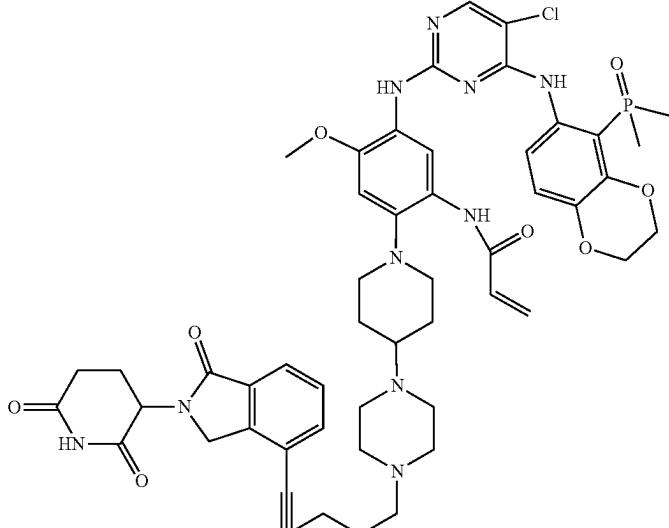
Compound No.	Structural formula	IC ₅₀ (nM)
D682		14.63
D683		22.26

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

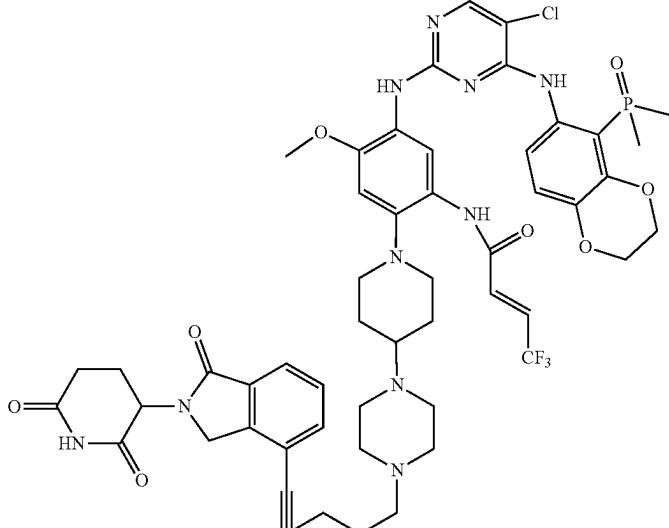
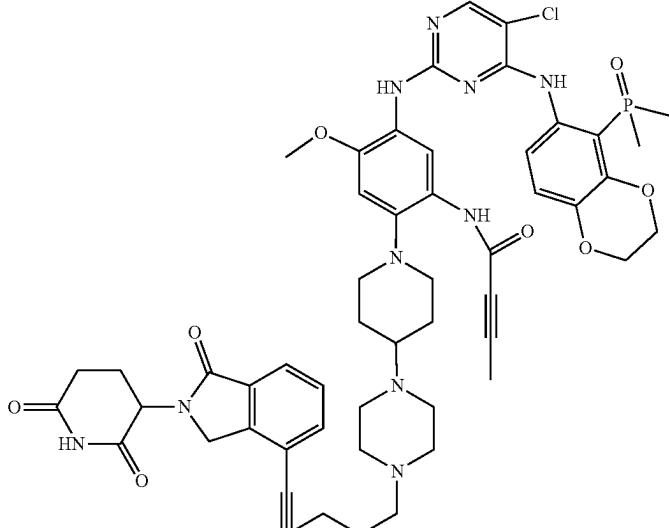
Compound No.	Structural formula	IC ₅₀ (nM)
D684		24.05
D685		22.47

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D741		10.17
D743		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

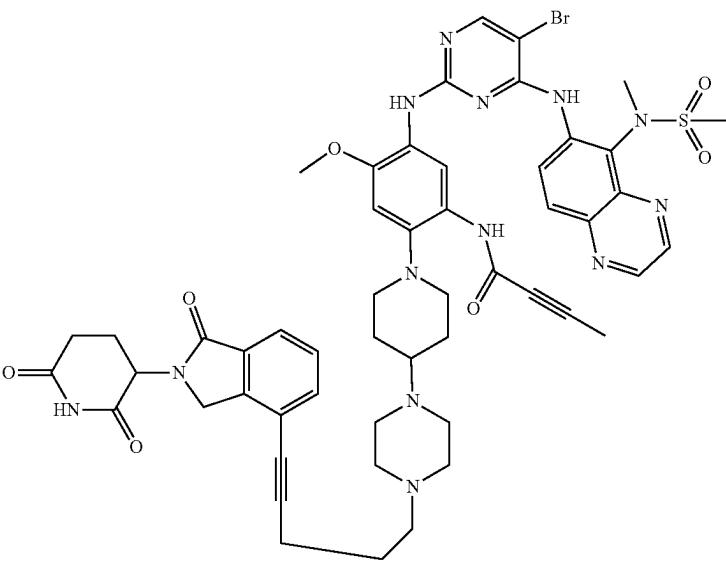
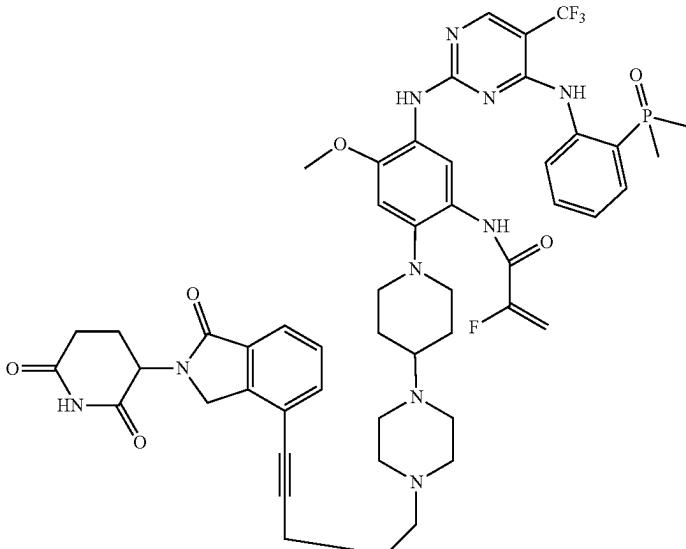
Compound No.	Structural formula	IC ₅₀ (nM)
D744		
D746		3.361

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

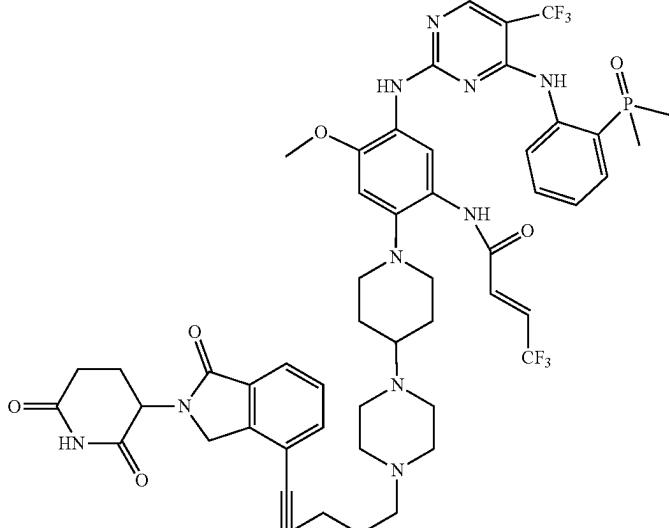
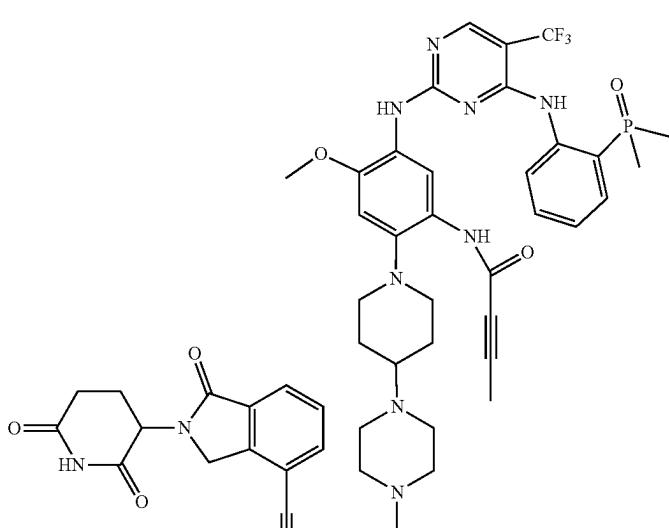
Compound No.	Structural formula	IC ₅₀ (nM)
D747		8.771
D748		7.757

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D755		
D756		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D757		
D758		

TABLE 1-continued

Compound No.	Structural formula	IC ₅₀ (nM)
D835		11.85
D845		16.92

TABLE 1-continued

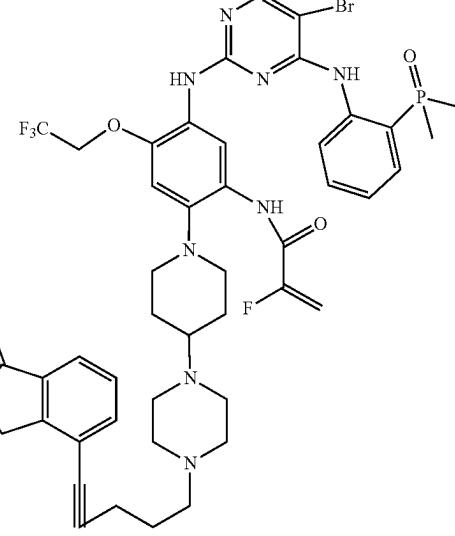
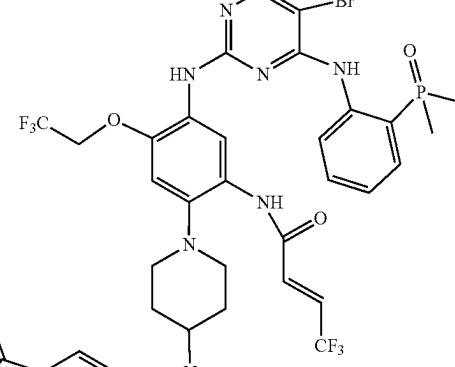
Compound No.	Structural formula	IC ₅₀ (nM)
D846		11.89
D847		16.26

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D856		27.43
D870		8.870

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D932		36.73
D933		12.29

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

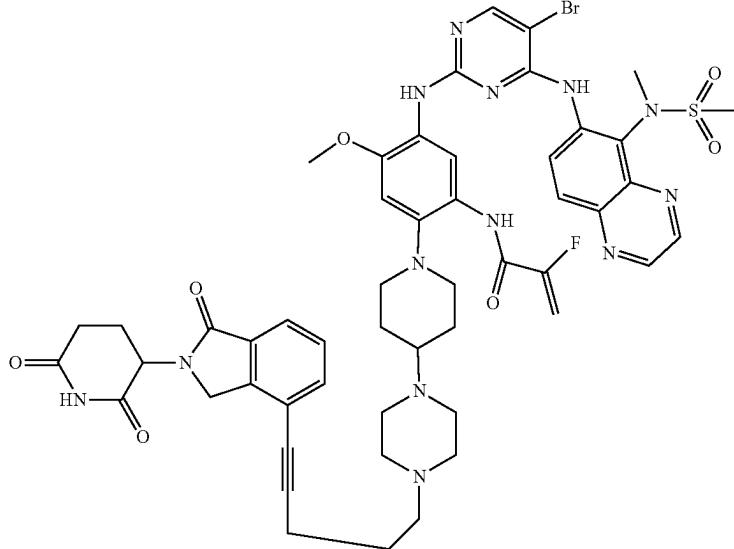
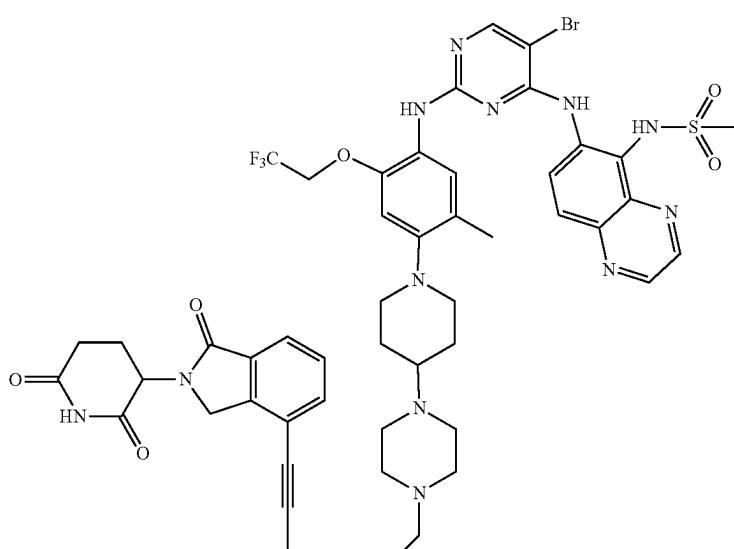
Compound No.	Structural formula	IC ₅₀ (nM)
D934		31.87
D966		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D967		
D968		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

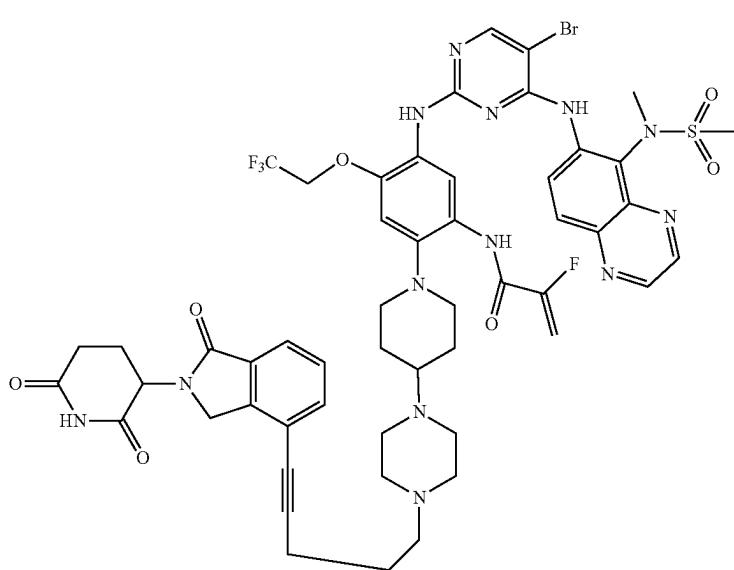
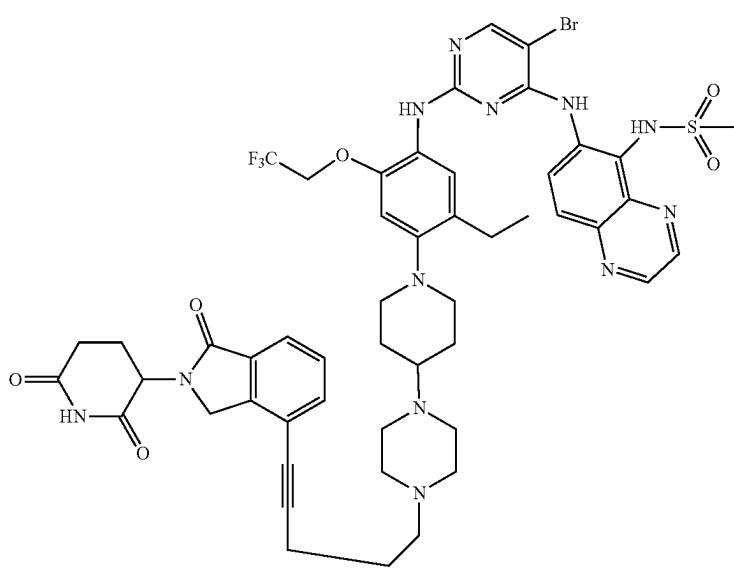
Compound No.	Structural formula	IC ₅₀ (nM)
D969		
D970		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
D971		
D972		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

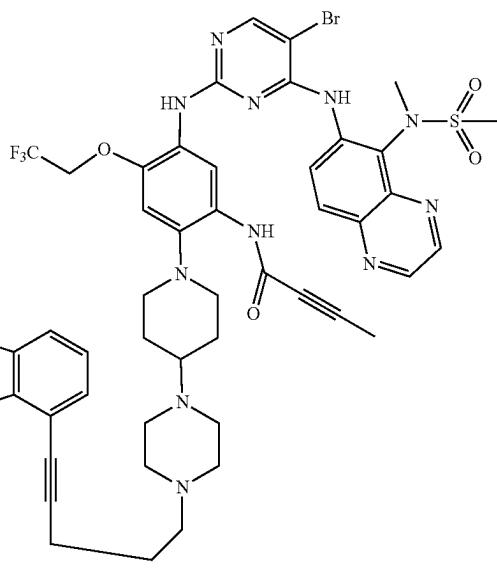
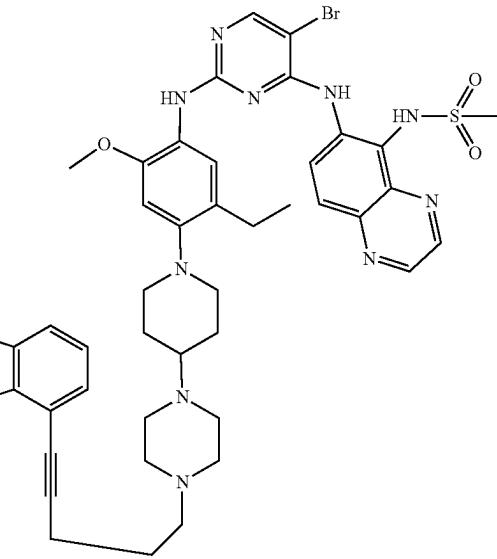
Compound No.	Structural formula	IC ₅₀ (nM)
D973		
D974		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

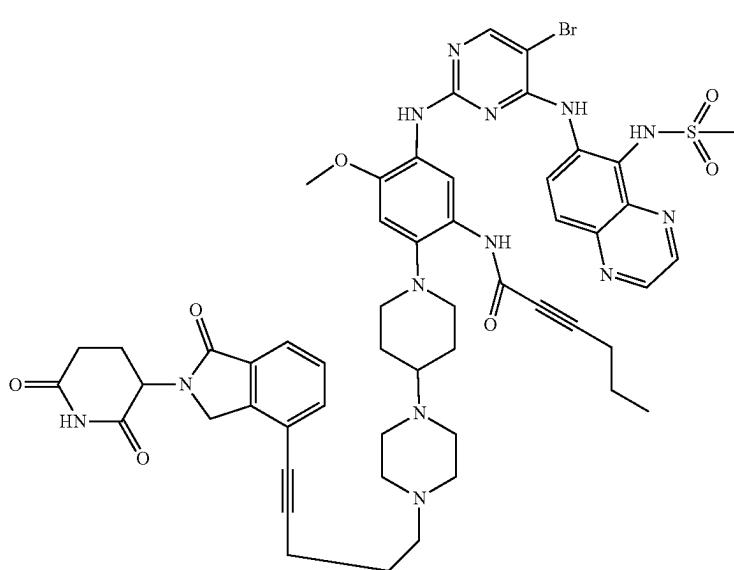
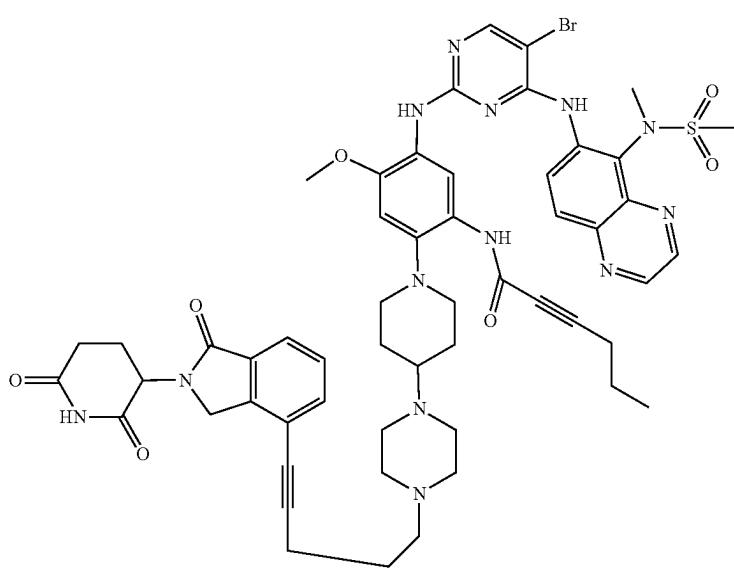
Compound No.	Structural formula	IC ₅₀ (nM)
D975		
D976		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

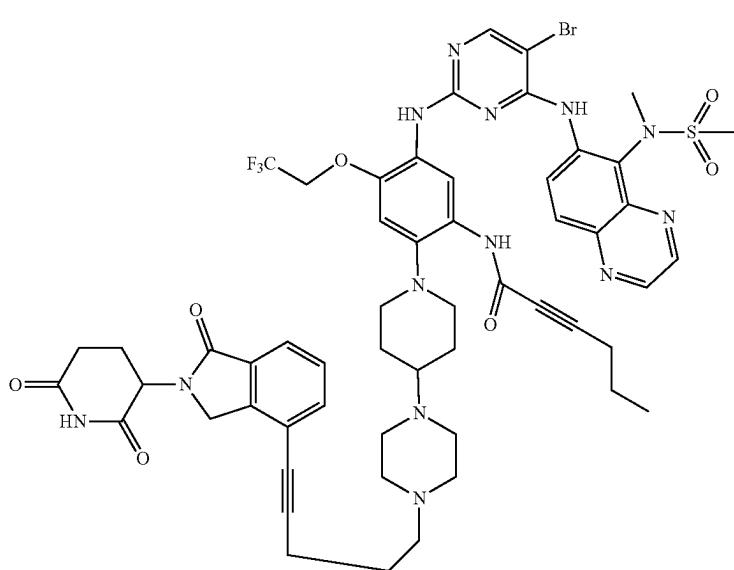
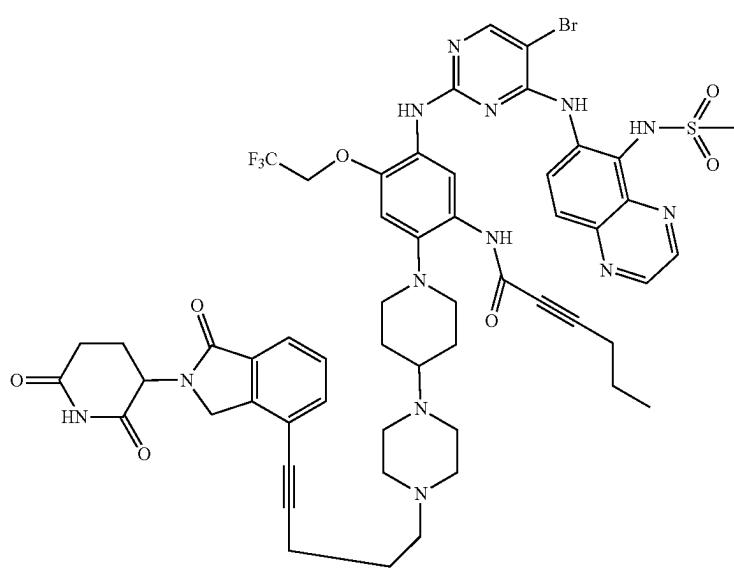
Compound No.	Structural formula	IC ₅₀ (nM)
D977		
D978		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

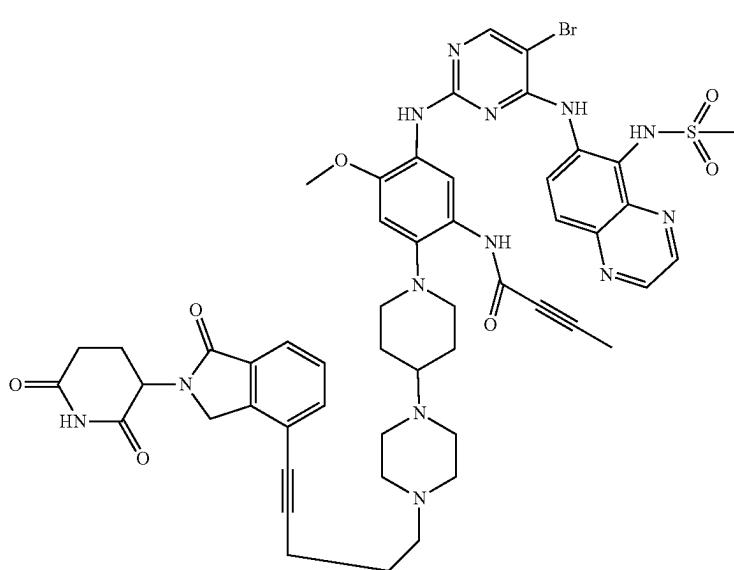
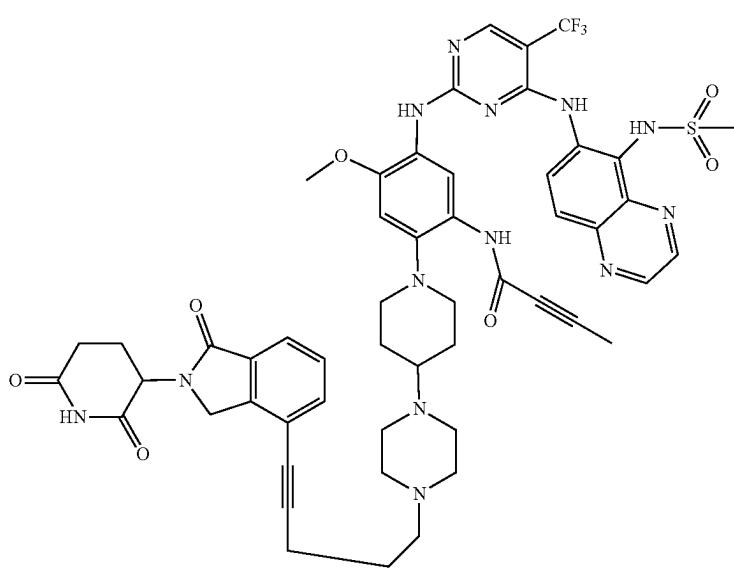
Compound No.	Structural formula	IC ₅₀ (nM)
D979		
D980		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

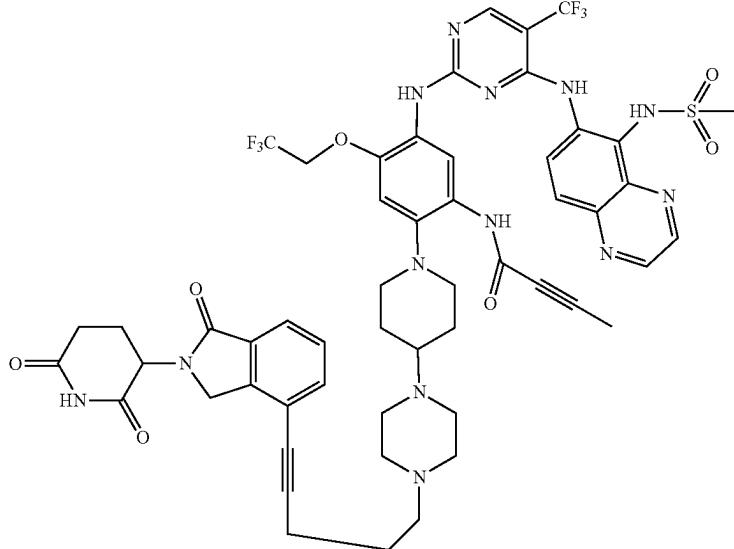
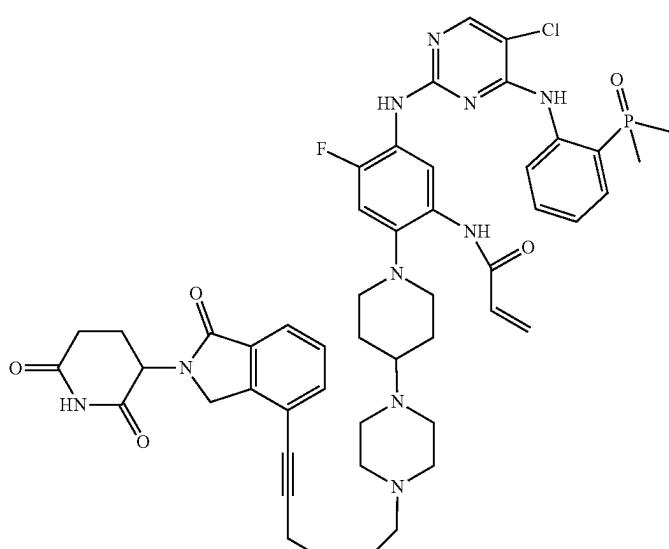
Compound No.	Structural formula	IC ₅₀ (nM)
D981		
D982		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

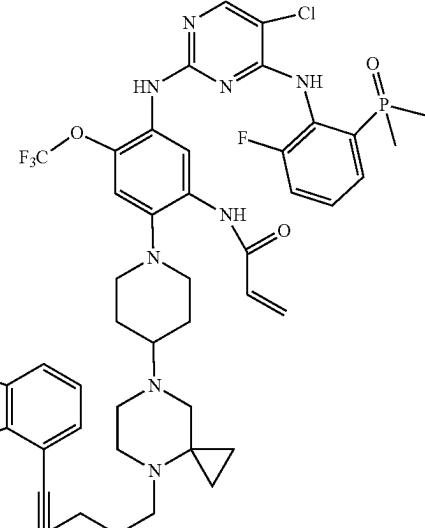
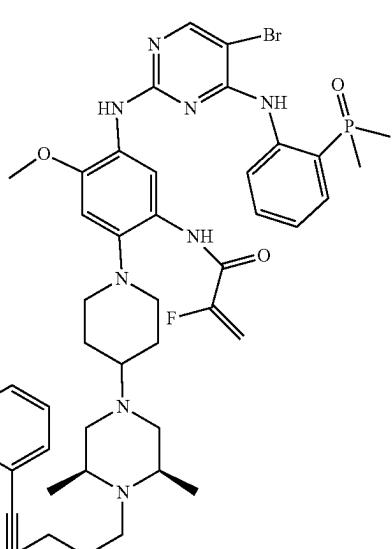
Compound No.	Structural formula	IC ₅₀ (nM)
D983		
D984		

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

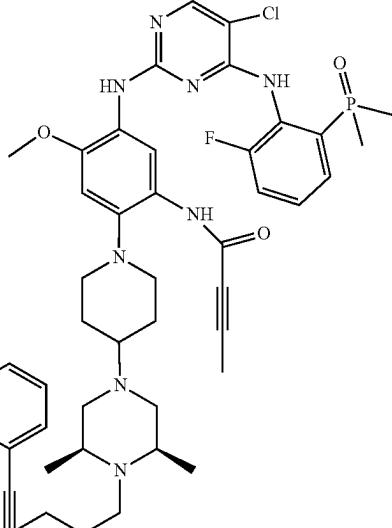
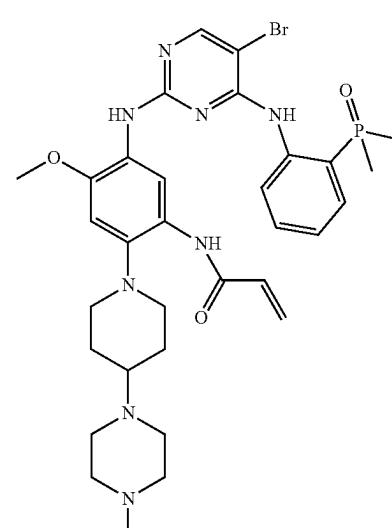
Compound No.	Structural formula	IC ₅₀ (nM)
D985		
Comparative compound L495		3742

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
Comparative compound L521		3048
Comparative compound L527		457.9

TABLE 1-continued

Antiproliferative activity of compounds on Ba/F3 (EGFR ^{L858R/T790M/C797S}) cells		
Compound No.	Structural formula	IC ₅₀ (nM)
Brigatinib		354.7
Osimertinib		1875

[0759] Conclusion: From the assay results in Table 1, it can be seen that the compounds of the present disclosure have better anti-proliferative activity on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells, and the anti-proliferative activity of most compounds is better than that of the positive drug Brigatinib. By comparing the representative compounds D058 and L521, it was found that the anti-proliferative activity of D058 on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells was significantly better than that of L521; by comparing the representative compounds D478 and L495, it was found that the anti-proliferative activity of D478 on Ba/F3 (EGFR^{L858R/T790M/C797S})

cells was significantly better than that of L495. It can be seen that the compound of the present disclosure, that is, the EGFR degrader, has potent anti-proliferative activity on Ba/F3 (EGFR^{L858R/T790M/C797S}) cells, and is superior to the anti-proliferative activity of its corresponding small molecule ligand, providing a strong basis for overcoming Osimertinib resistance.

Assay of H1975 (EGFR^{L858R/T790M}) Cell Activity

[0760] In order to further illustrate that the compounds of the present disclosure can also overcome the drug resistance

caused by EGFR T790M mutation, H1975 (EGFR^{L858R/T790M}) cells were used as the test cell line, and representative compounds D058 and D478 were selected to test the antiproliferative activity of the compounds of the present disclosure.

1. Assay Method

[0761] 1) H1975 (EGFR^{L858R/T790M}) cells were cultured according to the requirements of ATCC, incubated in an incubator at 37° C. and 5% CO₂, and analyzed by index; cells with viability of >90% can be used in the assay, and cells were seeded in a 384-well plate (PerkinElmer, 6007680) with 500 cells/well, 30 μL/well.

[0762] 2) A compound stock solution was prepared, and then diluted 3× to give a compound dilution. 30 nL of the compound dilution was added to a 384-well plate by Echo (Labcyte, Echo550). The cells were incubated in an incubator at 37° C. and 5% CO₂ for 72h.

[0763] 3) 30 μL of CTG was added to each well, and the 384-well plate was shaken on a Plate shaker (QILIN-BEIER, QB-9002). The 384-well plate was incubated at 37° C. and 5% CO₂ in the dark for 30 min, and the chemiluminescence value was read by Envision (PerkinElmer, EnVision 2104).

2. Data Analysis

[0764] The percent inhibition rate (% inhibition) was calculated by the following formula

$$\text{Inhibition}(\%) = \left[1 - \frac{\overline{LUM}_{\text{cmpd}} - \overline{LUM}_{\text{positive}}}{\overline{LUM}_{\text{vehicle}} - \overline{LUM}_{\text{positive}}} \right] \times 100$$

[0765] $\overline{LUM}_{\text{cmpd}}$: Luminescence value of assay compound.

[0766] $\overline{LUM}_{\text{positive}}$: Average LUM value of positive drug with a concentration of 10 μM.

[0767] $\overline{LUM}_{\text{vehicle}}$: Average LUM value of negative control group without drug treatment.

[0768] The nonlinear regression curve (dose response-variable slope) between the value of inhibition rate (%) and the logarithm of compound concentration was fitted with graphpad prism 8.0, the effect dose curve of compound was drawn, and the IC₅₀ value was calculated.

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\log IC_{50} - X) * \text{Hill-Slope})})$$

[0769] X-axis: logarithm of compound concentration; Y axis: inhibition rate (inhibition).

3. Assay Result

[0770] IC₅₀ values of the antiproliferative activity of the representative compounds of the present disclosure on H1975 (EGFR^{L858R/T790M}) cells are shown in the table 2.

TABLE 2

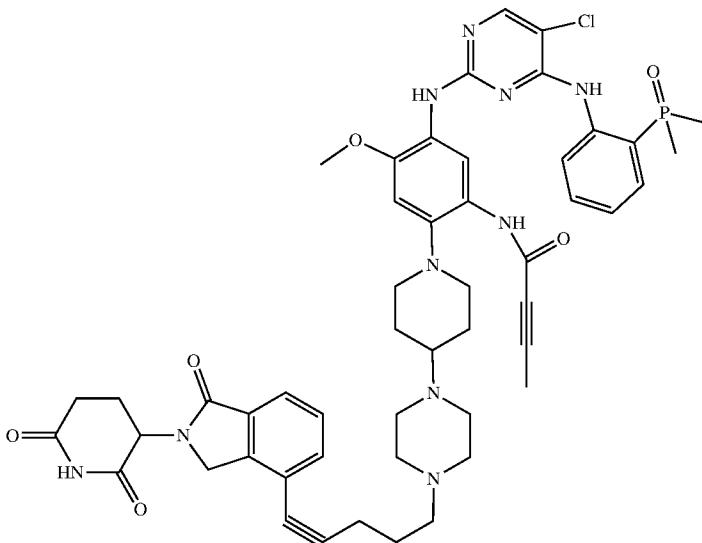
Antiproliferative activity of compounds on H1975 (EGFR ^{L858R/T790M}) cells		
Compound No.	Structural formula	IC ₅₀ (nM)
D058		14.60

TABLE 2-continued

Antiproliferative activity of compounds on H1975 (EGFR^{L858R/T790M}) cells

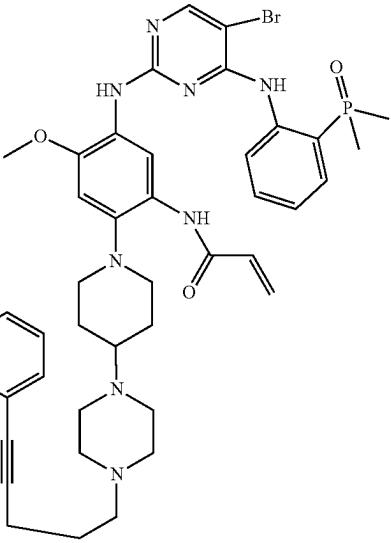
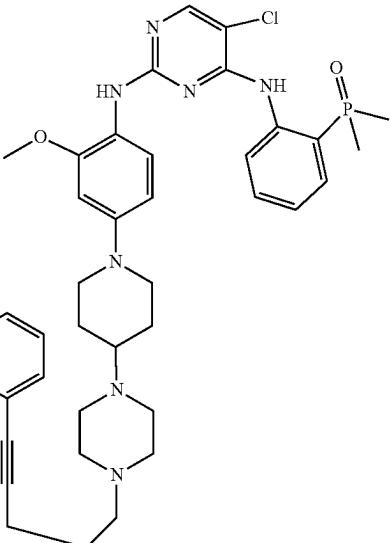
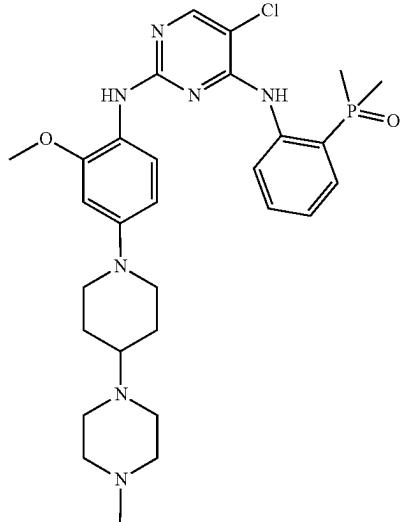
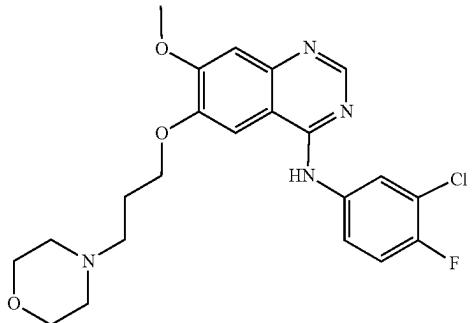
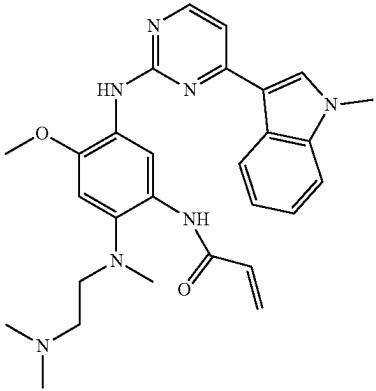
Compound No.	Structural formula	IC ₅₀ (nM)
D478		17.64
Comparative compound C126		1388

TABLE 2-continued

Antiproliferative activity of compounds on H1975 (EGFR^{L858R/T790M}) cells

Compound No.	Structural formula	IC ₅₀ (nM)
Brigatinib		747.0
Gefitinib		>10000
Osimertinib		10.73

[0771] Conclusion: From the assay results in Table 2, it can be seen that the representative compounds D058 and D478 of the present disclosure have better anti-proliferative activity against H1975 (EGFR^{L858R/T790M}), and their anti-proliferative activities are significantly better than that of the comparative compound C126. It can be seen that the compound of the present disclosure, that is, the EGFR degrader, can overcome the drug resistance caused by the EGFR T790M mutation.

Assay of Activity of Compounds for Inducing EGFR^{L858R/T790M/C797S} and EGFR^{Del19/T790M/C797S} Protein Degradation

[0772] In order to verify that the compounds of the present disclosure can induce the degradation of EGFR, Ba/F3 (EGFR^{L858R/T790M/C797S}) and Ba/F3 (EGFR^{Del19/T790M/C797S}) cells were used as test cell lines, and representative compounds D058, D078 and D552 were selected to study the mechanism of action of the compounds and observe their effects on the protein levels of EGFR^{L858R/T790M/C797S} and EGFR^{Del19/T790M/C797S}.

(1) Cell Culture:

[0773] Ba/F3 (EGFR^{L858R/T790M/C797S}) and Ba/F3 (EGFR^{Del19/T790M/C797S}) cells were cultured according to the culture conditions recommended by ATCC, and analyzed by index.

[0774] Complete medium: 1640 medium, 10% FBS, 1× glutamine, 1× penicillin-streptomycin.

[0775] Culture conditions: incubated at 37° C., 95% air, 5% CO₂ incubator.

(2) Compound Stock Solution: 10 mM Stock Solution in DMSO, Stored at -20° C.

(3) Preparation of Cell Suspension:

[0776] The cells in the cell culture bottle were collected, and the cells with viability of >90% can be used in the assay. Cells were seeded in a 96-well plate with 40 μL cells, 1*10⁵ cells/well.

(4) Compound Treatment:

[0777] The compounds were serially diluted 3× with DMSO, with the starting concentrations of the compounds being 1.0 mM (EGFR^{L858R/T790M/C797S} assay) and 10 mM (EGFR^{Del19/T790M/C797S} assay), respectively, into 10 concentrations to prepare working solutions.

(5) Compound was Pipetted into the 96-Well Plate to Treat Cells in a 37° C., 95% Air, 5% CO₂ Incubator for 24h.

(6) Detection:

[0778] 1) 1 μg/mL EGF stimulated cells for 10 min;

[0779] 2) After the compound treatment was completed, lysis buffer was added to lyse cells; 10 μL of cell lysate was transferred to the 384-well plate; in addition, control lysate, negative control and 5 μL of acceptor mix were added to the 384-well plate; The plate was shaken on a shaker for 1-2 min;

[0780] 3) 5 μL of donor mix was added to each well; the 384-well plate was sealed, shaken on a shaker for 1-2 min, and left in the dark at room temperature overnight; then the plate was read with ELISA reader.

(7) Data Analysis:

[0781] Alpha counts were fitted by logarithmic treatment of compound concentration with Graphpad Prism 8.0.

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\log IC_{50}} - X) * \text{HillSlope}))$$

[0782] X: logarithm of compound concentration; Y: Alpha Counts.

(8) Assay Result:

[0783] The effects of the compounds of the present disclosure on the protein levels of mutant EGFR^{L858R/T790M/C797S} and EGFR^{Del19/T790M/C797S} are shown in FIGS. 1, 2 and 3.

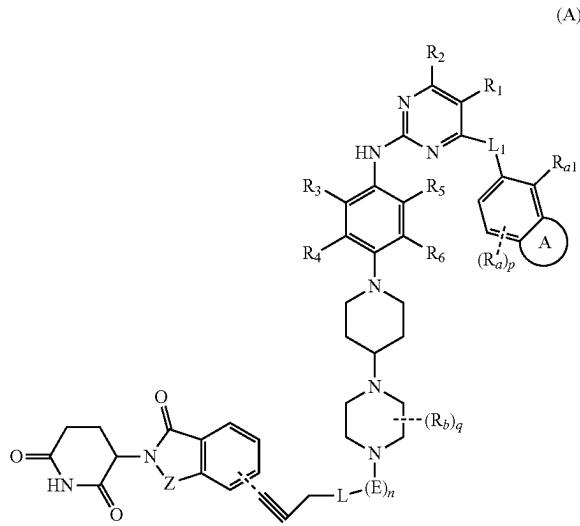
[0784] As shown in FIG. 1, the assay results show that in the range of 1 nM to 1000 nM, as the concentration of compound D078 increases, the level of EGFR^{L858R/T790M/C797S} protein decreases. Compound D078 significantly reduces the level of EGFR^{L858R/T790M/C797S} protein with DC₅₀ of 84.74 nM, proving that compound D078 has a significant degradation effect on EGFR^{L858R/T790M/C797S} protein in a dose-dependent manner; while Osimertinib and Brigatinib have no degradation effect on EGFR^{L858R/T790M/C797S} protein.

[0785] As shown in FIG. 2, the assay results show that in the range of 1 nM to 1000 nM, as the concentration of compound D552 increases, the level of EGFR^{L858R/T790M/C797S} protein decreases. Compound D552 significantly reduces the level of EGFR^{L858R/T790M/C797S} protein with DC₅₀ of 117.1 nM, proving that compound D552 has a significant degradation effect on EGFR^{L858R/T790M/C797S} protein in a dose-dependent manner; while the comparative compound L527 has no degradation effect on EGFR^{L858R/T790M/C797S} protein.

[0786] As shown in FIG. 3, the assay results show that in the range of 1 nM to 10000 nM, as the concentration of compound D058 or D552 increases, the level of EGFR^{Del19/T790M/C797S} protein decreases. Compounds D058 and D552 significantly decrease the levels of EGFR^{Del19/T790M/C797S} protein, respectively, with DC₅₀ of 25.06 nM and 29.71 nM respectively, proving that compounds D058 and D552 respectively have significant degradation effects on EGFR^{Del19/T790M/C797S} protein in a dose-dependent manner, while Osimertinib has no degradation effect on EGFR^{Del19/T790M/C797S} protein.

[0787] Conclusion: The compound of the present disclosure can significantly induce the degradation of EGFR^{Del19/T790M/C797S} and EGFR^{L858R/T790M/C797S} proteins in cells in a dose-dependent manner.

1. A compound of formula (A), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof:



wherein

— represents that the point of attachment to the rest of the molecule can be located at an available point of a ring where it is located;

Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;

R₁ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₂ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₃ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OC₁₋₆ alkyl, —OC₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

R₄ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₅ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

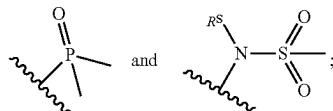
R₆ is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, —NH—C(O)—CR=CR' and —NH—C(O)—C≡CR';

wherein R, R' and R'' are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;

R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

Z is CH₂, C=O, C=S or C=NH;

R_{a1} is selected from



R_s is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R_a is selected from H, halogen, —OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;

alternatively, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C₄₋₁₀ cycloalkyl, a 5-8 membered heterocyclyl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;

R_b is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C₃₋₁₀ cycloalkyl, a 3-10 membered heterocyclyl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;

R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocyclyl;

L is selected from a chemical bond, —O—, —NR #-, —CR #R #-, —S—, —SO— and —S(O)₂—;

L₁ is selected from a chemical bond, —O—, —NR #-, —CR #R #-, —S—, —SO— and —S(O)₂—;

E is selected from a chemical bond and —CR #R ##;

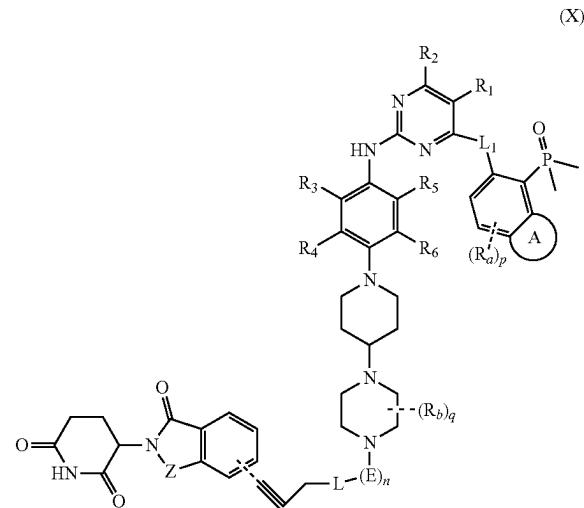
wherein R # and R ## are independently selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4, or 5.

2. A compound of formula (X), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof:



wherein

— represents that the point of attachment to the rest of the molecule can be located at an available point of a ring where it is located;

Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;

R₁ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₂ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₃ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OC₁₋₆ alkyl, —OC₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

R₄ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₅ is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are

each optionally substituted with 0, 1, 2, 3, 4 or 5 R*, as long as the valence permits;

R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

Z is CH₂, C=O, C=S or C=NH;

R_a is selected from H, halogen, —OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c;

alternatively, two R_a on the same carbon atom or on different carbon atoms are taken together to form a C₄₋₁₀ cycloalkyl, a 5-8 membered heterocyclyl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;

R_b is selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C₃₋₁₀ cycloalkyl, a 3-10 membered heterocyclyl, a C₆₋₁₀ aryl, or a 5-10 membered heteroaryl;

R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocyclyl;

L is selected from a chemical bond, —O—, —NR #-, —CR #R #-, —S—, —SO— and —S(O)₂—;

L₁ is selected from a chemical bond, —O—, —NR #-, —CR #R #-, —S—, —SO— and —S(O)₂—;

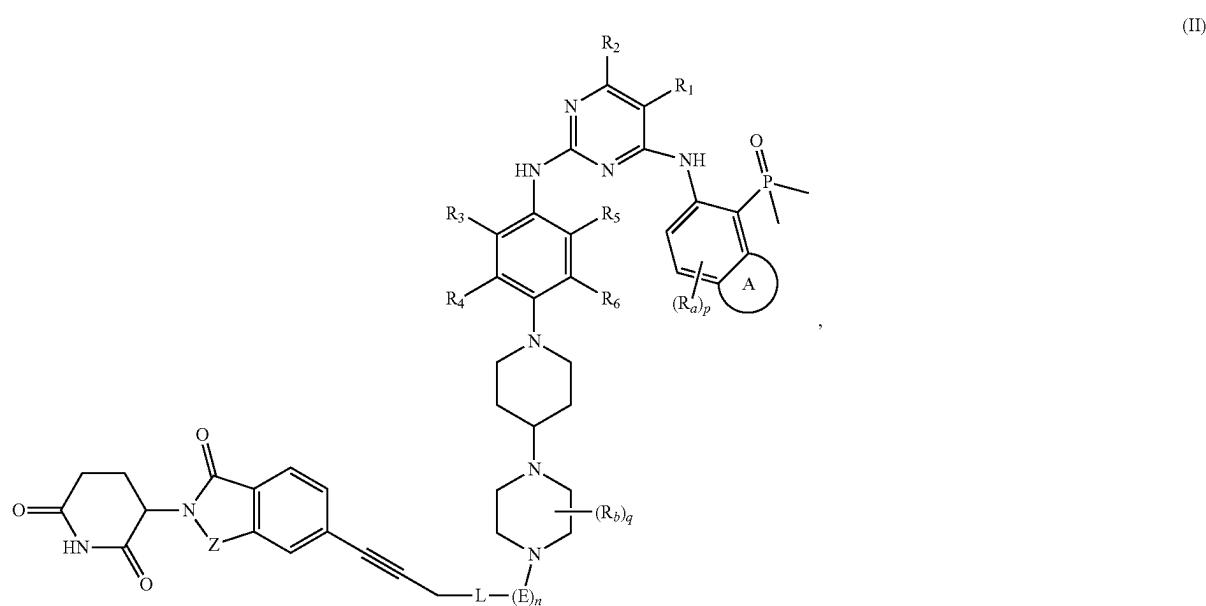
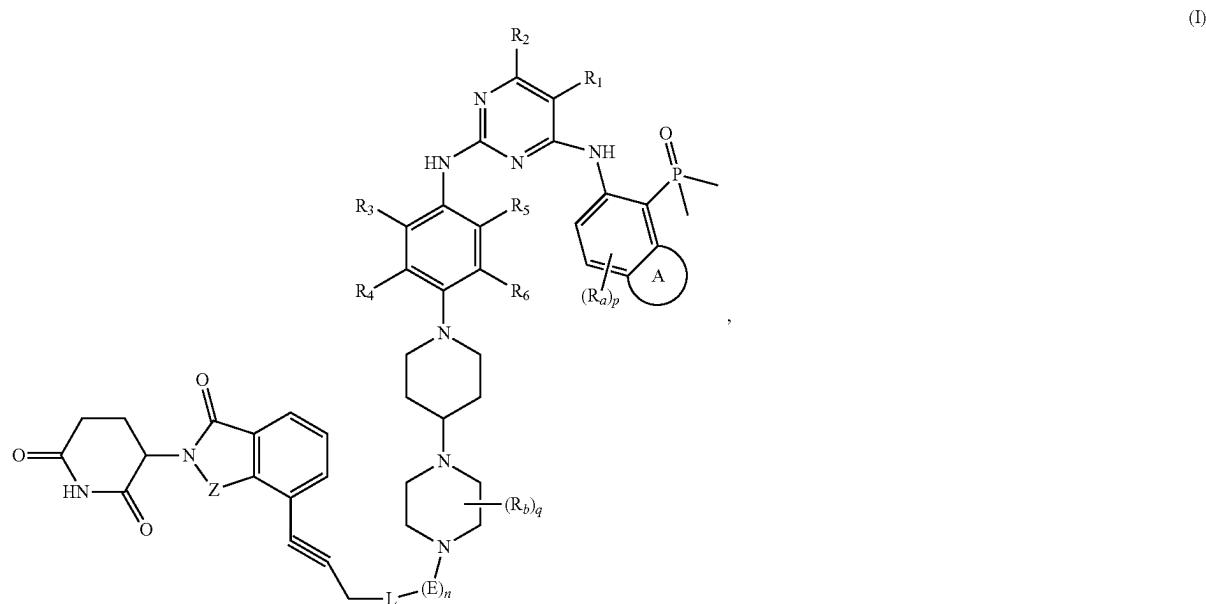
E is selected from a chemical bond and —CR #R ##-, wherein R # and R ## are independently selected from H, halogen, —OH, —NH₂, —CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4;

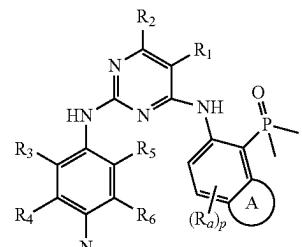
n is 0, 1, 2, 3, 4, or 5.

3. The compound of claim 2, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has the following general structure:

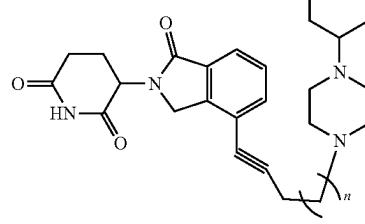
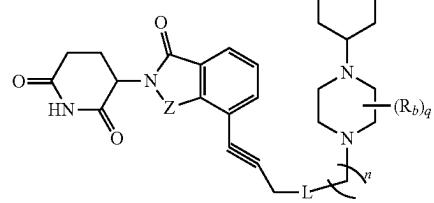
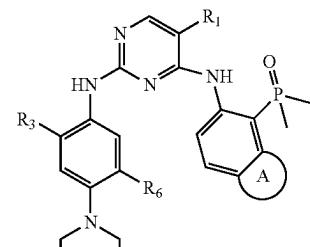


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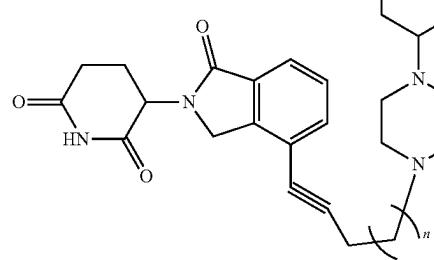
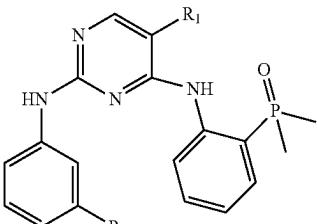
(III)



(IV)

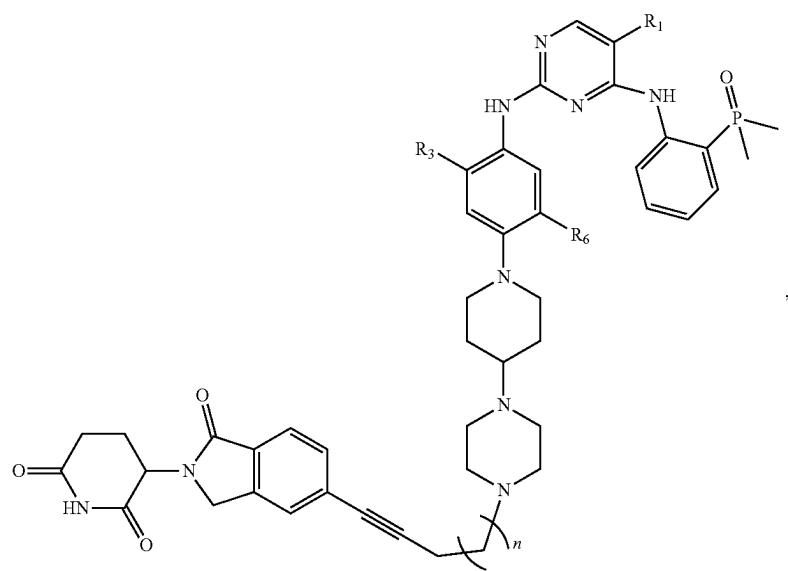


(V)

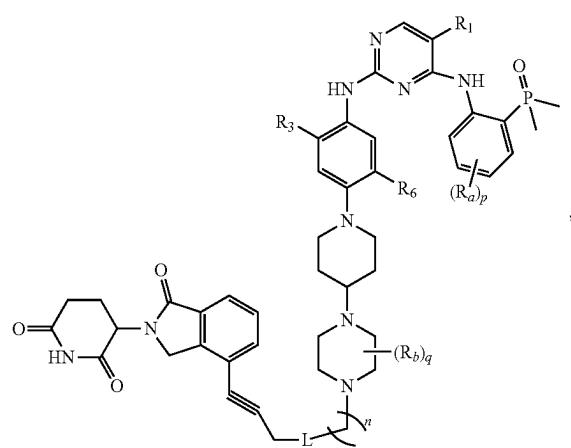


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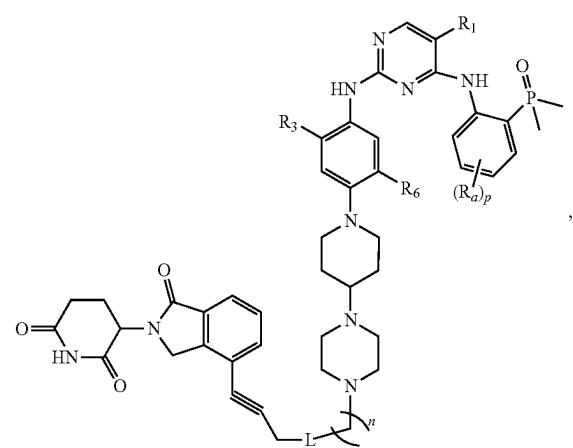
(VI)



(VII)

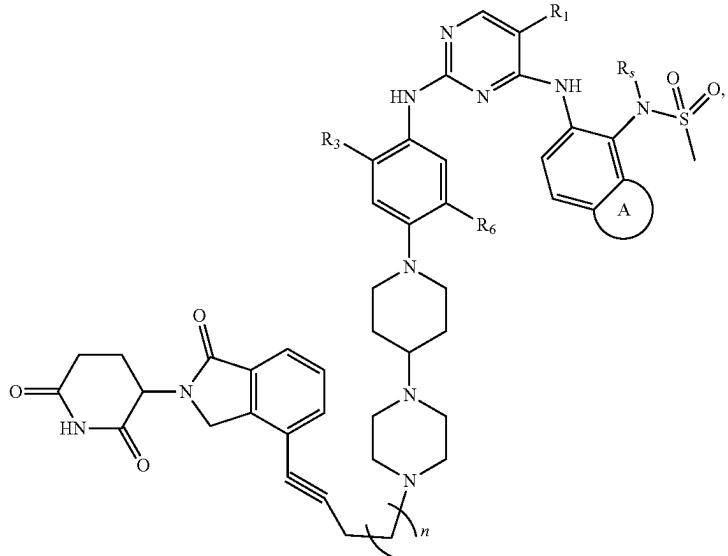


(VIII)



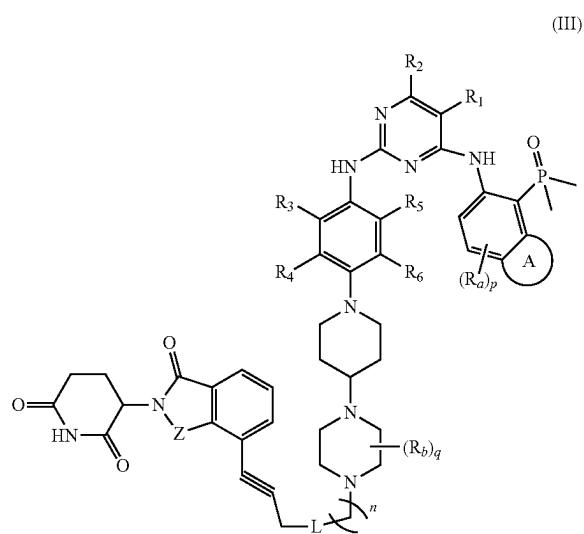
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(IX)



wherein each group is as defined in claim 2.

4. The compound of claim 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, which has a structure of formula (III):



wherein

Ring A is absent, or is selected from C_{4-10} cycloalkyl, 5-8 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

R_1 is selected from H, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

R_2 is selected from H, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

R_3 is selected from H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

R_4 is selected from H, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

R_5 is selected from H, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;

wherein R, R' and R'' are each independently selected from H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2, 3, 4 or 5 R^* , as long as the valence permits;

R^* is selected from H, halogen, $-OR_c$, $-NR_cR_d$, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

Z is CH_2 , $C=O$, $C=S$ or $C\equiv NH$;

R_a is selected from H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-CN$, $-NR_cR_d$, $-NH(CH_2)_{0-5}R_c$ and $-NHC(O)(CH_2)_{0-5}R_c$;

R_b is selected from H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

alternatively, two R_b on the same carbon atom or on different carbon atoms are taken together to form a C_{3-10} cycloalkyl or a 3-10 membered heterocyclyl;

R_c is selected from H, $-OH$, $-NH_2$, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

R_d is selected from H, $-OH$, $-NH_2$, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl;

alternatively, R_c and R_d are taken together with the N atom to which they are attached to form 3-10 membered heterocyclyl;

L is selected from a chemical bond, —O—, —NR #-, —S—, —SO— and —S(O)₂—; wherein R # is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl; p is 0, 1, 2, 3, or 4; q is 0, 1, 2, 3, or 4; n is 0, 1, 2, 3, 4, or 5.

5. The compound of claim 4, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has any one of the following definitions:

i) wherein:

Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R₁ is selected from H, halogen and C₁₋₆ haloalkyl;

R₂ is selected from H and halogen;

R₃ is selected from H, halogen, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl;

R₄ is selected from H and halogen;

R₅ is selected from H and halogen;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'; wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 0, 1, 2 or 3 R*, as long as the valence permits;

R* is selected from H, halogen, —OR_c, —NR_cR_d, —CN,

C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl;

Z is selected from CH₂, C=O and C=S;

R_a is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH

(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c; R_b is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; alternatively, two R_b on the same carbon atom are taken together to form a C₃₋₇ cycloalkyl or a 5-6 membered heterocyclyl;

R_c is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl,

C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R_d is selected from H, —OH, —NH₂, halogen, C₁₋₆ alkyl,

C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl; or R_c and R_d are taken together with the N atom to which they are attached to form 3-7 membered heterocyclyl;

L is selected from a chemical bond, —O—, —S— and —NR #;

wherein R # is selected from H, halogen, C₁₋₄ alkyl and

C₁₋₄ haloalkyl;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

n is 1, 2, 3, 4 or 5;

ii) wherein:

Ring A is absent, or Ring A is selected from a 5-6 membered heteroaryl and a 5-6 membered heterocyclyl;

R₁ is selected from halogen and C₁₋₄ haloalkyl;

R₂ is H;

R₃ is selected from H, halogen, —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl;

R₄ is H;

R₅ is H;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'; wherein R is selected from H, halogen, C₁₋₄ alkyl and C₆₋₁₀ aryl, wherein the C₁₋₄ alkyl and C₆₋₁₀ aryl are each optionally substituted with 0, 1, or 2 R*;

R' and R" are each independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl, wherein the C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl are each optionally substituted with 0, 1 or 2 R*, as long as the valence permits;

R* is selected from H, halogen, —OR_c, —NR_cR_d, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl, C₆₋₁₀ aryl and 5-6 membered heteroaryl;

Z is CH₂ or C=O;

R_a is selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, —CN, —NR_cR_d, —NH(CH₂)₀₋₅R_c and —NHC(O)(CH₂)₀₋₅R_c, alternatively H, halogen, —NR_cR_d and —NH(CH₂)₀₋₅R_c, still alternatively H and halogen;

R_b is selected from H and C₁₋₄ alkyl;

alternatively, two R_b on the same carbon atom are taken together to form a C₃₋₇ cycloalkyl group;

R_c is selected from H, —OH, —NH₂, halogen, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, alternatively H, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl and 3-10 membered heterocyclyl, still alternatively H and C₁₋₄ alkyl;

R_d is selected from H, —OH, —NH₂, halogen, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, alternatively H, C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl and 3-10 membered heterocyclyl, still alternatively H and C₁₋₄ alkyl;

or R_c and R_d are taken together with the N atom to which they are attached to form 5-6 membered heterocyclyl:

L is selected from a chemical bond and —O—:

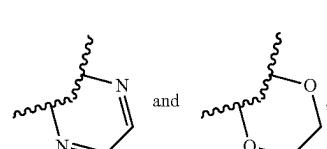
p is 0, 1, or 2;

q is 0, 1, or 2;

n is 1, 2, 3, 4 or 5; and

iii) wherein:

Ring A is absent, or Ring A is selected from



R₁ is selected from Cl, Br and —CF₃;

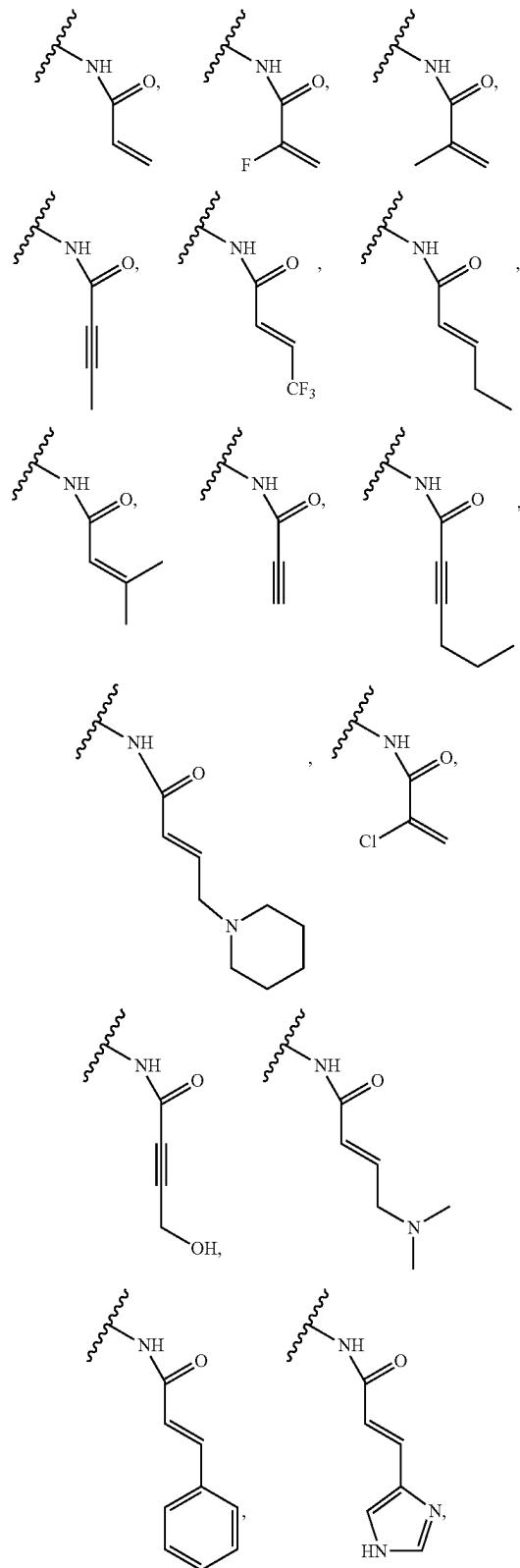
R₂ is H;

R₃ is selected from H, F, Cl, —OCH₃ and —OCF₃; alternatively, R₃ is selected from H, F, —OCH₃ and —OCF₃;

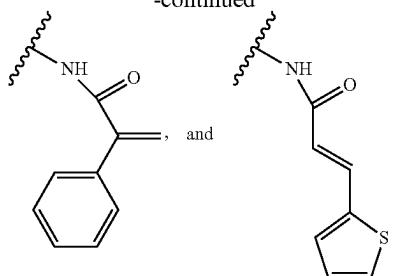
R₄ is H;

R₅ is H;

R_6 is selected from



-continued



Z is CH_2 or $\text{C}=\text{O}$;

R_a is selected from H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-\text{CN}$, $-\text{NR}_c\text{R}_d$, $-\text{NH}(\text{CH}_2)_{0-5}\text{R}_c$ and $-\text{NHC(O)}(\text{CH}_2)_{0-5}\text{R}_c$, alternatively H, F, C_1 , $-\text{NR}_c\text{R}_d$ and $-\text{NH}(\text{CH}_2)_{0-5}\text{R}_c$, still alternatively H and F;

R_b is selected from H and $-\text{CH}_3$;

alternatively, two R_b on the same carbon atom are taken together to form a cyclopropyl group;

R_c is selected from H, $-\text{OH}$, $-\text{NH}_2$, halogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, 5-6 membered heterocycl, C_6-10 aryl and 5-6 membered heteroaryl, alternatively H, C_{1-4} alkyl, C_{3-7} cycloalkyl and 5-6 membered heterocycl, still alternatively H and C_{1-4} alkyl;

R_d is selected from H, $-\text{OH}$, $-\text{NH}_2$, halogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, 5-6 membered heterocycl, C_6-10 aryl and 5-6 membered heteroaryl, alternatively H, C_{1-4} alkyl, C_{3-7} cycloalkyl and 5-6 membered heterocycl, still alternatively H and C_{1-4} alkyl:

L is selected from a chemical bond and $-\text{O}-$;

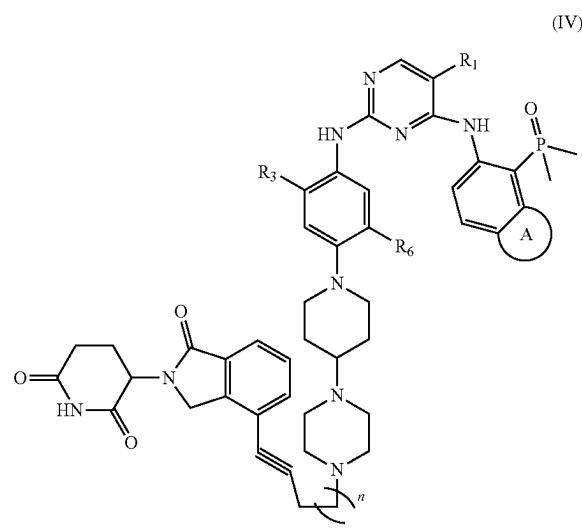
p is 0 or 1;

q is 0, 1, or 2;

n is 2, 3 or 4.

6-7. (canceled)

8. The compound of claim 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, which has a structure of formula (IV):



wherein

Ring A is absent, or is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl;

R₁ is selected from H, halogen and C₁₋₄ haloalkyl, alternatively H and halogen;

R₃ is selected from H, halogen, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively H and —OC₁₋₆ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-10 membered heterocyclyl and C₃₋₁₀ cycloalkyl, wherein the C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-10 membered heterocyclyl and C₃₋₁₀ cycloalkyl are each optionally substituted with 0, 1, 2 or 3 R*;

R* is selected from H, halogen, —OH, —NH₂, —CN, 3-10 membered heterocyclyl, and C₃₋₁₀ cycloalkyl;

n is 1, 2, 3 or 4.

9. The compound of claim 8, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has any one of the following definitions:

i) wherein:

Ring A is absent, or Ring A is selected from 5-10 membered heteroaryl and 5-8 membered heterocyclyl;

R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen;

R₃ is selected from H, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively H and —OC₁₋₆ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R, R' and R" are each independently selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl, wherein the C₁₋₆ alkyl and C₁₋₆ haloalkyl are each optionally substituted with 0, 1 or 2 R*;

R* is selected from H, halogen, —OH and 3-10 membered heterocyclyl;

n is 1, 2, 3 or 4;

ii) wherein:

Ring A is absent, or Ring A is selected from 5-6 membered heteroaryl and 5-6 membered heterocyclyl;

R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen;

R₃ is selected from H, —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl, alternatively H and —OC₁₋₄ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R is selected from H, halogen and C₁₋₄ alkyl;

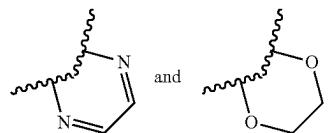
R' and R" are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl, wherein the C₁₋₄ alkyl and C₁₋₄ haloalkyl are each optionally substituted with 0, 1 or 2 R*;

R* is selected from H, halogen, —OH and 5-6 membered heterocyclyl;

n is 1, 2, 3 or 4;

iii) wherein:

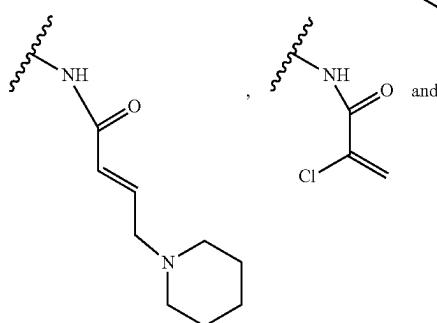
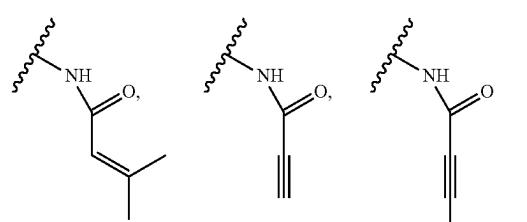
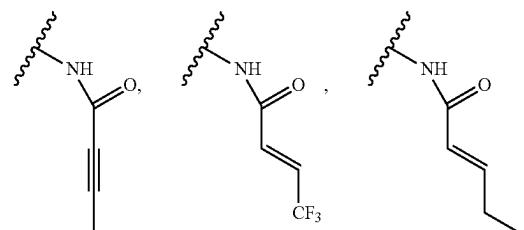
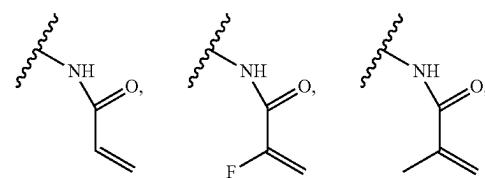
Ring A is absent, or Ring A is selected from

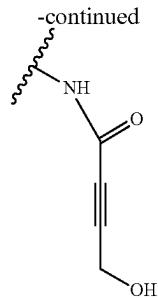


R₁ is selected from Cl, Br and —CF₃, alternatively Cl and Br;

R₃ is selected from H and —OCH₃;

R₆ is selected from





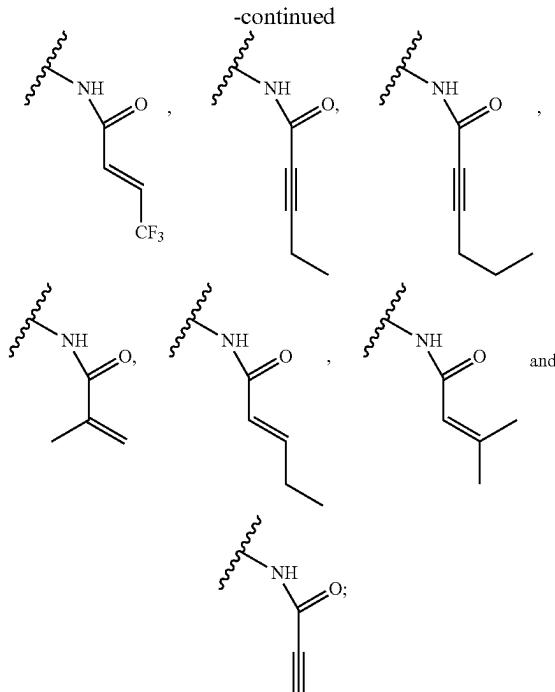
Ring A is absent, or Ring A is selected from 5-10 membered heteroaryl and 5-8 membered heterocycl; R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen; R₃ is selected from H, —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively H and —OC₁₋₆ alkyl; R₆ is selected from —NH—C(O)—CR=CR'R'' and —NH—C(O)—C≡CR'; wherein R, R' and R'' are each independently selected from H, F, C₁₋₆ alkyl and C₁₋₆ haloalkyl; n is 1, 2, 3, 4 or 5;

v) wherein:

Ring A is absent, or Ring A is selected from 5-6 membered heteroaryl and 5-6 membered heterocycl; R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen; R₃ is selected from H and —OC₁₋₄ alkyl; R₆ is selected from —NH—C(O)—CR=CR'R'' and —NH—C(O)—C≡CR'; wherein R is selected from H, F and C₁₋₄ alkyl; R' and R'' are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl; n is 1, 2, 3 or 4;

vi) wherein:

Ring A is absent, or Ring A is selected from



n is 1, 2 or 3;
vii) wherein:

Ring A is selected from 5-10 membered heteroaryl and 5-8 membered heterocycl;

R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen;

R₃ is selected from —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl, alternatively —OC₁₋₆ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R'' and —NH—C(O)—C≡CR';

wherein R, R' and R'' are each independently selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

n is 1, 2 or 3;

viii) wherein:

Ring A is selected from 5-6 membered heteroaryl and 5-6 membered heterocycl;

R₁ is selected from halogen and C₁₋₄ haloalkyl, alternatively halogen;

R₃ is —OC₁₋₄ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R'' and —NH—C(O)—C≡CR';

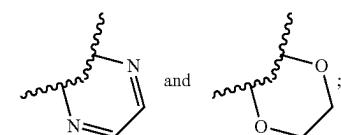
wherein R is selected from H and halogen;

R' and R'' are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

n is 1, 2 or 3;

ix) wherein:

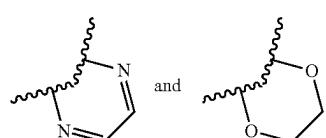
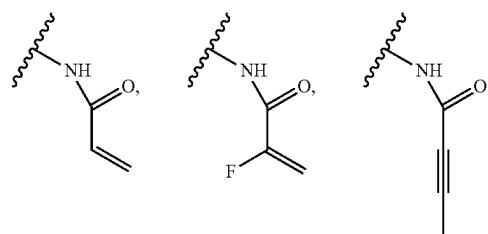
Ring A is selected from



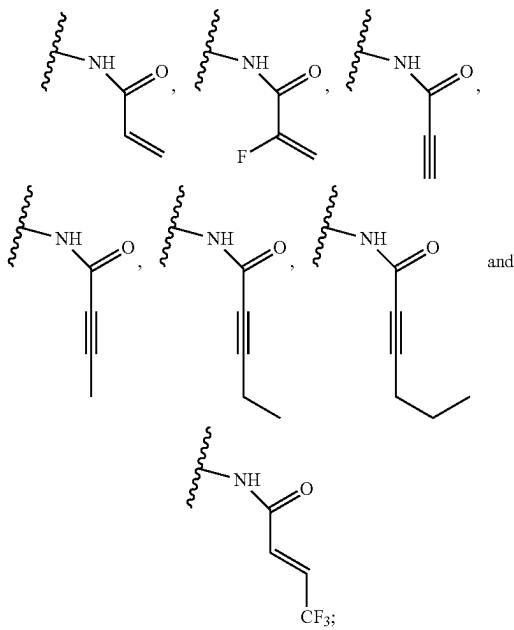
R₁ is selected from Cl, Br and —CF₃, alternatively Cl and Br;

R₃ is selected from H and —OCH₃;

R₆ is selected from



R_1 is selected from Cl, Br and $-CF_3$, alternatively Cl and Br, still alternatively Cl;
 R_3 is $-OCH_3$;
 R_6 is selected from



n is 2;

x) wherein:

Ring A is absent;

R_1 is halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R_3 is selected from $-OC_{1-6}$ alkyl and $-OC_{1-6}$ haloalkyl;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R is H, F or Me;

R' and R'' are each independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl;

n is 2;

xi) wherein:

Ring A is absent;

R_1 is Br or C_{1-2} haloalkyl;

R_3 is selected from $-OC_{1-2}$ alkyl and $-OC_{1-2}$ haloalkyl;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R is H or F; R' is H, C_{1-4} alkyl or C_{1-4} haloalkyl;

R'' is H;
 n is 2;

xii) wherein:

Ring A is absent;

R_1 is Br or CF_3 ;

R_3 is selected from $-OMe$ and $-OCH_2CF_3$;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R is H or F; R' is H, Me, iPr or CF_3 ; R'' is H;

n is 2;

xiii) wherein:

Ring A is absent;

R_1 is C_{1-4} haloalkyl;

R_3 is selected from $-OC_{1-6}$ alkyl and $-OC_{1-6}$ haloalkyl;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R is H or halogen; R' is H, C_{1-2} alkyl or C_{1-2} haloalkyl; R'' is H;

n is 2;

xiv) wherein:

Ring A is absent;

R_1 is C_{1-2} haloalkyl;

R_3 is selected from $-OC_{1-2}$ alkyl and $-OC_{1-2}$ haloalkyl;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R is H, F or Br; R' is H, C_{1-2} alkyl or C_{1-2} haloalkyl; R'' is H;

n is 2; and

xv) wherein:

Ring A is absent;

R_1 is CF_3 ;

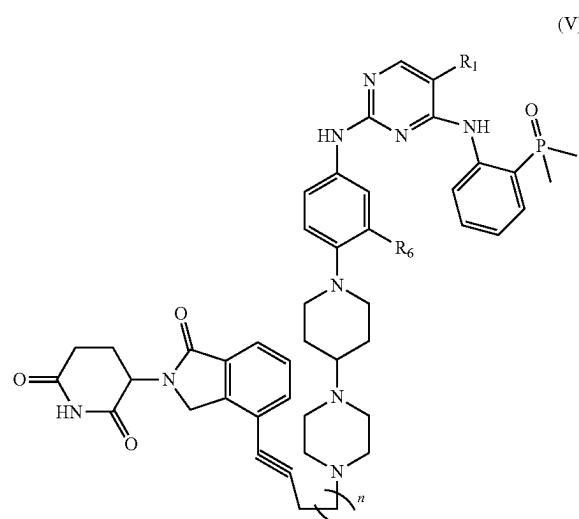
R_3 is selected from $-OMe$ and $-OCH_2CF_3$;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R is H or F; R' is H, Me or CF_3 ; R'' is H;

n is 2.

10-23. (canceled)

24. The compound of claim 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, which has a structure of formula (V):



wherein

R_1 is halogen;

R_6 is selected from $-NH-C(O)-CR=CR'R''$ and $-NH-C(O)-C\equiv CR'$;
 wherein R, R' and R'' are each independently selected

from H, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;
 n is 0, 1, 2, 3, 4, or 5.

25. The compound of claim **24**, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has any one of the following definitions:

i) wherein:

R₁ is halogen;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R is selected from H and halogen;

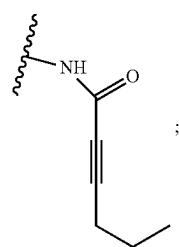
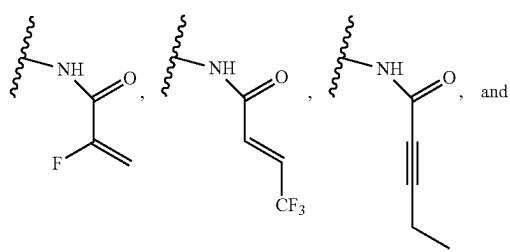
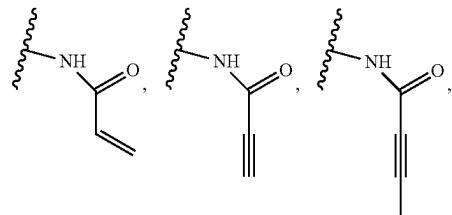
R' and R" are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

n is 1, 2, 3 or 4; and

ii) wherein:

R₁ is selected from Br and Cl;

R₆ is selected from

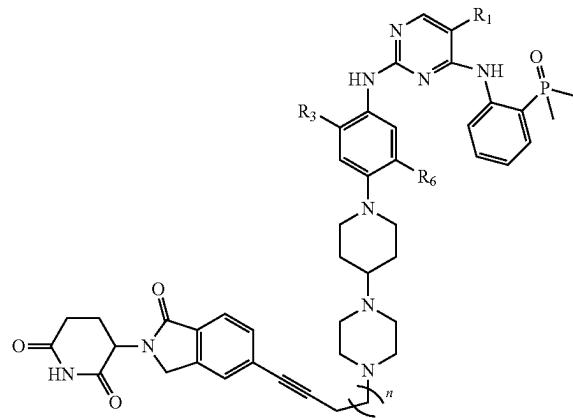


n is 2, 3 or 4.

26. (canceled)

27. The compound of claim **3**, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, which has the structure of formula (VI):

(VI)



wherein

R₁ is halogen;

R₃ is —OC₁₋₆ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R, R' and R" are independently selected from H, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

n is 1, 2, 3 or 4.

28. The compound of claim **27**, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has any one of the following definitions:

i) wherein:

R₁ is halogen;

R₃ is —OC₁₋₆ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

wherein R, R' and R" are independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

n is 2, 3 or 4;

ii) wherein:

R₁ is halogen;

R₃ is —OC₁₋₄ alkyl;

R₆ is selected from —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR';

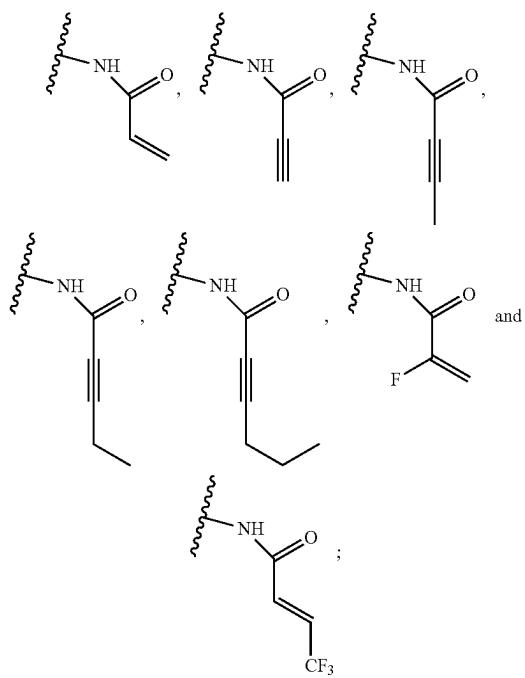
wherein R is H;

R' and R" are independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

n is 3; and

iii) wherein:

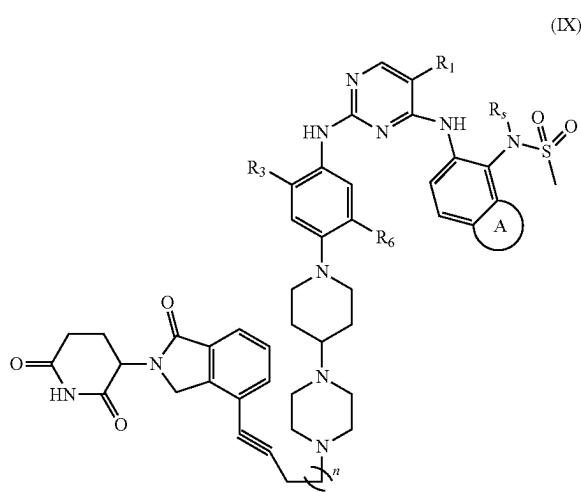
R₁ is Cl;
R₃ is —OCH₃;
R₆ is selected from



n is 3.

29-30. (canceled)

31. The compound of claim 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, which has a structure of formula (IX):



wherein

Ring A is selected from C₄₋₁₀ cycloalkyl, 5-8 membered heterocycl, C₆₋₁₀ aryl and 5-14 membered heteroaryl;

R₁ is H, halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl; alternatively, R₁ is halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R₃ is selected from —OC₁₋₆ alkyl and —OC₁₋₆ haloalkyl; R₆ is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'; wherein R is H, halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl; R' and R" are each independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; R is selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; n is 2.

32. The compound of claim 31, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound has any one of the following definitions:

i) wherein:

Ring A is selected from C₆₋₁₀ aryl and 5-6 membered heteroaryl; R₁ is H, halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl; alternatively, R₁ is halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R₃ is selected from —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl; R₆ is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'; wherein R is H or halogen; R' is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R" is H;

R is selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl; n is 2;

ii) wherein:

Ring A is selected from phenyl and 5-6 membered heteroaryl;

R₁ is H, halogen or C₁₋₄ haloalkyl; alternatively, R₁ is halogen or C₁₋₄ haloalkyl;

R₃ is selected from —OC₁₋₄ alkyl and —OC₁₋₄ haloalkyl; R₆ is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, —NH—C(O)—CR=CR'R" and —NH—C(O)—C≡CR'; wherein R is H or halogen; R' is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl; R" is H;

R is selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl; n is 2;

iii) wherein:

Ring A is a 5-6 membered heteroaryl group;

R₁ is H, Cl, Br or CF₃; alternatively, R₁ is Br or CF₃;

R₃ is selected from —OC₁₋₂ alkyl and —OC₁₋₂ haloalkyl;

R₆ is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl and —NH—C(O)—CR=CR'R"; wherein R is H or halogen; R' and R" are H;

R is selected from H and C₁₋₄ alkyl;

n is 2; and

iv) wherein:

Ring A is pyrazinyl;

R₁ is H, Cl, Br or CF₃; alternatively, R₁ is Br or CF₃;

R₃ is selected from —OC₁₋₂ alkyl and —OC₁₋₂ haloalkyl;

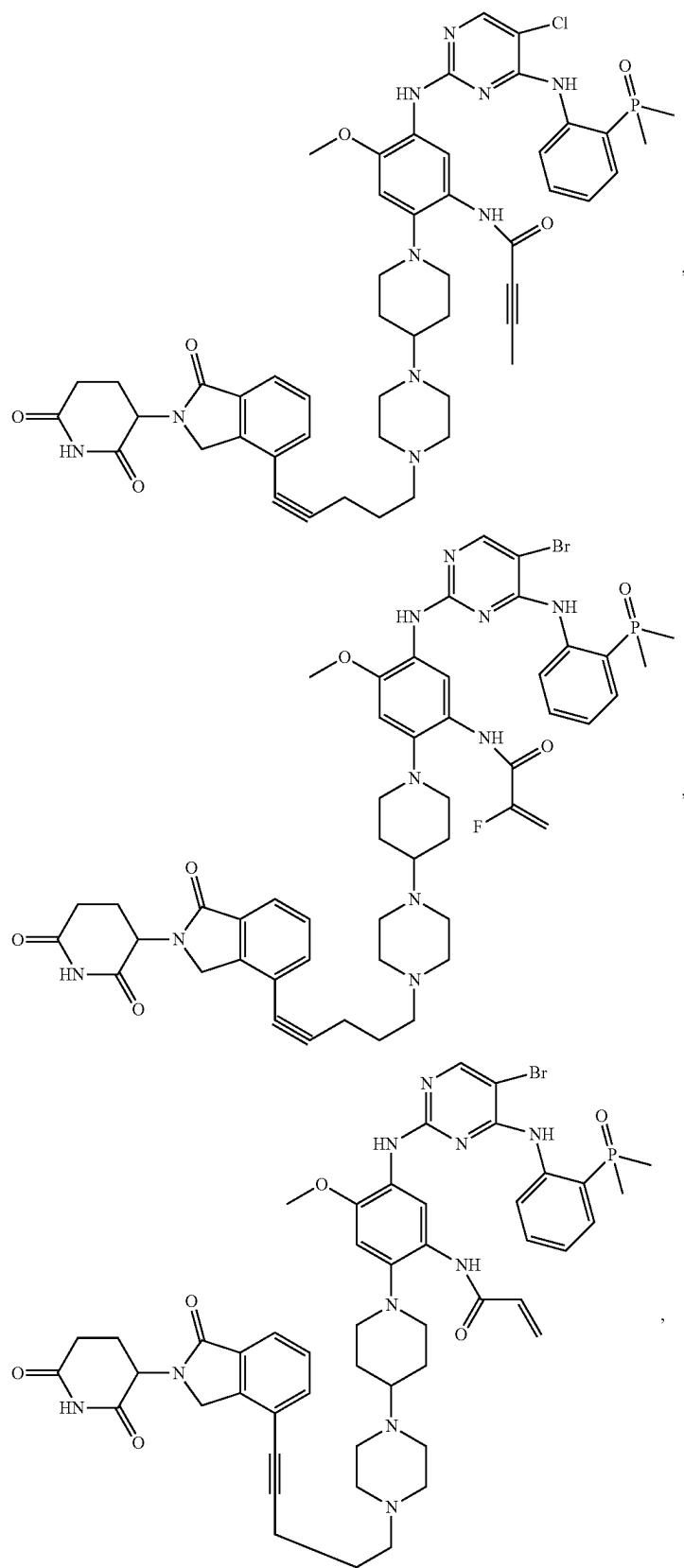
R₆ is selected from C₁₋₄ alkyl and —NH—C(O)—CR=CR'R"; wherein R is H or F; R' and R" are H;

R_s is H;

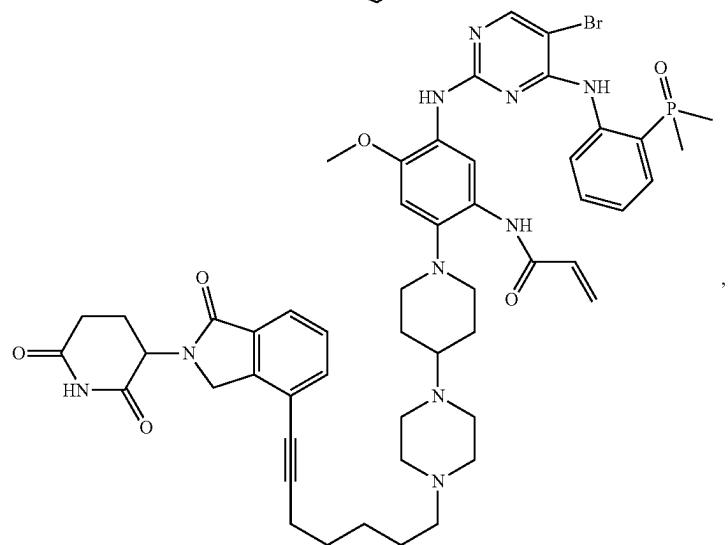
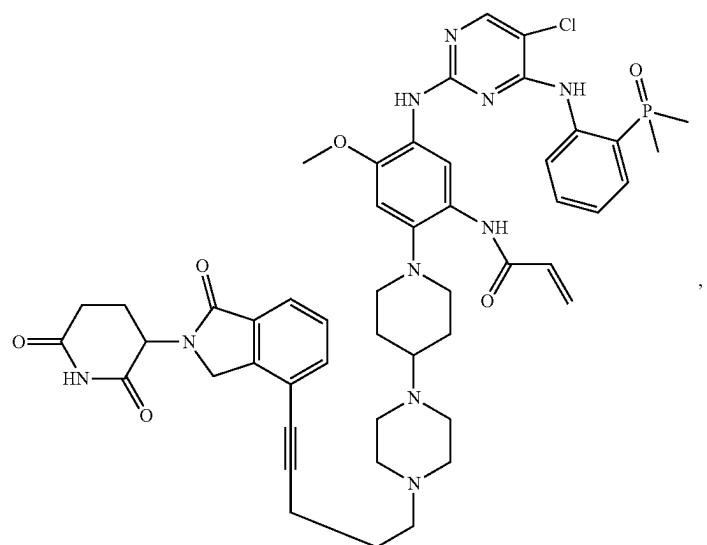
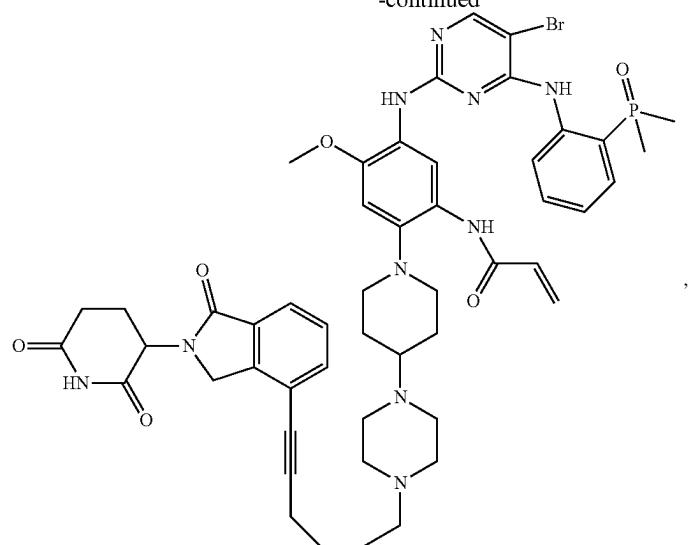
n is 2.

33-35. (canceled)

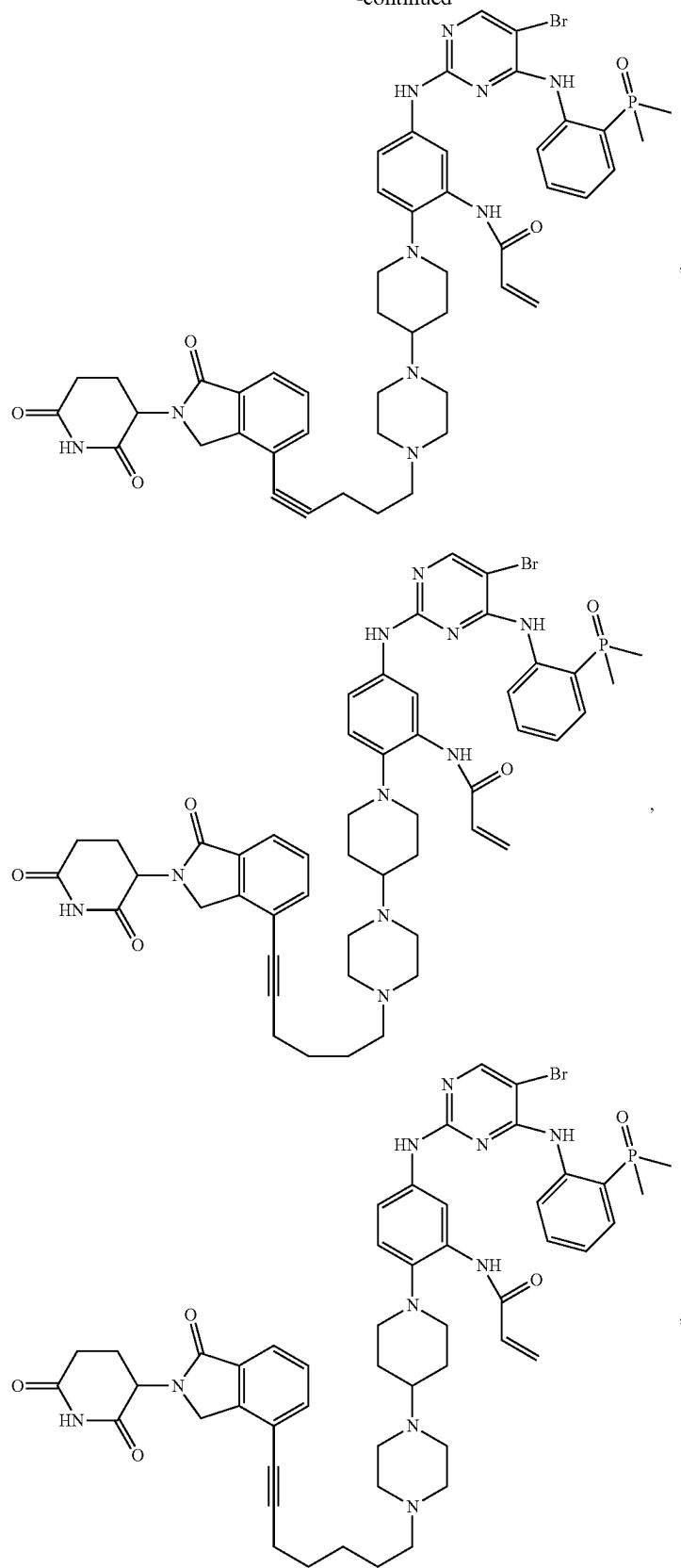
36. A compound, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the compound is selected from:



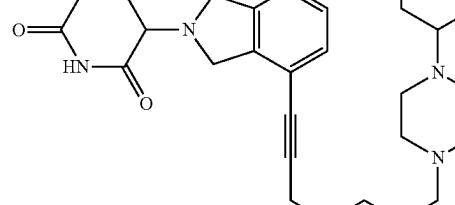
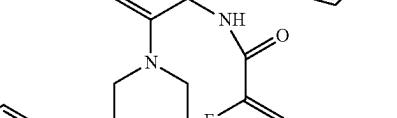
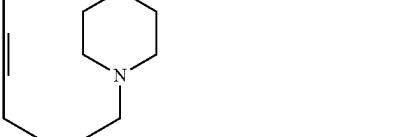
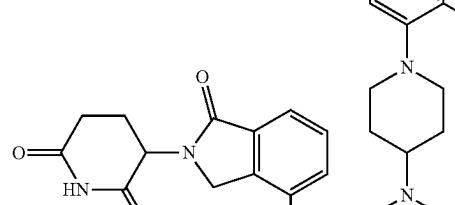
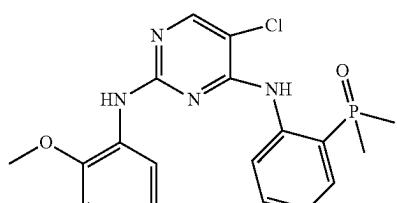
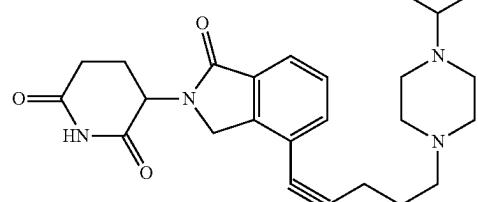
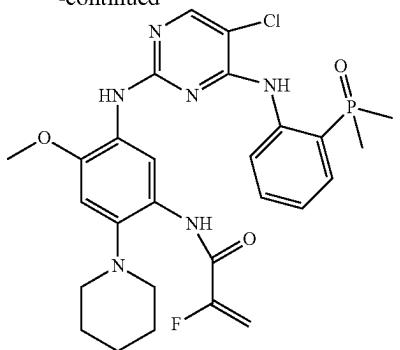
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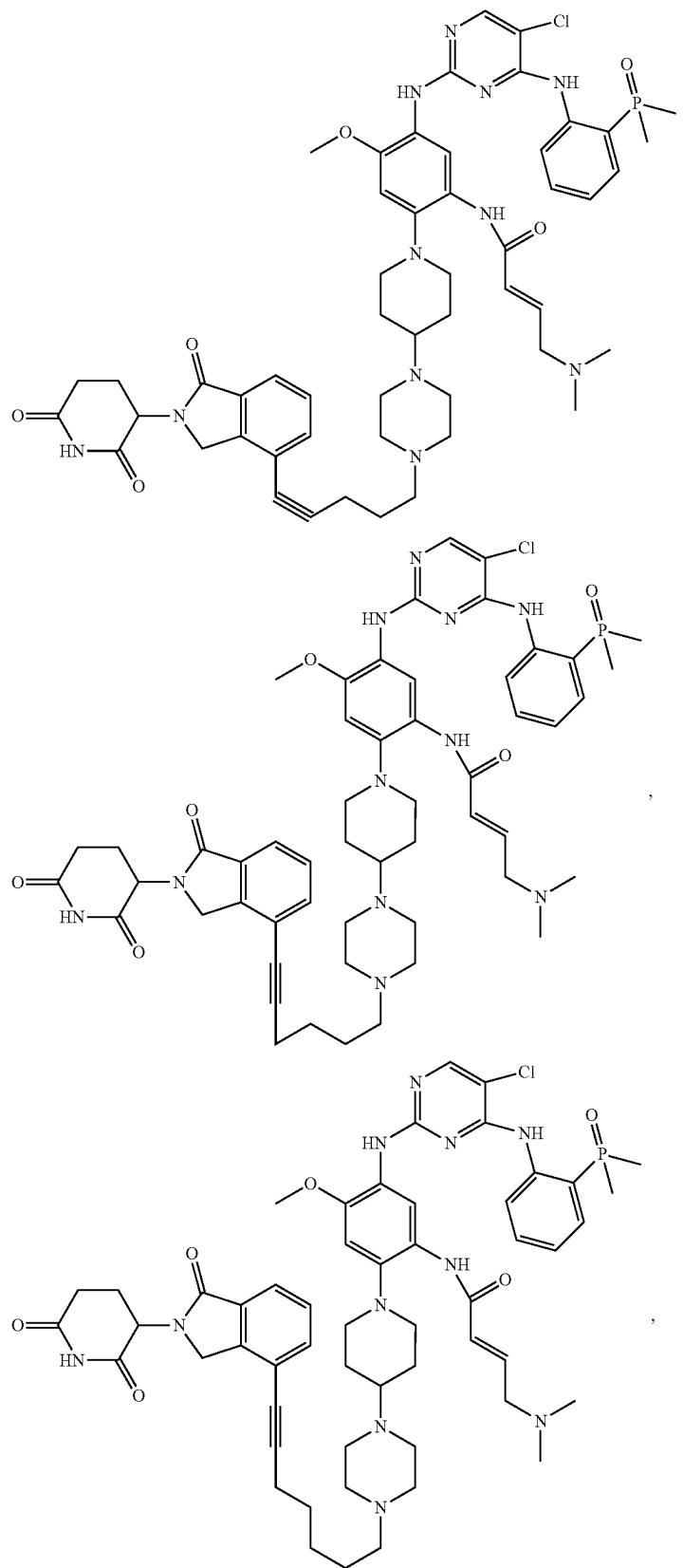
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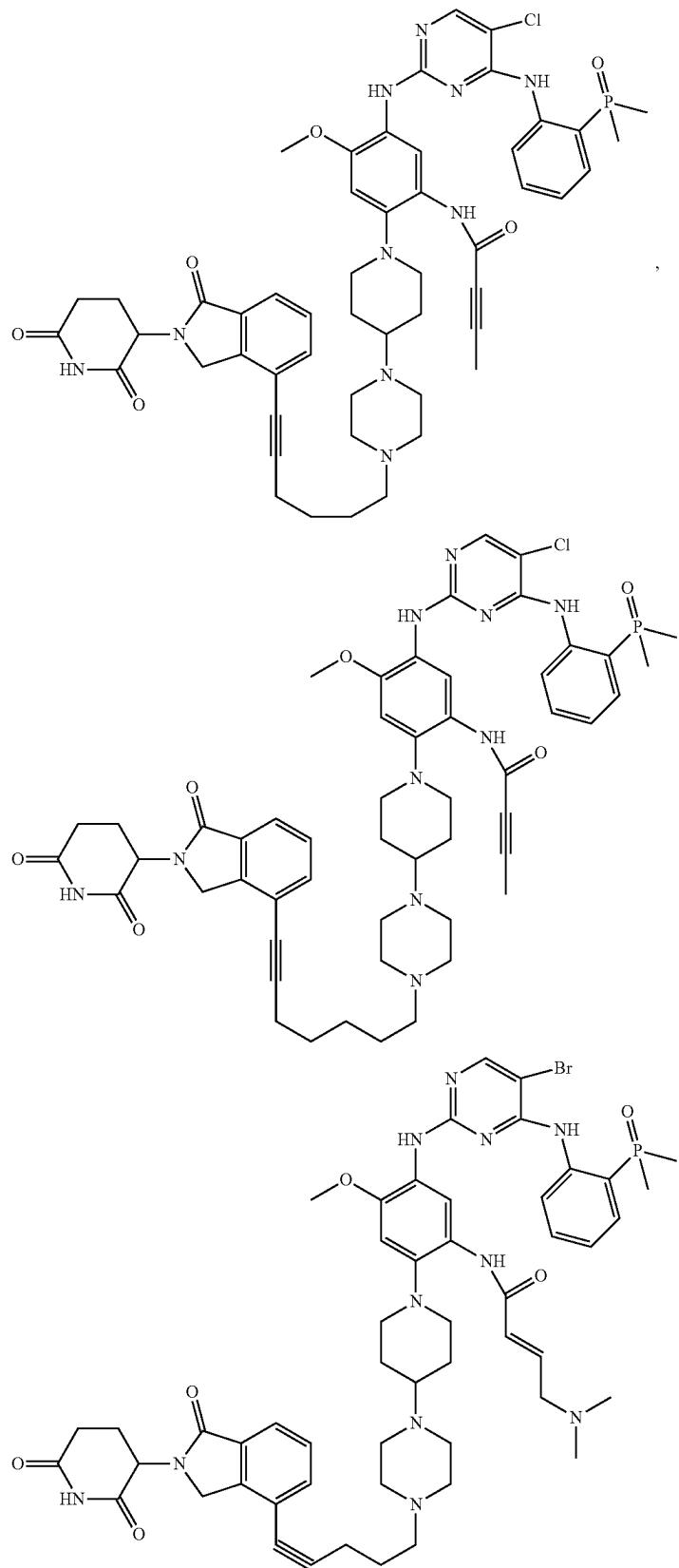
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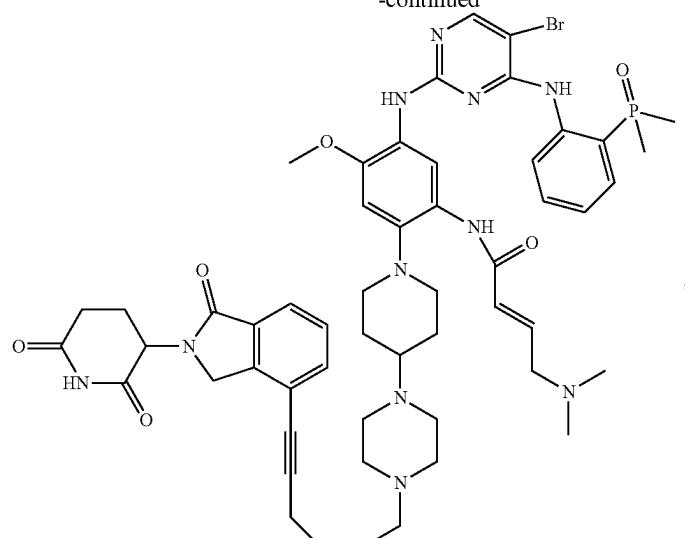
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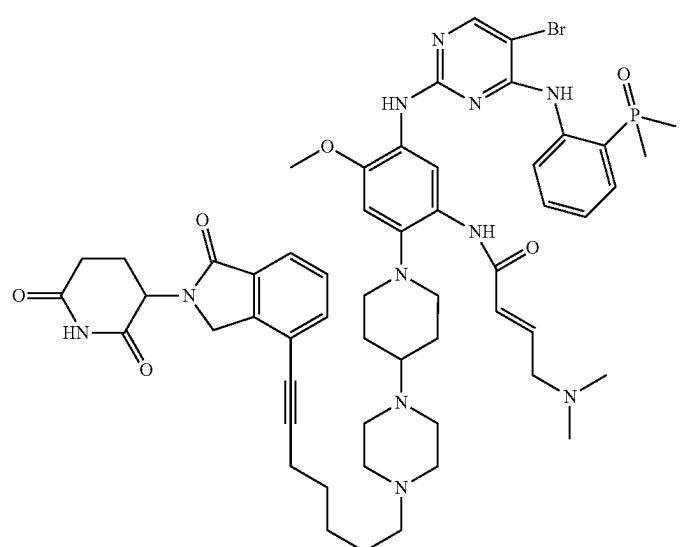
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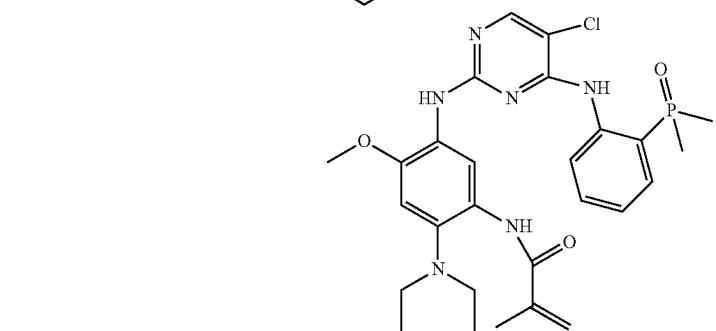
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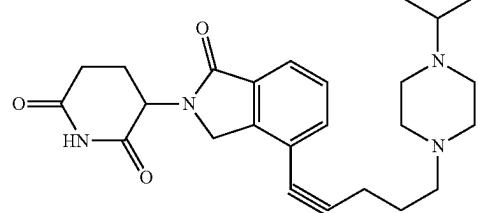
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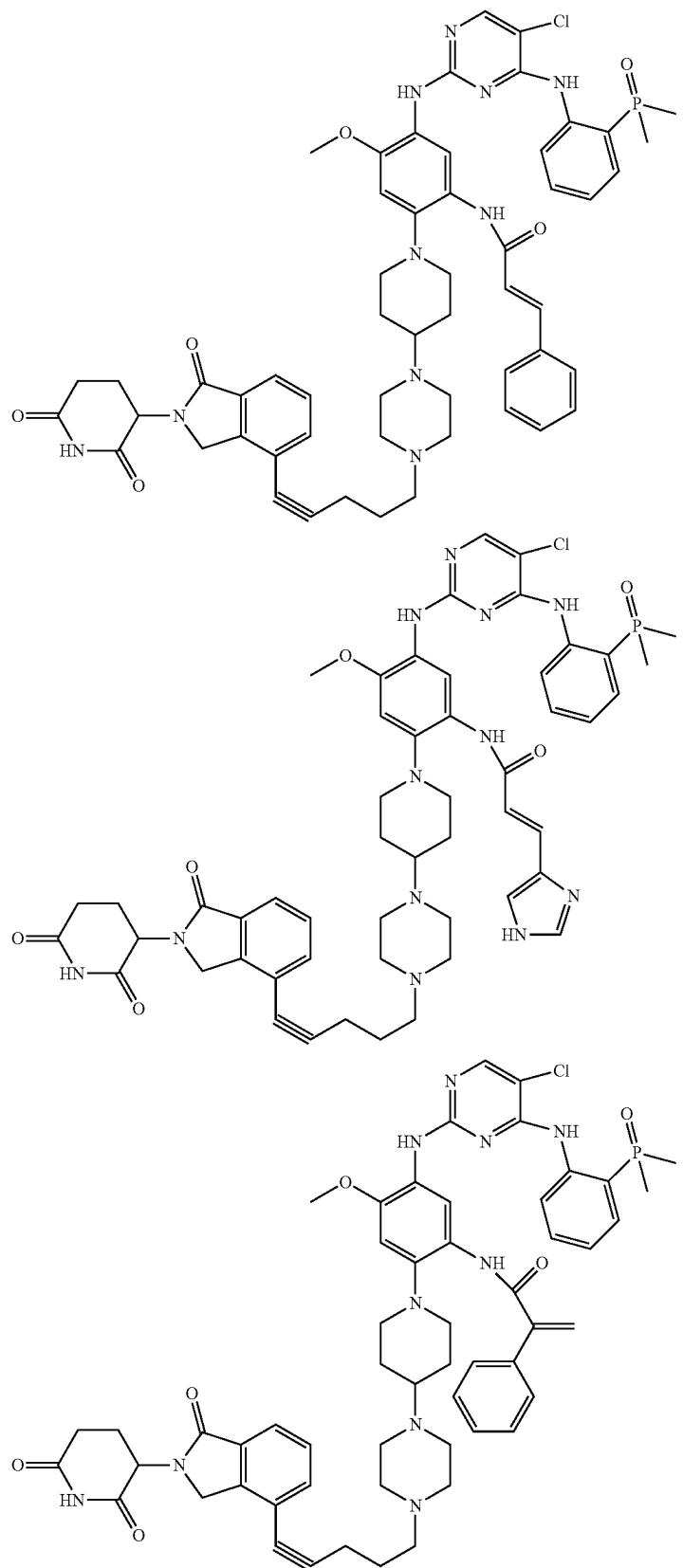
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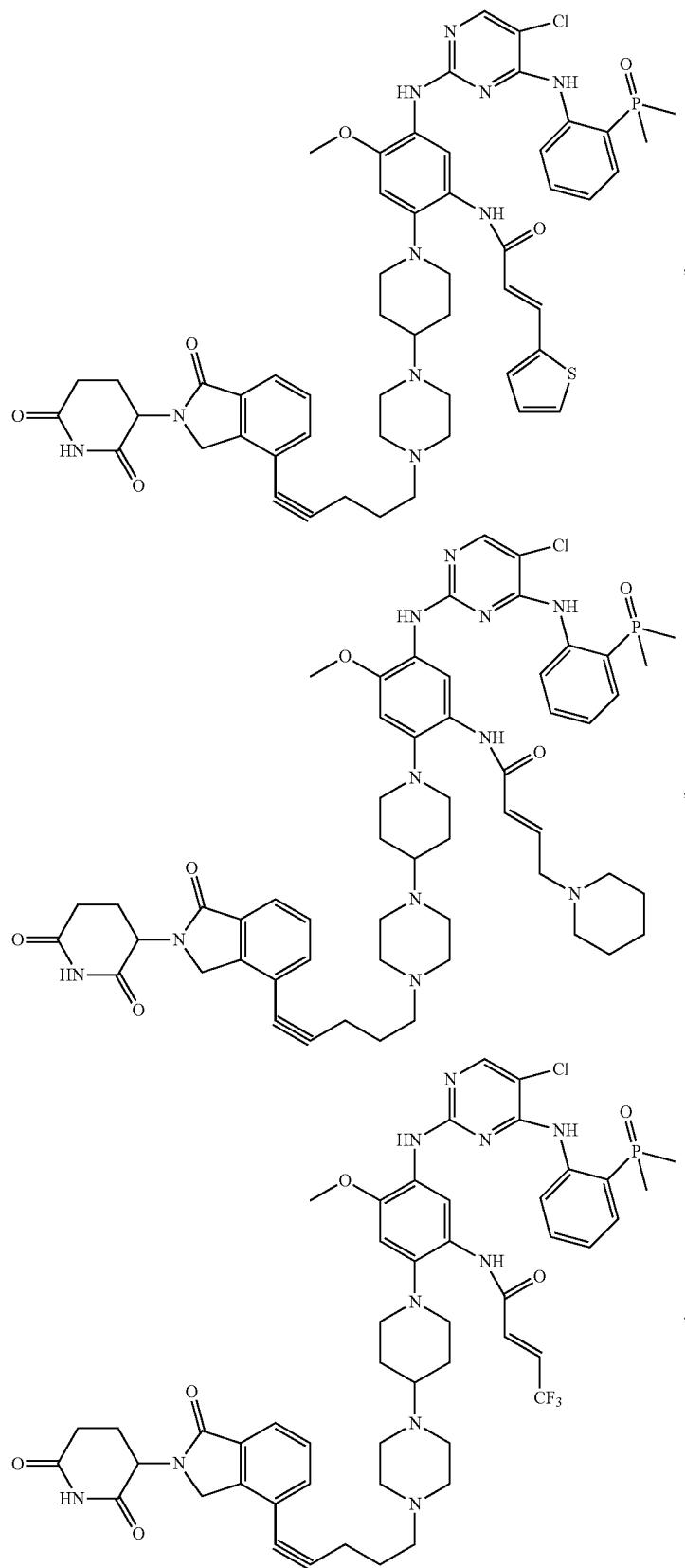
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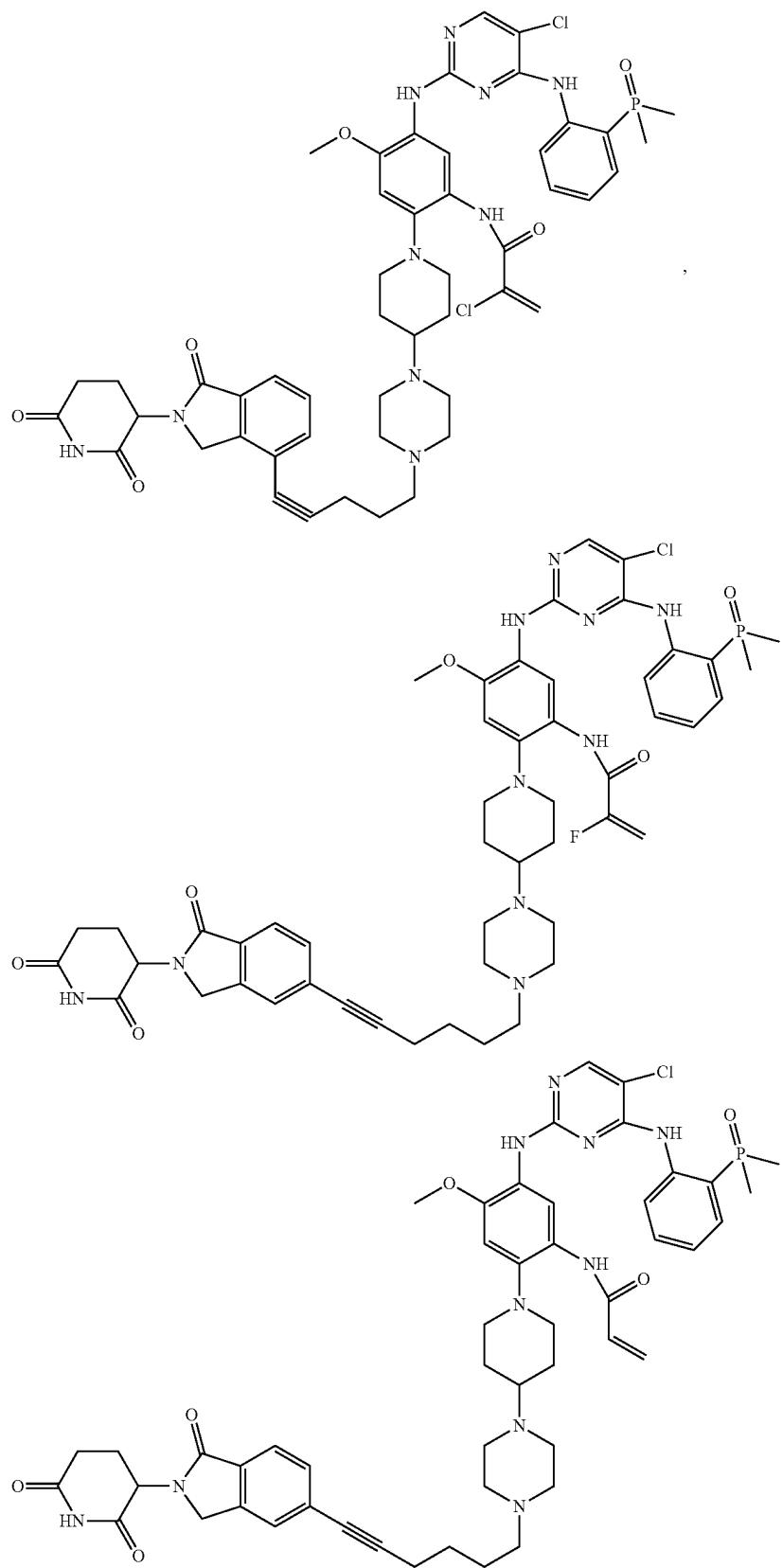
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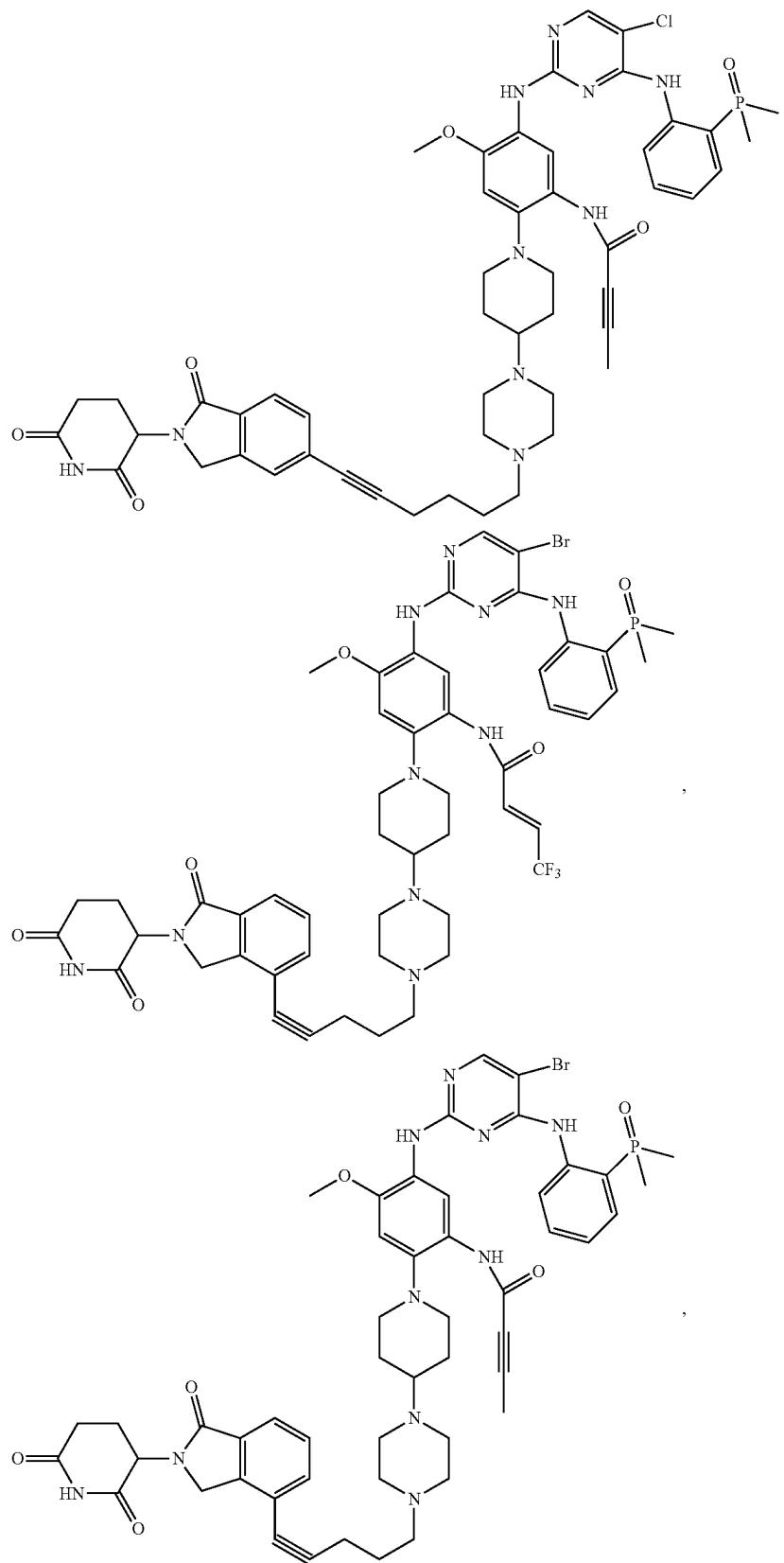
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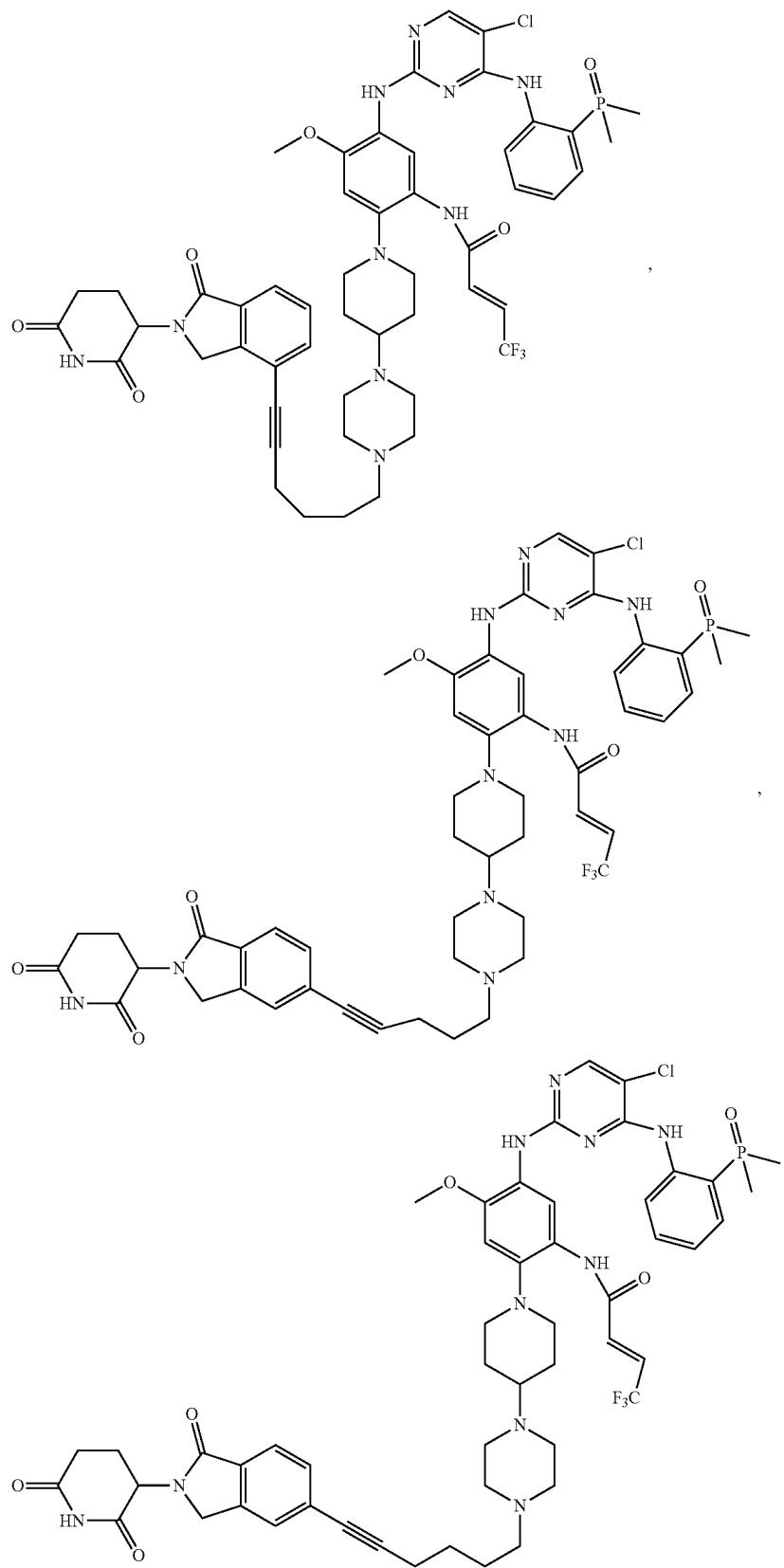
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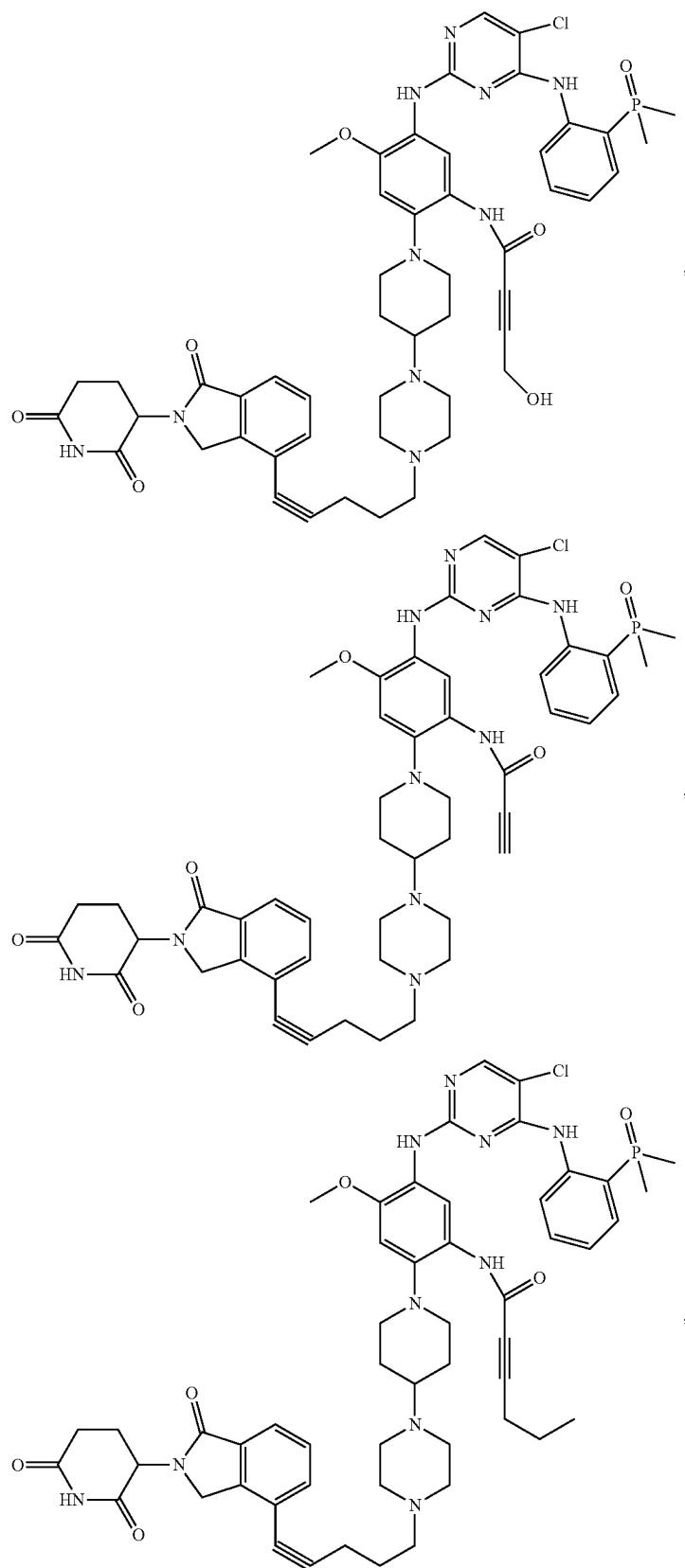
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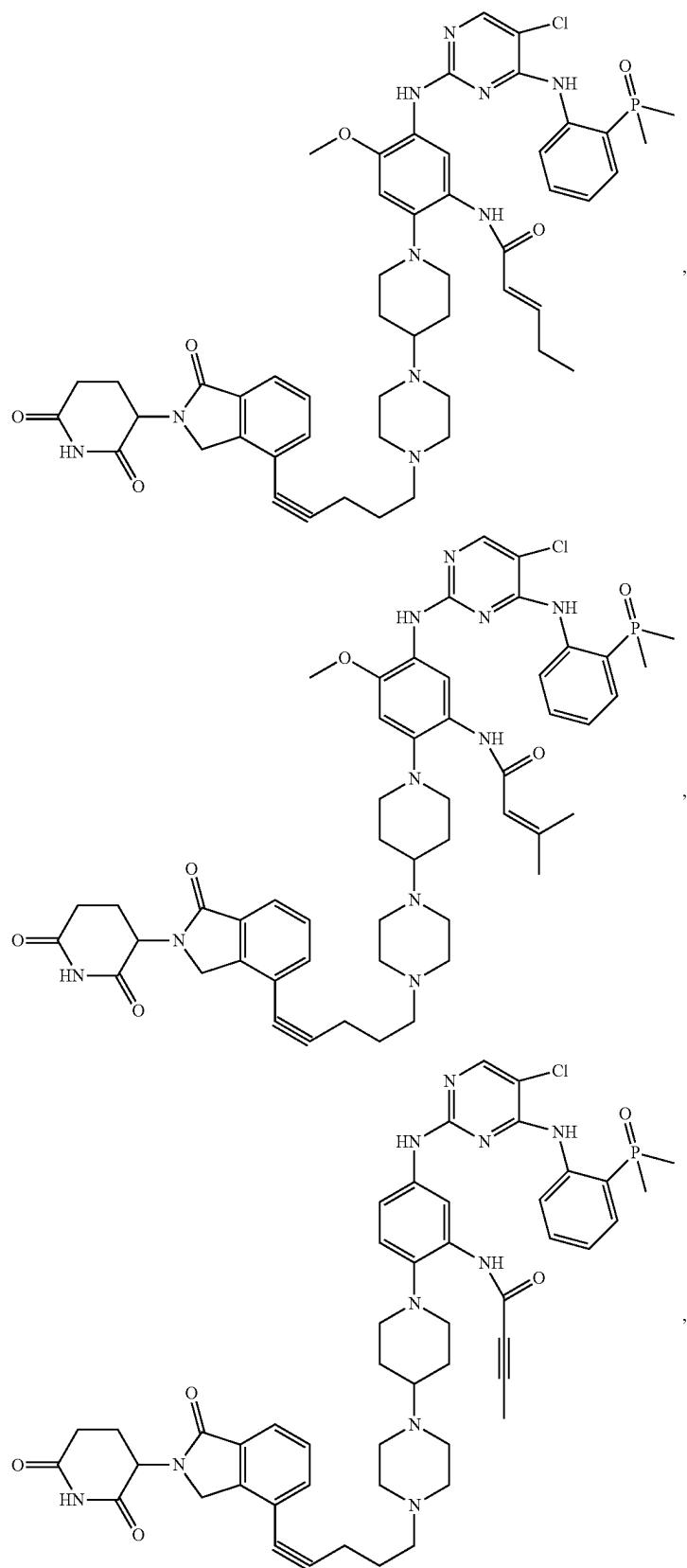
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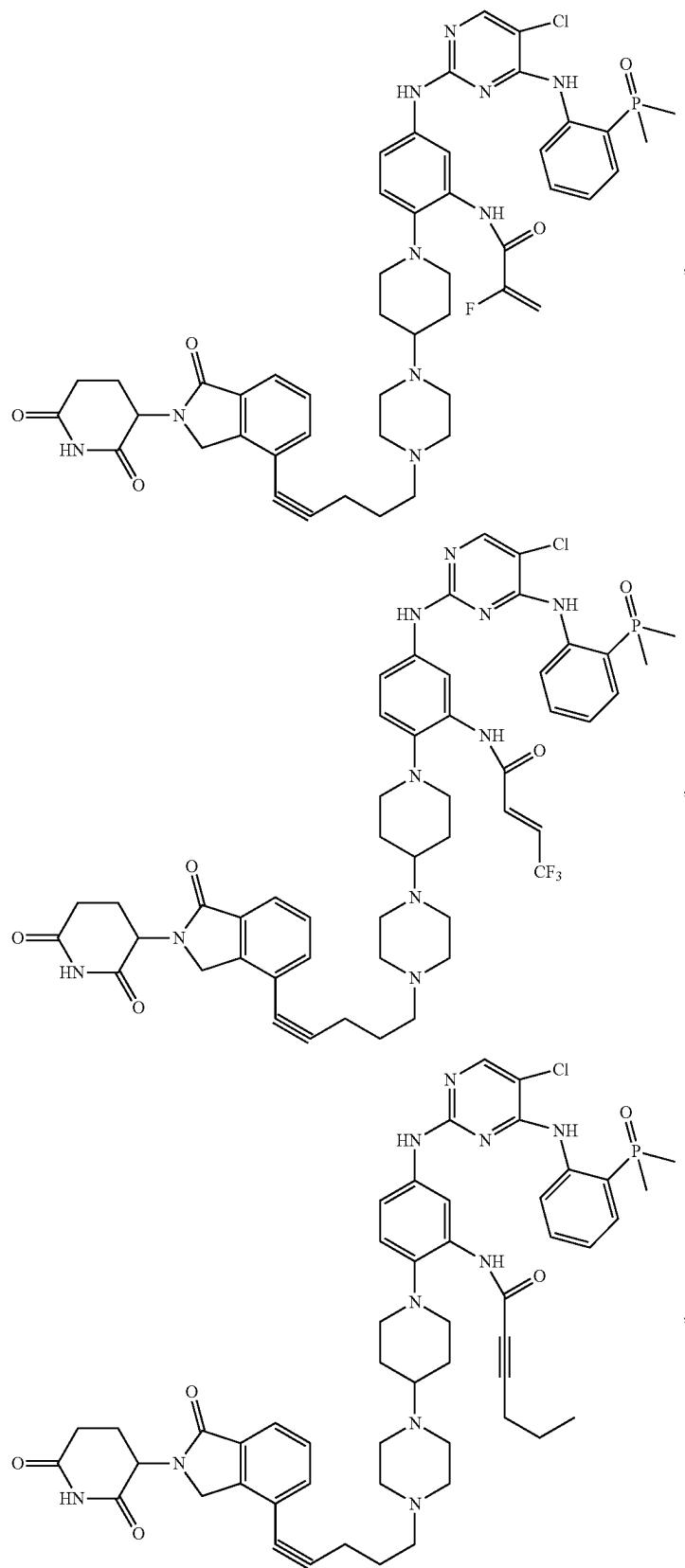
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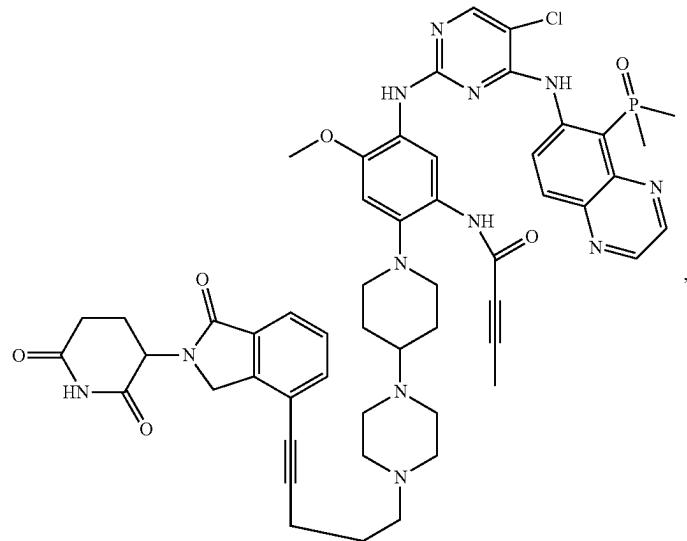
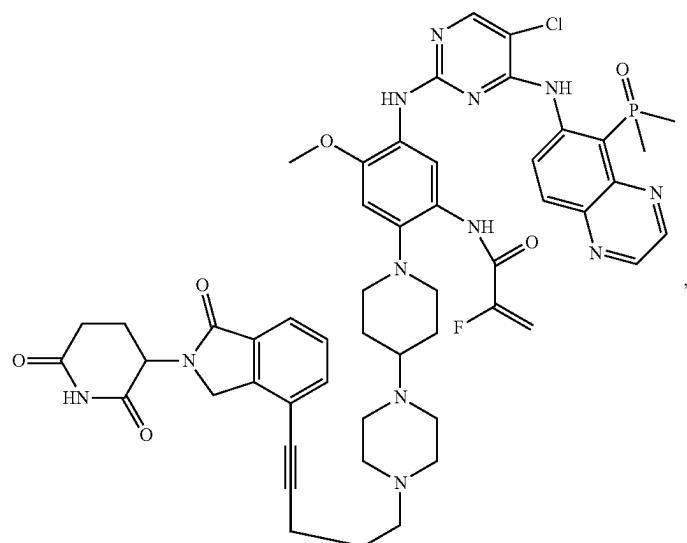
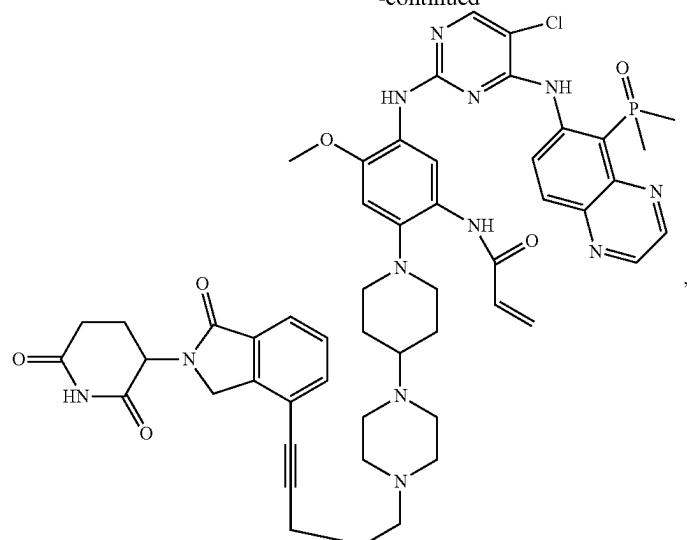
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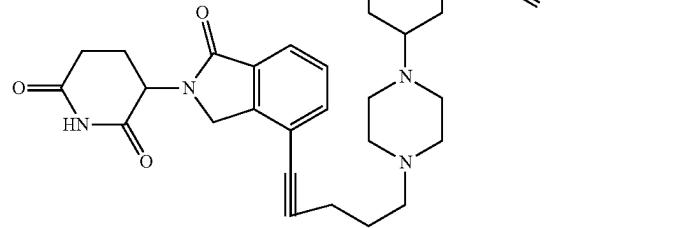
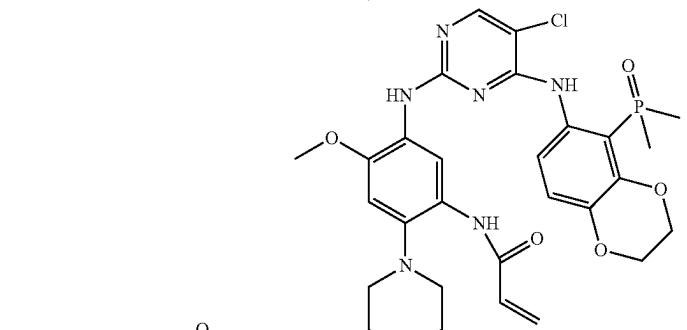
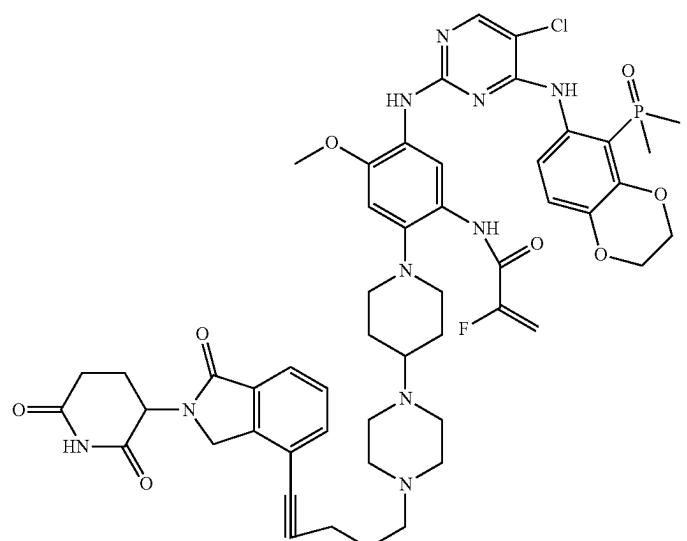
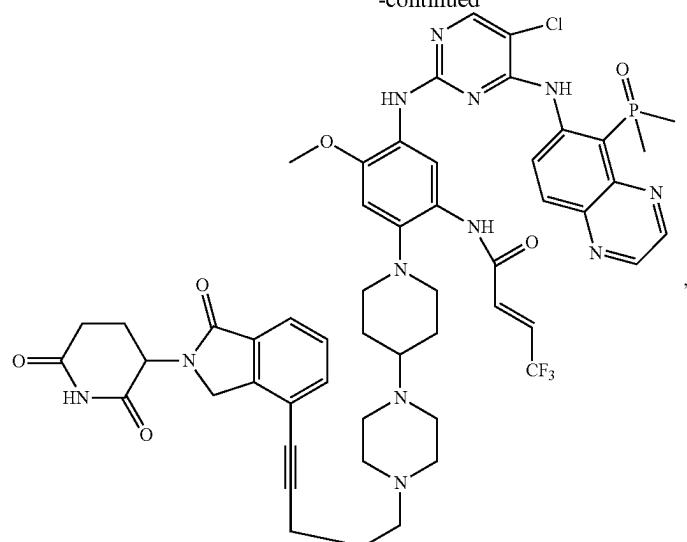
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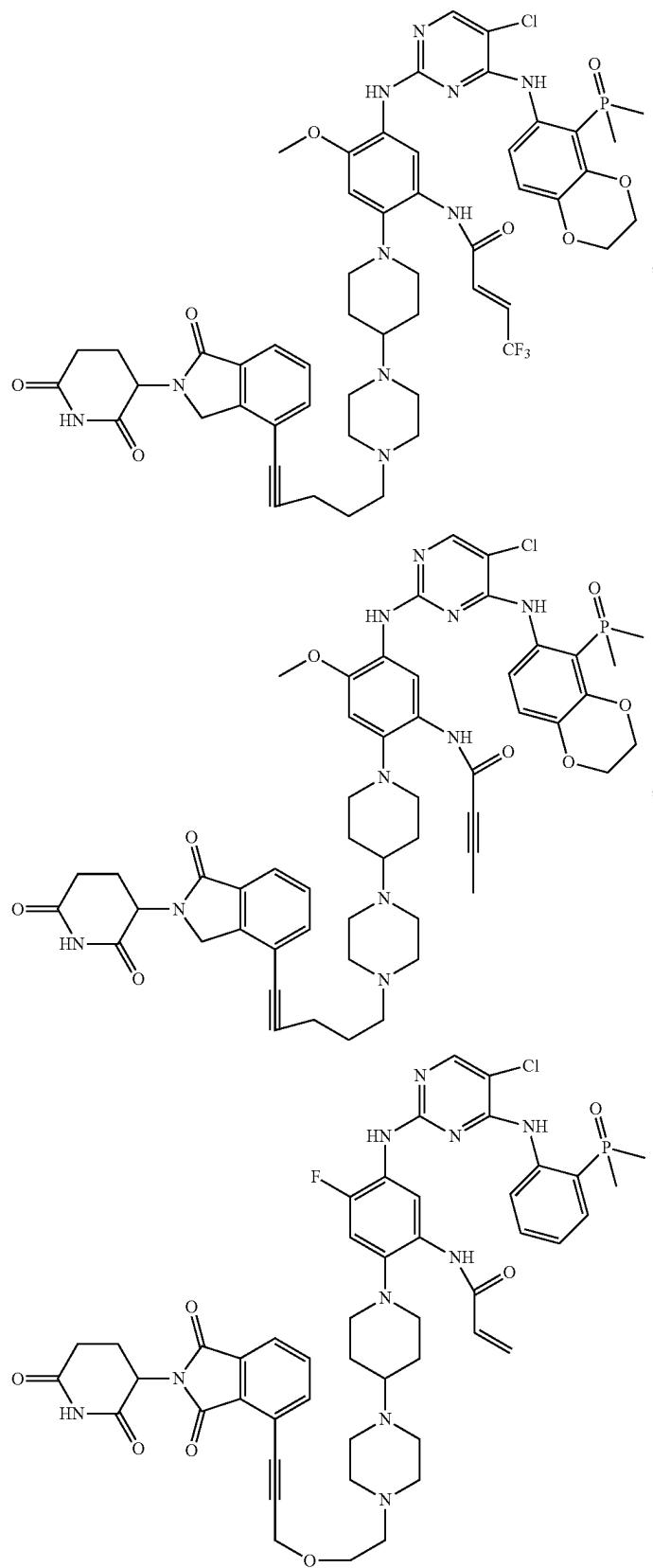
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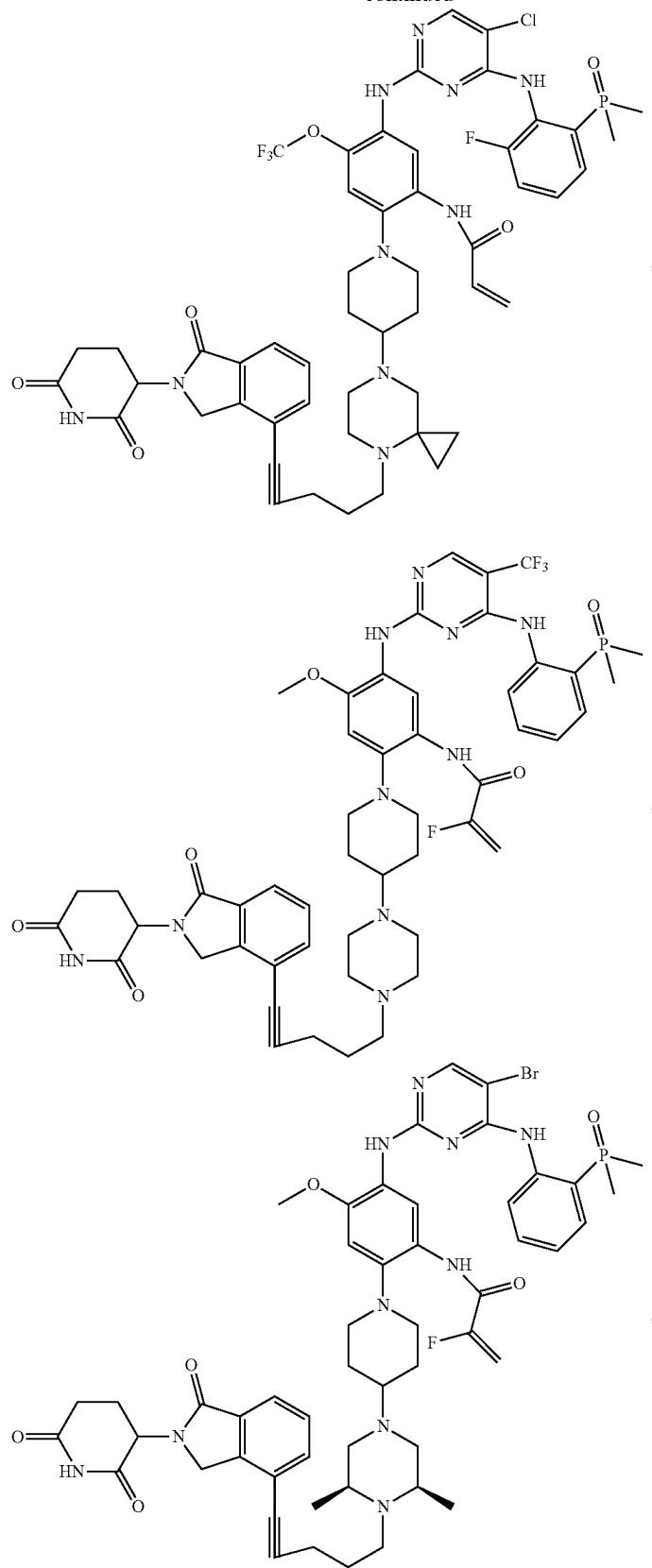
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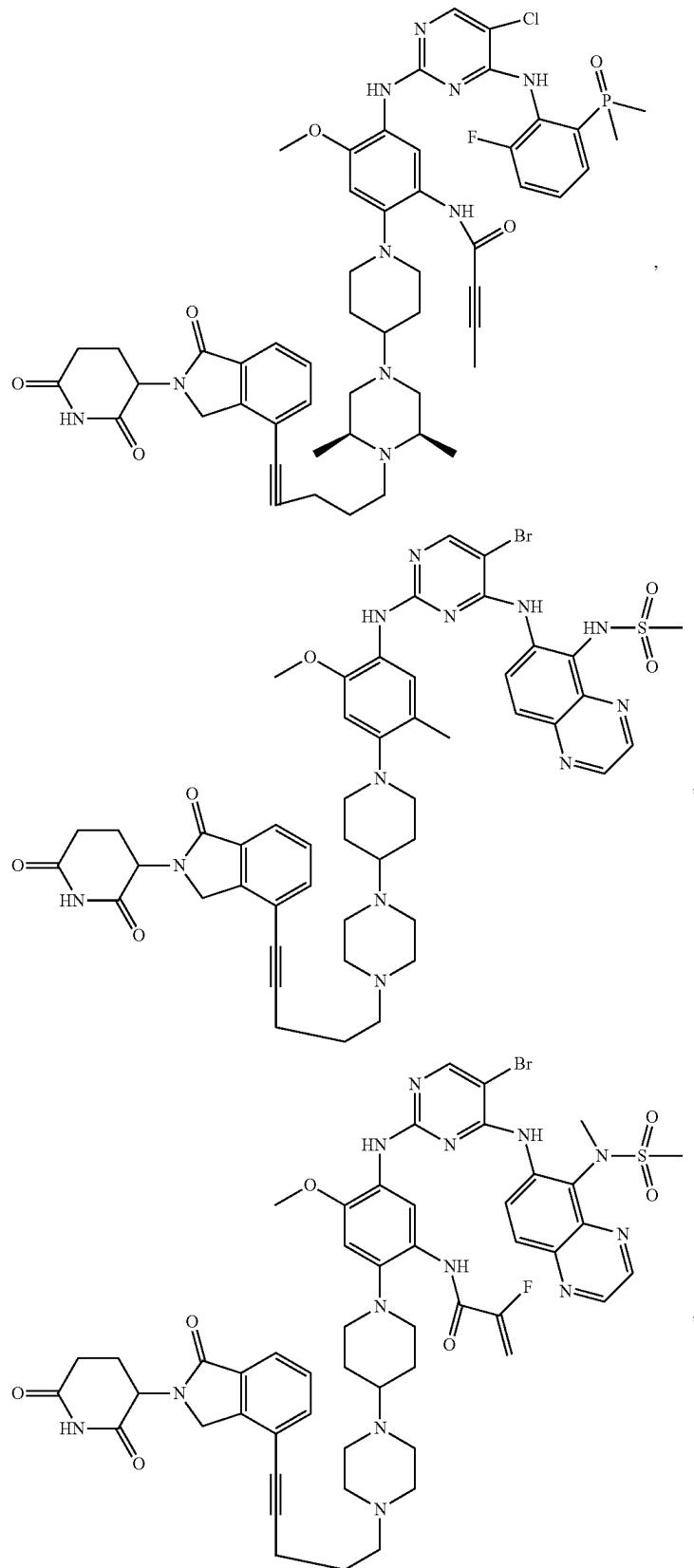
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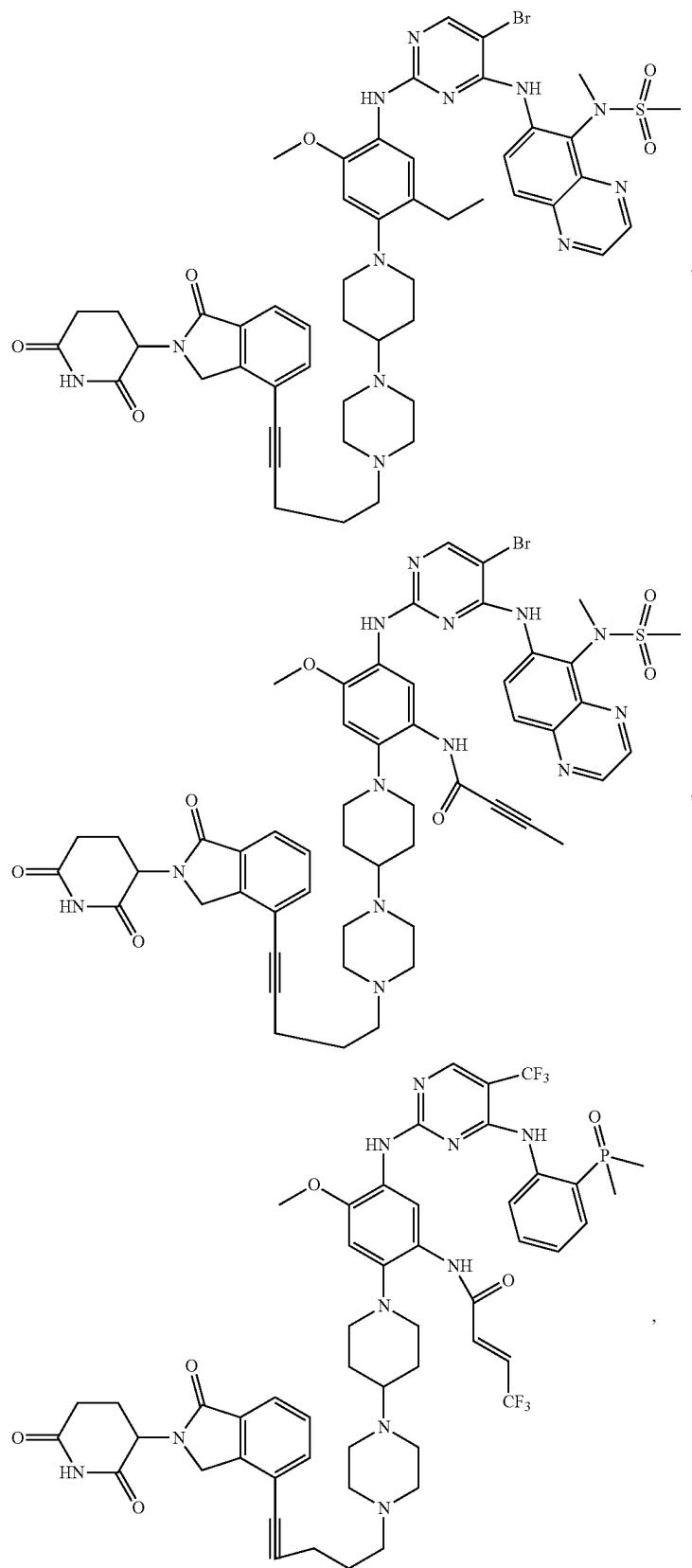
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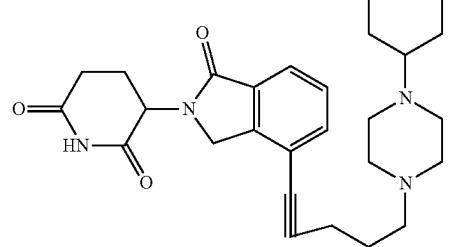
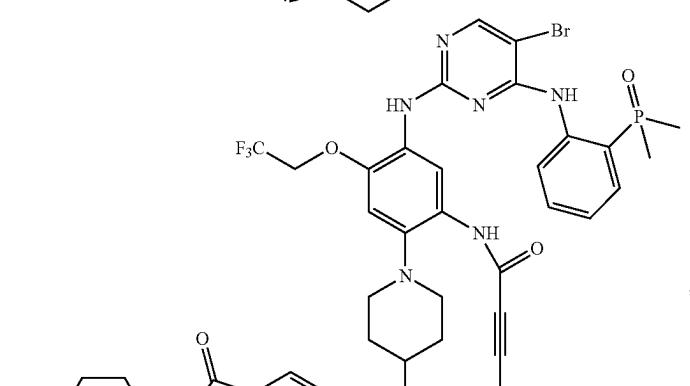
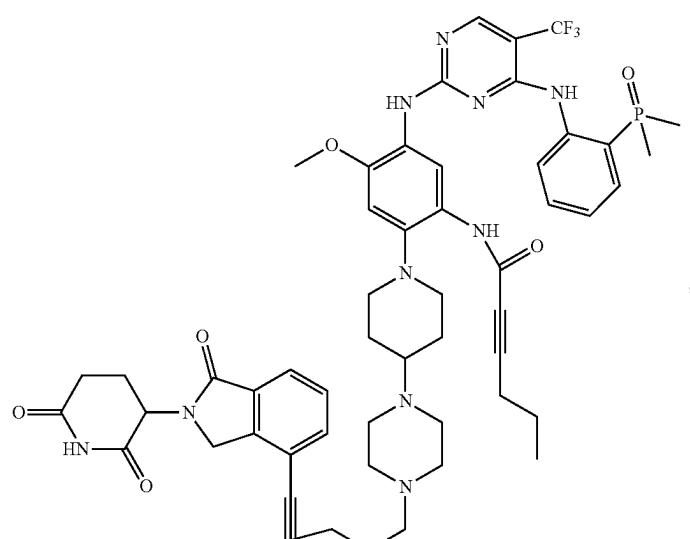
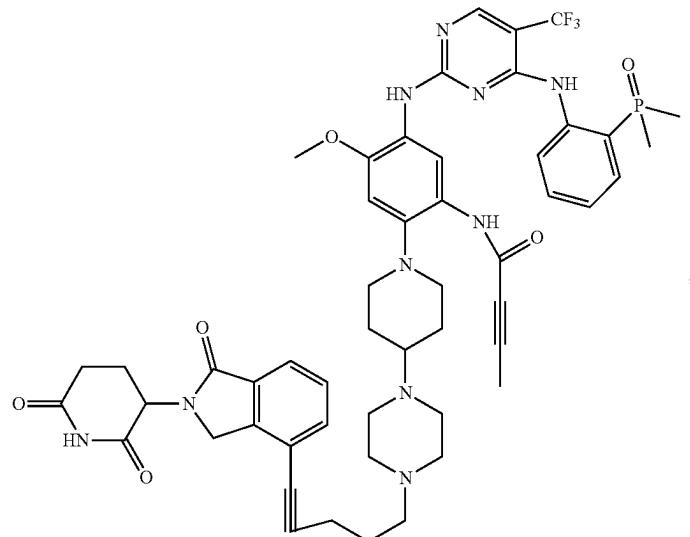
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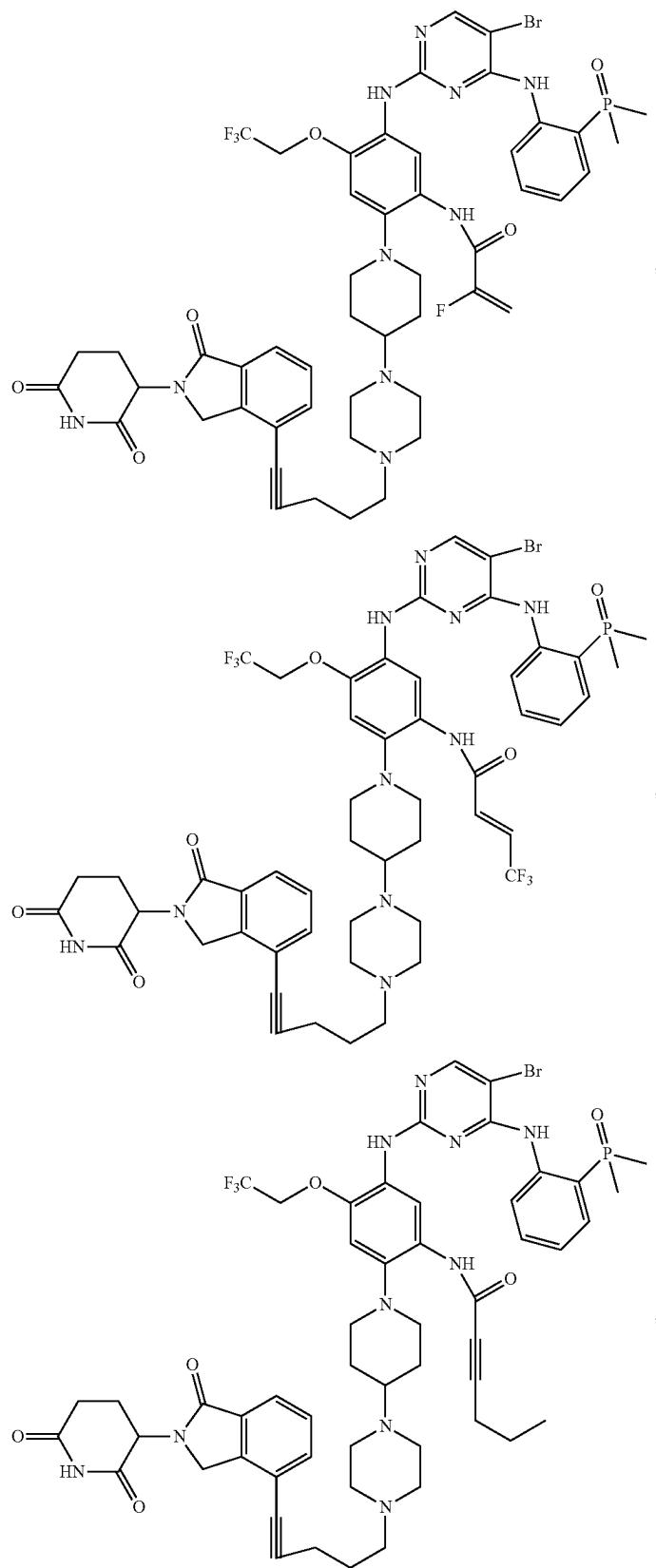
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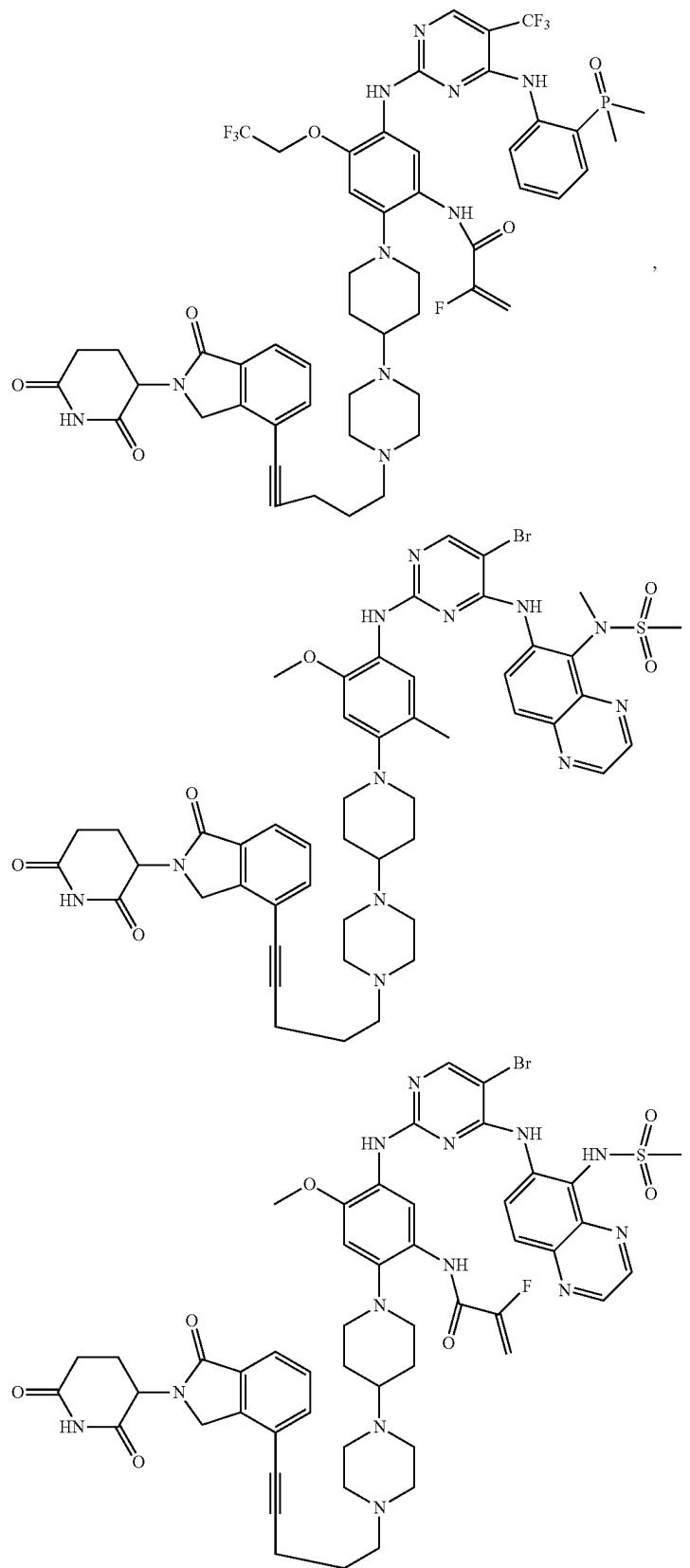
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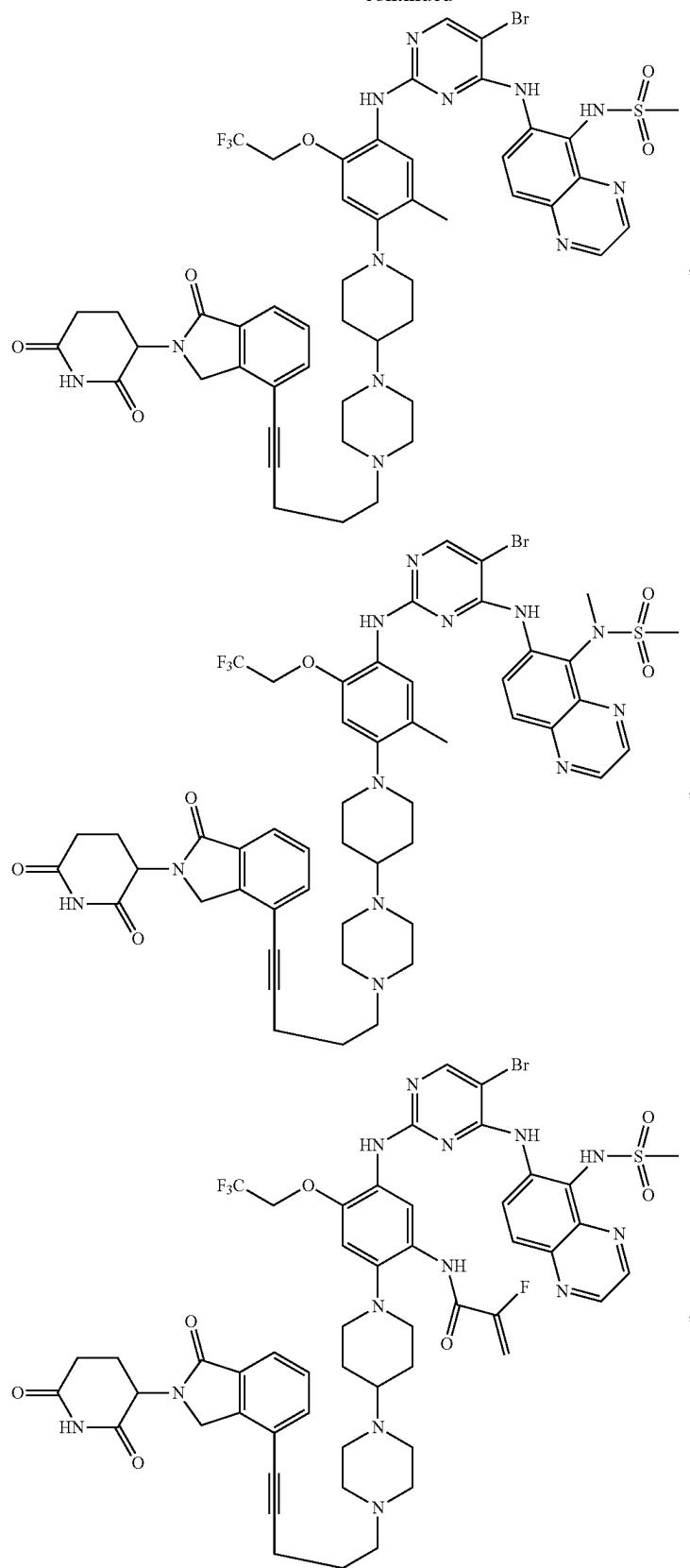
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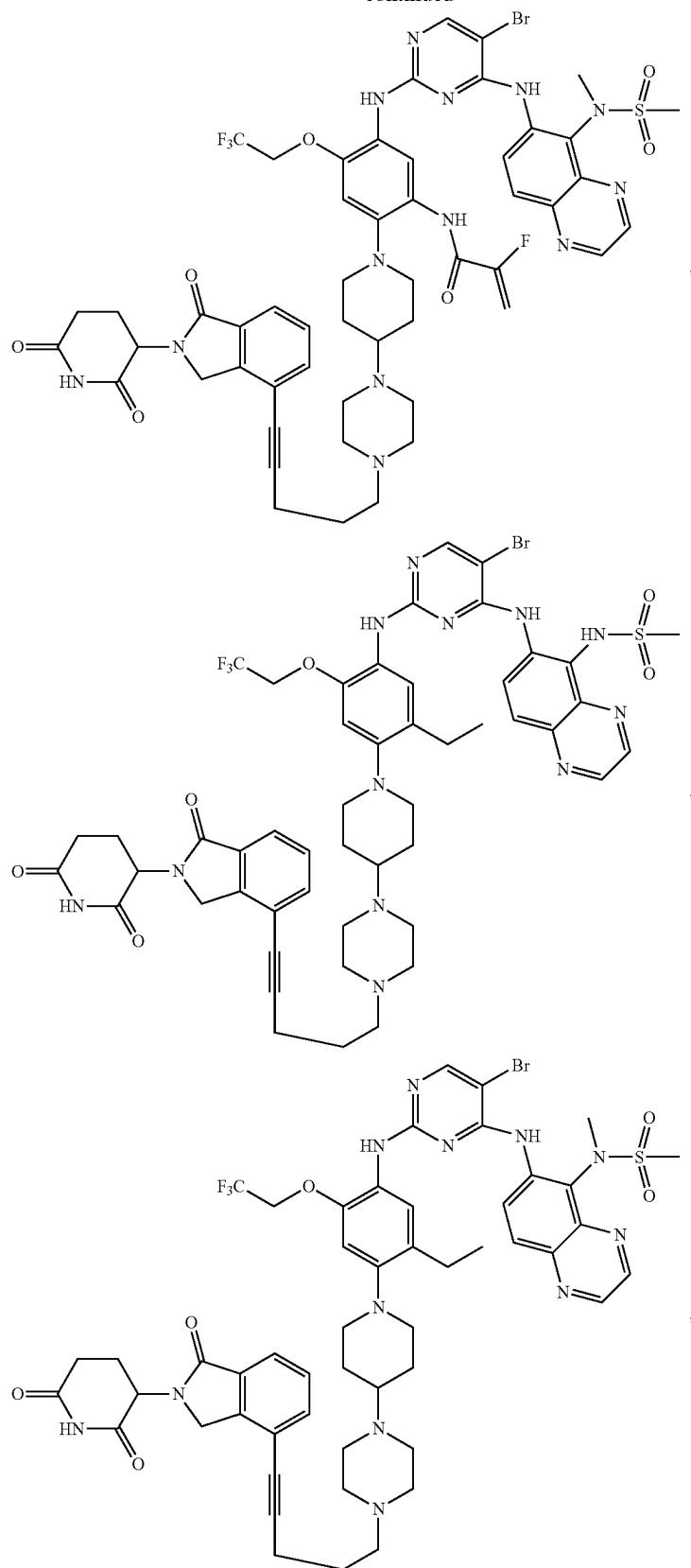
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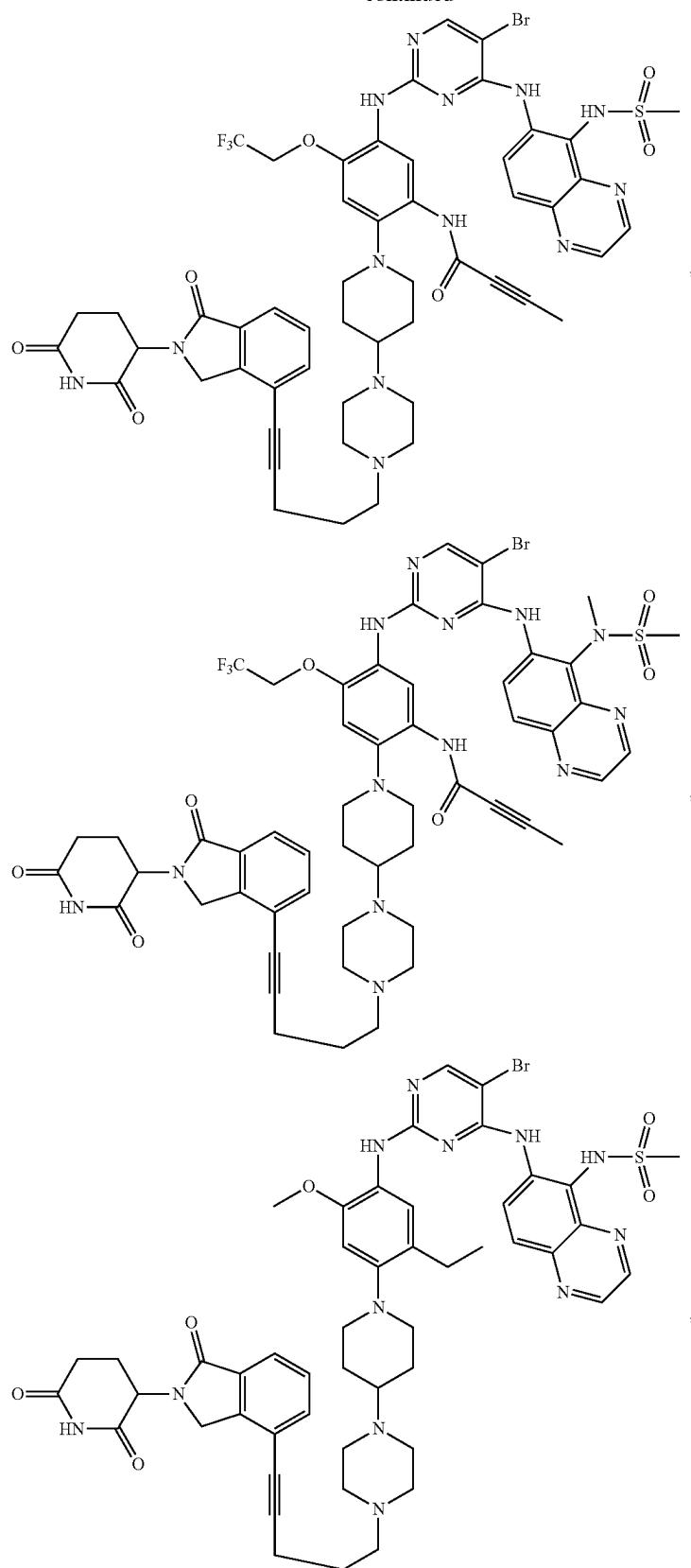
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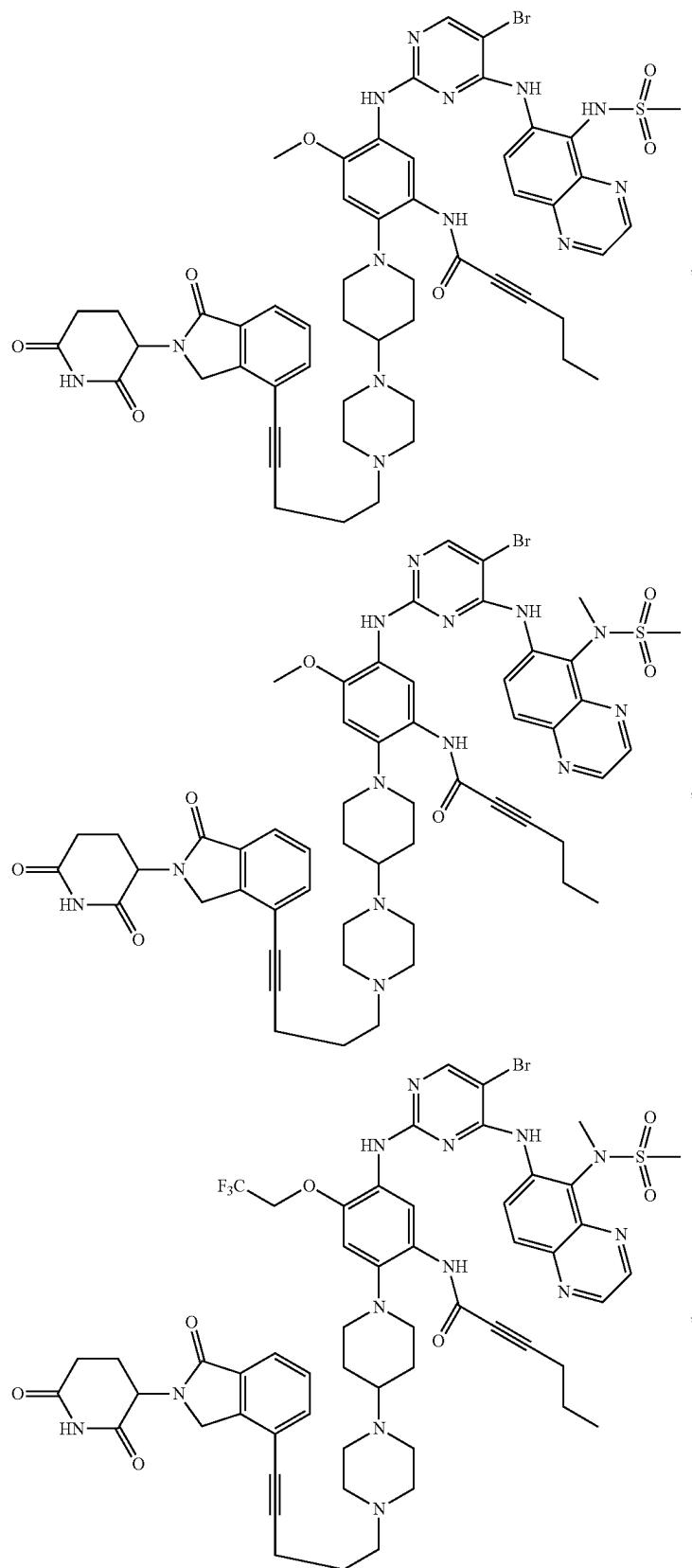
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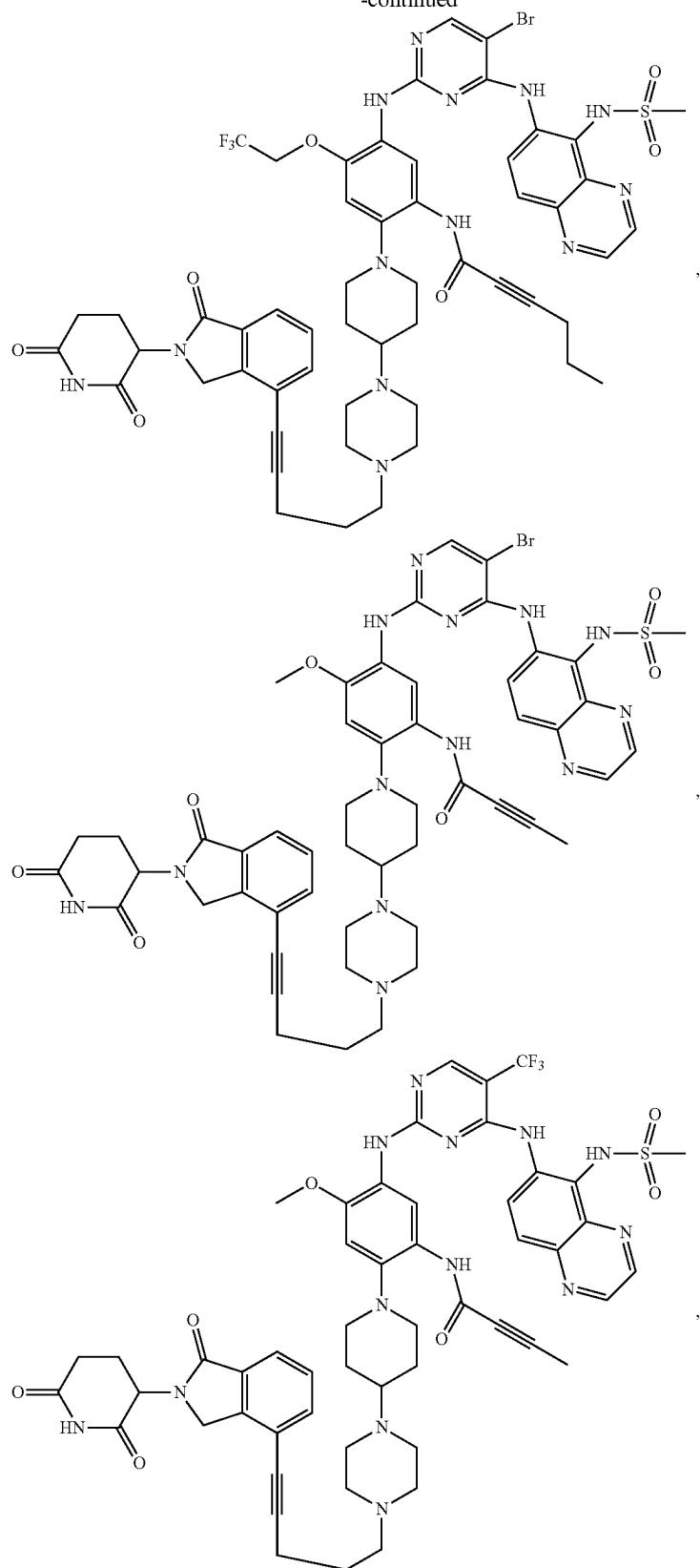
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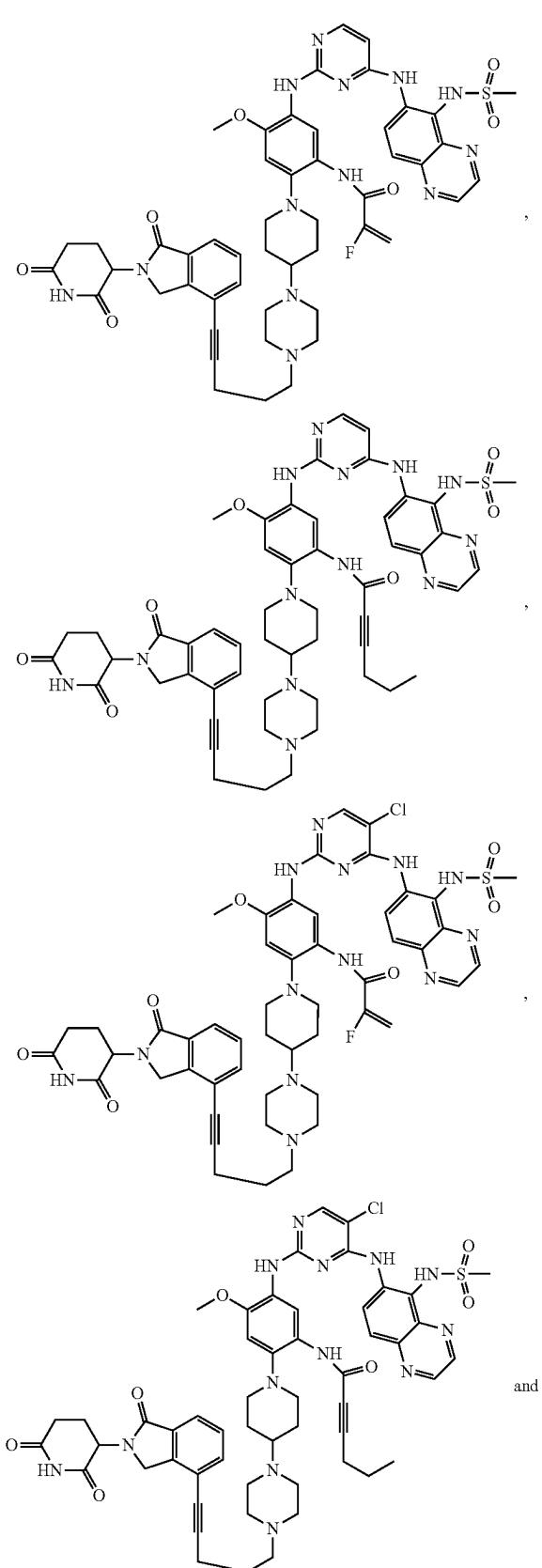


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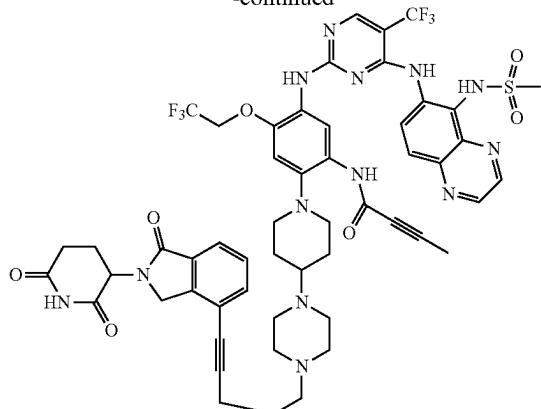


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37. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, and a pharmaceutically acceptable excipient; optionally, further comprising other therapeutic agents.

38. (canceled)

39. A method for treating and/or preventing a disease in a subject, the method comprising administering to the subject a compound of claim 1 or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the disease has any one of the following definitions:

i) wherein the disease is an EGFR kinase-mediated disease;

ii) wherein the disease is an EGFR kinase-mediated disease, wherein the EGFR kinase-mediated disease comprises cancer, such as ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukemia, lymphoma, non-Hodgkin lymphoma, gastric cancer, lung cancer, hepatocellular carcinoma, gastrointestinal stromal tumor (GIST), thyroid cancer, bile duct cancer, endometrial cancer, renal cancer, anaplastic large cell lymphoma, acute myeloid leukemia (AML), multiple myeloma, melanoma, mesothelioma; and

iii) wherein the disease is an EGFR kinase-mediated disease, wherein the EGFR kinase-mediated disease is lung cancer, particularly non-small cell lung cancer.

40-42. (canceled)

43. A pharmaceutical composition comprising a compound according to claim 2, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, and a pharmaceutically acceptable excipient; optionally, further comprising other therapeutic agents.

44. A pharmaceutical composition comprising a compound according to claim 36, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, and a pharmaceutically acceptable excipient; optionally, further comprising other therapeutic agents.

45. A method for treating and/or preventing a disease in a subject, the method comprising administering to the sub-

ject a compound of claim **2** or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the disease has any one of the following definitions:

- i) wherein the disease is an EGFR kinase-mediated disease;
 - ii) wherein the disease is an EGFR kinase-mediated disease, wherein the EGFR kinase-mediated disease comprises cancer, such as ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukemia, lymphoma, non-Hodgkin lymphoma, gastric cancer, lung cancer, hepatocellular carcinoma, gastric cancer, gastrointestinal stromal tumor (GIST), thyroid cancer, bile duct cancer, endometrial cancer, renal cancer, anaplastic large cell lymphoma, acute myeloid leukemia (AML), multiple myeloma, melanoma, mesothelioma; and
 - iii) wherein the disease is an EGFR kinase-mediated disease, wherein the EGFR kinase-mediated disease is lung cancer, particularly non-small cell lung cancer.
- 46.** A method for treating and/or preventing a disease in a subject, the method comprising administering to the sub-

ject a compound of claim **36** or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate, solvate, hydrate, polymorph, prodrug or isotopic variant thereof, or a mixture thereof, wherein the disease has any one of the following definitions:

- i) wherein the disease is an EGFR kinase-mediated disease;
- ii) wherein the disease is an EGFR kinase-mediated disease, wherein the EGFR kinase-mediated disease comprises cancer, such as ovarian cancer, cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, melanoma, prostate cancer, leukemia, lymphoma, non-Hodgkin lymphoma, gastric cancer, lung cancer, hepatocellular carcinoma, gastric cancer, gastrointestinal stromal tumor (GIST), thyroid cancer, bile duct cancer, endometrial cancer, renal cancer, anaplastic large cell lymphoma, acute myeloid leukemia (AML), multiple myeloma, melanoma, mesothelioma; and
- iii) wherein the disease is an EGFR kinase-mediated disease, wherein the EGFR kinase-mediated disease is lung cancer, particularly non-small cell lung cancer.

* * * * *