WEE1 INHIBITORS AND METHODS FOR TREATING CANCER

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application Nos. 63/562,624, filed March 7, 2024 and 63/654,767, filed May 31, 2024, each of which is incorporated by reference in their entireties.

BACKGROUND

Field

[0002] The present application relates generally to compounds that are WEE1 inhibitors and/or degraders thereof, and methods of using them to treat conditions characterized by excessive cellular proliferation, such as cancer.

Description

[0003] DNA is constantly damaged from the environment. Light, chemicals, stress, and cellular replication lead to single- or double-stranded breakage along DNA's backbone. Typically, organisms defend against DNA damage using repair proteins that either re-connect, or re-synthesize damaged DNA. The correct functioning of these proteins are essential for life. The incorrect replacement of nucleotides into DNA can cause mutations (and other genetic alterations including, but not limited to, insertions, deletions and frameshifts), genetic disease and loss of protein function. The altogether loss of DNA repair can cause cell death, tumor progression and/or cancer.

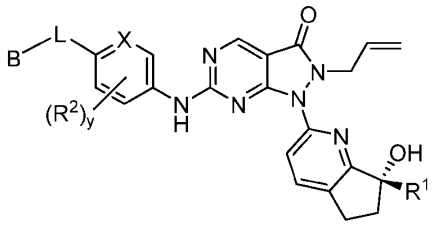
[0004] Cell cycle checkpoints are important for proper DNA repair, ensuring that cells do not progress with cellular replication until their genomic integrity is restored. WEE1 is a nuclear kinase involved in the G2–M cell-cycle checkpoint arrest for DNA repair before mitotic entry. Normal cells repair damaged DNA during G1 arrest. Cancer cells often have a deficient G1–S checkpoint and depend on a functional G2–M checkpoint for DNA repair. WEE1 is overexpressed in various cancer types.

[0005] Various inhibitors and/or degraders of WEE1 are known to those skilled in the art. *See, e.g.*, International Patent Application Publication Nos. WO

2019/173082 and WO 2020/069105. However, there remains an urgent need for inhibitors and/or degraders of WEE1 that are useful for the treatment of conditions characterized by excessive cellular proliferation, such as cancer.

SUMMARY

[0006] Various embodiments provide a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein the variables **X**, **L**, **B**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, **n**, **p**, **q**, **r**, **s**, **t**, **u**, **v**, **w** and **y** are as defined herein.

[0007] Another embodiment provides a compound, or a pharmaceutically acceptable salt thereof, wherein the compound has a structure selected from those of Compound Nos. 1 to 44 as described herein.

[0008] Another embodiment provides a pharmaceutical composition comprising an effective amount of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0009] Another embodiment provides a method of ameliorating or treating a cancer in a subject comprising administering to the subject an effective amount of a compound of Formula (I) as described herein, or a compound selected from Compound Nos. 1 to 44 as described herein, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as described herein, wherein the cancer is selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant

melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.

[0010] Another embodiment provides a method of inhibiting replication of a malignant growth or a tumor in a subject comprising administering to the subject and/or contacting the malignant growth or the tumor with an effective amount of a compound of Formula (I) as described herein, or a compound selected from Compound Nos. 1 to 44 as described herein, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as described herein, wherein the malignant growth or tumor is due to a cancer selected from the list of cancers described herein.

[0011] Another embodiment provides a method of ameliorating or treating a malignant growth or a tumor in a subject and/or contacting the malignant growth or the tumor with comprising administering to the subject an effective amount of a compound of Formula (I) as described herein, or a compound selected from Compound Nos. 1 to 44 as described herein, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as described herein, wherein the malignant growth or tumor is due to a cancer selected from the list of cancers described herein.

DETAILED DESCRIPTION

[0012] WEE1 is a tyrosine kinase that is a critical component of the ATR-mediated G2 cell cycle checkpoint control that prevents entry into mitosis in response to cellular DNA damage. ATR phosphorylates and activates CHK1, which in turn activates WEE1, leading to the selective phosphorylation of cyclin-dependent kinase 1 (CDK1) at Tyr15, thereby stabilizing the CDK1-cyclin B complex and halting cell-cycle progression. This process confers a survival advantage by allowing tumor cells time to repair damaged DNA prior to entering mitosis. Inhibition of WEE1 abrogates the G2 checkpoint, promoting cancer cells with DNA damage to enter into unscheduled mitosis and undergo cell death via mitotic catastrophe. Therefore, WEE1 inhibition and/or degradation has the potential to sensitize tumors to DNA-damaging agents, such as cisplatin, and to induce tumor cell death.

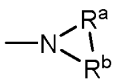
Definitions

[0013] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0014] Whenever a group is described as being "substituted or unsubstituted" or "a substituted or an unsubstituted," that group may be unsubstituted or substituted with one or more of the indicated substituents. If no substituents are indicated, it is meant that the group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), cycloalkyl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, nitro, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, haloalkoxy, an amino, a mono-substituted amine group, a di-substituted amine group and an amine(C_1-C_6 alkyl).

[0015] As used herein, "C_a to C_b" in which "a" and "b" are integers refer to the number of carbon atoms in a group. The indicated group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated, the broadest range described in these definitions is to be assumed.

[0016] If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0017] As used herein, the term "alkyl" refers to a fully saturated aliphatic hydrocarbon group. The alkyl moiety may be branched or straight chain. Examples of

branched alkyl groups include, but are not limited to, iso-propyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and the like. The alkyl group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as "1 to 30" refers to each integer in the given range; *e.g.*, "1 to 30 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. An alkyl group may be substituted or unsubstituted.

[0018] The term "alkenyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon double bond(s) including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like. An alkenyl group may be unsubstituted or substituted.

[0019] The term "alkynyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond(s) including, but not limited to, 1-propynyl, 1-butynyl, 2-butynyl and the like. An alkynyl group may be unsubstituted or substituted.

[0020] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term "fused" refers to two rings which have two atoms and one bond in common. As used herein, the term "bridged cycloalkyl" refers to compounds wherein the cycloalkyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term "spiro" refers to two rings which have one atom in common and the two rings are not linked by a bridge. Cycloalkyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Examples of mono-cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Examples of fused cycloalkyl groups are decahydronaphthalenyl, dodecahydro-1H-phenalenyl and tetradecahydroanthracenyl; examples of bridged cycloalkyl groups are bicyclo[1.1.1]pentyl, adamantanyl and norbornanyl; and examples of spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane.

[0021] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0022] As used herein, "carbocyclyl" refers to a non-aromatic a mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion, as described herein. Carbocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A carbocyclyl group may be unsubstituted or substituted. Examples of carbocyclyl groups include, but are in no way limited to, cycloalkyl groups and cycloalkenyl groups, as defined herein, and the non-aromatic portions of 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1*H*-indene, 5,6,7,8-tetrahydroquinoline and 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine.

[0023] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0024] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1, 2 or 3 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 16 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s), such as nine carbon atoms and one heteroatom; eight carbon atoms and two heteroatoms; seven carbon atoms and three heteroatoms; eight carbon atoms and one heteroatom; seven carbon atoms and two heteroatoms; six carbon atoms and three

heteroatoms; five carbon atoms and four heteroatoms; five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; or two carbon atoms and three heteroatoms. Furthermore, the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0025] As used herein, "heterocyclyl" refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems (*e.g.*, piperazin-2-one) and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term "fused" refers to two rings which have two atoms and one bond in common. As used herein, the term "bridged heterocyclyl" refers to compounds wherein the heterocyclyl contains a linkage of one or more atoms connecting non-adjacent atoms, *e.g.*, bicyclo[1.1.1]pentane. As used herein, the term "spiro" refers to two rings which have one atom in common and the two rings are not linked by a bridge. Heterocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). For example, five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; two carbon atoms and three heteroatoms; one carbon atom and four heteroatoms; three carbon atoms

and one heteroatom; or two carbon atoms and one heteroatom. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. Examples of such "heterocyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, azepane, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and/or 3,4-methylenedioxyphenyl). Examples of spiro heterocyclyl groups include 1-oxa-4λ^2,9λ^2-diazaspiro[5.5]undecane, 1-oxa-4,9-diazaspiro[5.5]undecane, 5-oxa-2,8-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxaspiro[3.4]octane and 2-azaspiro[3.4]octane.

[0026] As used herein, "alkylene groups" are straight-chained alkyl groups that are -CH_2- tethering, forming bonds to connect molecular fragments via their terminal carbon atoms. Embodiments of alkylene groups may be represented herein by –$(CH_2)_n$– where n is an integer in the range of 1 to 30. "Lower" alkylene groups are alkylene groups that contain 1 to 6 carbon atoms. Examples of lower alkylene groups include but are not limited to methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-) and butylene (-$CH_2CH_2CH_2CH_2$-). An alkylene group can be substituted by replacing one or more hydrogen of the alkylene group and/or by substituting both hydrogens on the same carbon with a cycloalkyl group (e.g., ).

[0027] As used herein, the term "hydroxy" refers to a –OH group.

[0028] As used herein, "alkoxy" refers to the Formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (iso-

propoxy), *n*-butoxy, iso-butoxy, *sec*-butoxy, *tert*-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0029] As used herein, "acyl" refers to a hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) and heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0030] A "cyano" group refers to a "-CN" group.

[0031] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0032] A "thiocarbonyl" group refers to a "-C(=S)R" group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0033] An "O-carbamyl" group refers to a "-OC(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0034] An "N-carbamyl" group refers to an "ROC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0035] An "O-thiocarbamyl" group refers to a "-OC(=S)-N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0036] An "N-thiocarbamyl" group refers to an "ROC(=S)N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0037] A "C-amido" group refers to a "-C(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0038] An "N-amido" group refers to a "RC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0039] An "S-sulfonamido" group refers to a "-SO_2N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0040] An "N-sulfonamido" group refers to a "RSO_2N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0041] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0042] The terms "ester" and "C-carboxy" refer to a "-C(=O)OR" group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0043] A "nitro" group refers to an "–NO_2" group.

[0044] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0045] A "sulfinyl" group refers to an "-S(=O)-R" group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0046] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0047] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl, tri-haloalkyl and polyhaloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl, 2-fluoroisobutyl and pentafluoroethyl. A haloalkyl may be substituted or unsubstituted.

[0048] As used herein, "haloalkoxy" refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0049] The term "amino" as used herein refers to a $-NH_2$ group.

[0050] A "mono-substituted amine" group refers to a "$-NHR_A$" group in which R_A can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. The R_A may be substituted or unsubstituted. Examples of mono-substituted amino groups include, but are not limited to, $-NH$(methyl), $-NH$(phenyl) and the like.

[0051] A "di-substituted amine" group refers to a "$-NR_AR_B$" group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. R_A and R_B can independently be substituted or unsubstituted. Examples of di-substituted amino groups include, but are not limited to, $-N(\text{methyl})_2$, $-N$(phenyl)(methyl), $-N$(ethyl)(methyl) and the like.

[0052] As used herein, "amine(alkyl)" group refers to an -(alkylene)-NR'R" radical where R' and R" are independently hydrogen or alkyl as defined herein. An amine(alkyl) may be substituted or unsubstituted. Examples of amine(alkyl) groups include, but are not limited to, $-CH_2NH$(methyl), $-CH_2NH$(phenyl), $-CH_2CH_2NH$(methyl), $-CH_2CH_2NH$(phenyl), $-CH_2N(\text{methyl})_2$, $-CH_2N$(phenyl)(methyl), $-NCH_2$(ethyl)(methyl), $-CH_2CH_2N(\text{methyl})_2$, $-CH_2CH_2N$(phenyl)(methyl), $-NCH_2CH_2$(ethyl)(methyl) and the like.

[0053] Where the number of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may

include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0054] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term "radical" can be used interchangeably with the term "group."

[0055] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, trifluoroacetic, benzoic, salicylic, 2-oxopentanedioic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine and salts with amino acids such as arginine and lysine. For compounds of Formula (I), those skilled in the art understand that when a salt is formed by protonation of a nitrogen-based group (for example, NH_2), the nitrogen-based group can be associated with a positive charge (for example, NH_2 can become NH_3^+) and the positive charge can be balanced by a negatively charged counterion (such as Cl^-).

[0056] The terms "WEE1 inhibition", "WEE1 inhibitor" and similar terms as used herein refer to inhibiting the activity or function of a WEE1 tyrosine kinase, e.g., by degrading WEE1 tyrosine kinase and/or by reducing the activity of WEE1 tyrosine kinase with regard to mediating phosphorylation of CDK1. A WEE1 inhibitor that functions by degrading WEE1 tyrosine kinase may be referred to herein as a WEE1 degrader.

[0057] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0058] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0059] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0060] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol or the like. Hydrates are formed when the solvent is water or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general,

the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

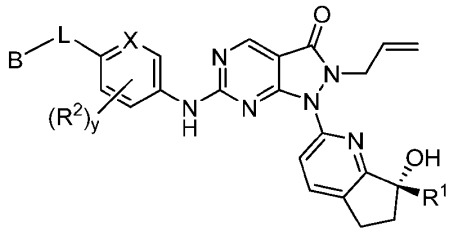
[0061] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0062] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes, but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components.

[0063] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

Compounds

[0064] This disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

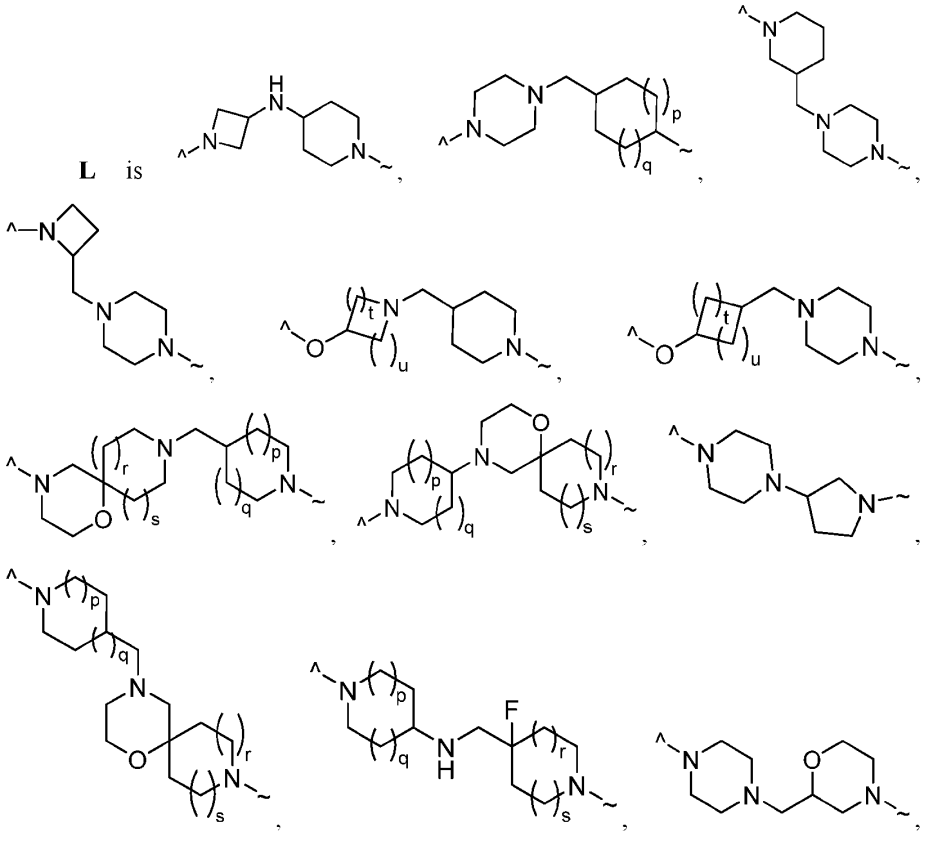
wherein:

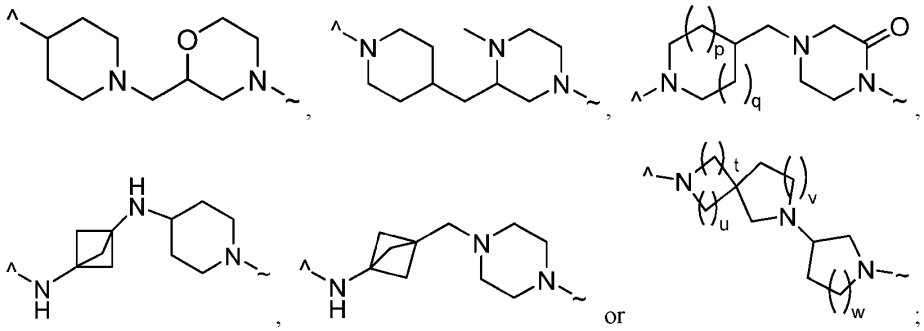
X is N (nitrogen) or −CH;

R^1 is a substituted or an unsubstituted C_1-C_6 alkyl;

R^2 is halogen, −CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

y is 0, 1 or 2;

L is 



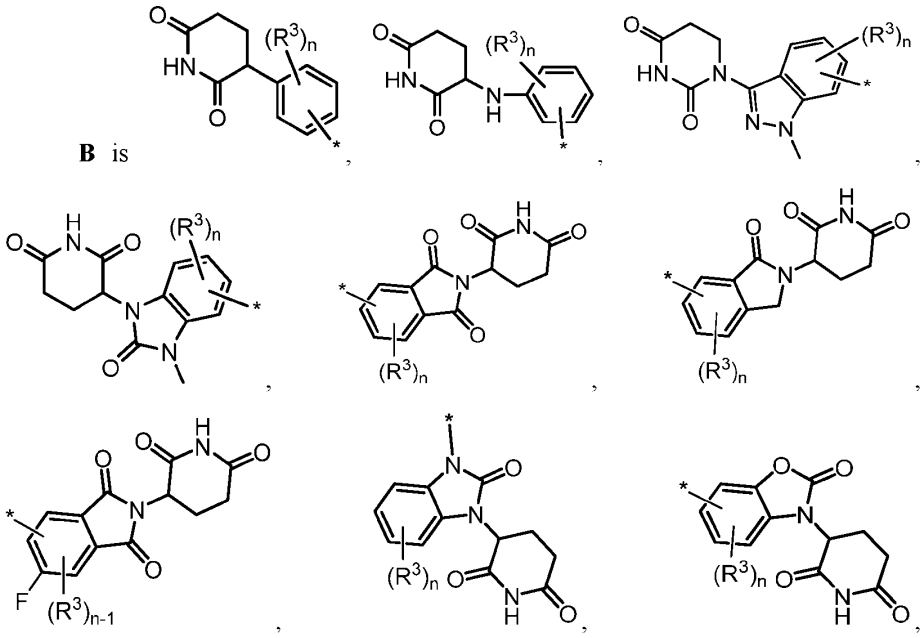
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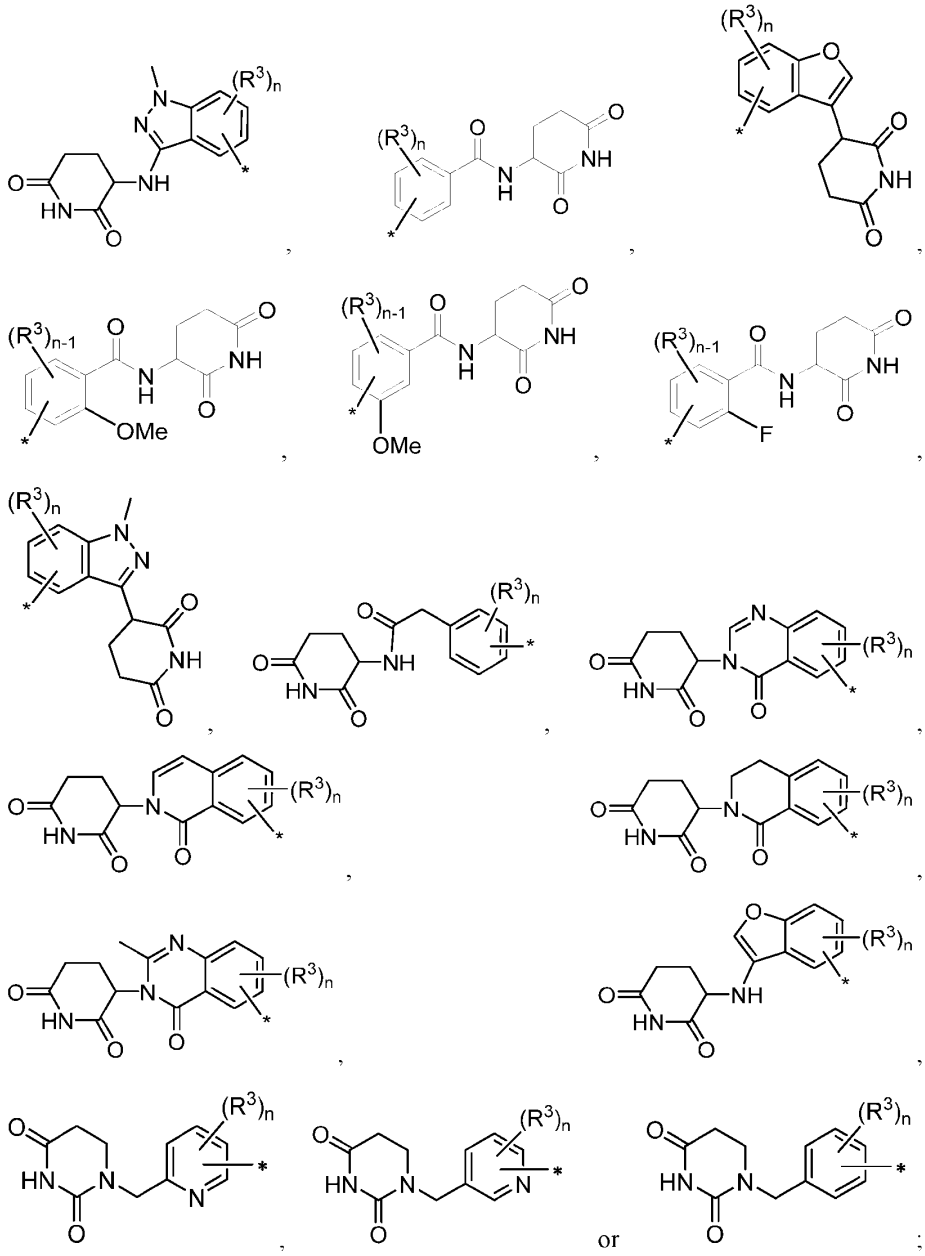
^ and ~ each indicate the point of attachment to **B** or the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$;

p, **q**, **r**, and **s**, for each instance, and **v** and **w**, are each independently 0, 1 or 2;

t and **u**, for each instance, are each independently 1 or 2; and

B is





wherein:

* indicates the point of attachment to **L**;

$\mathbf{R^3}$ is halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkoxy; and

n, for each instance, is 0, 1 or 2.

[0065] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **X** is −CH. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **X** is N (nitrogen). All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0066] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, ~ indicates the point of attachment to **B** and ^ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0067] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **p** and **q**, for each instance, are each 0. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **p**, for each instance, is 0 and **q**, for each instance, is 1; or **p**, for each instance, is 1 and **q**, for each instance, is 0. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **p** and **q**, for each instance, are each 1. In yet another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **p**, for each instance, is 1 and **q**, for each instance, is 2; or **p**, for each instance, is 2 and **q**, for each instance, is 1. In still another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **p** and **q**, for each instance, are each 2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

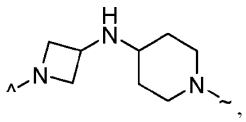
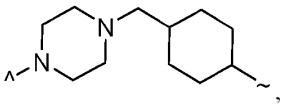
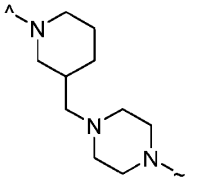
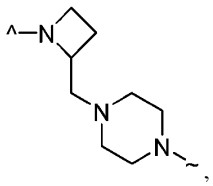
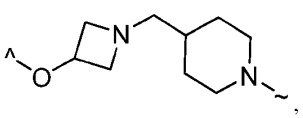
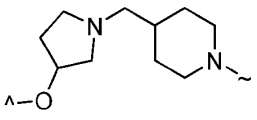
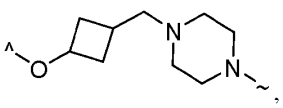
[0068] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **r** and **s**, for each instance, are each 0. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **r**, for each instance, is 0 and **s**, for each instance, is 1; or **r**, for each instance, is 1 and **s**, for each instance, is 0. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **r** and **s**, for each instance, are each 1. In yet another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **r**, for each instance, is 1 and **s**, for each instance, is 2; or **r**, for each instance, is 2 and **s**, for each instance, is 1. In still another embodiment, in a compound of Formula (I),

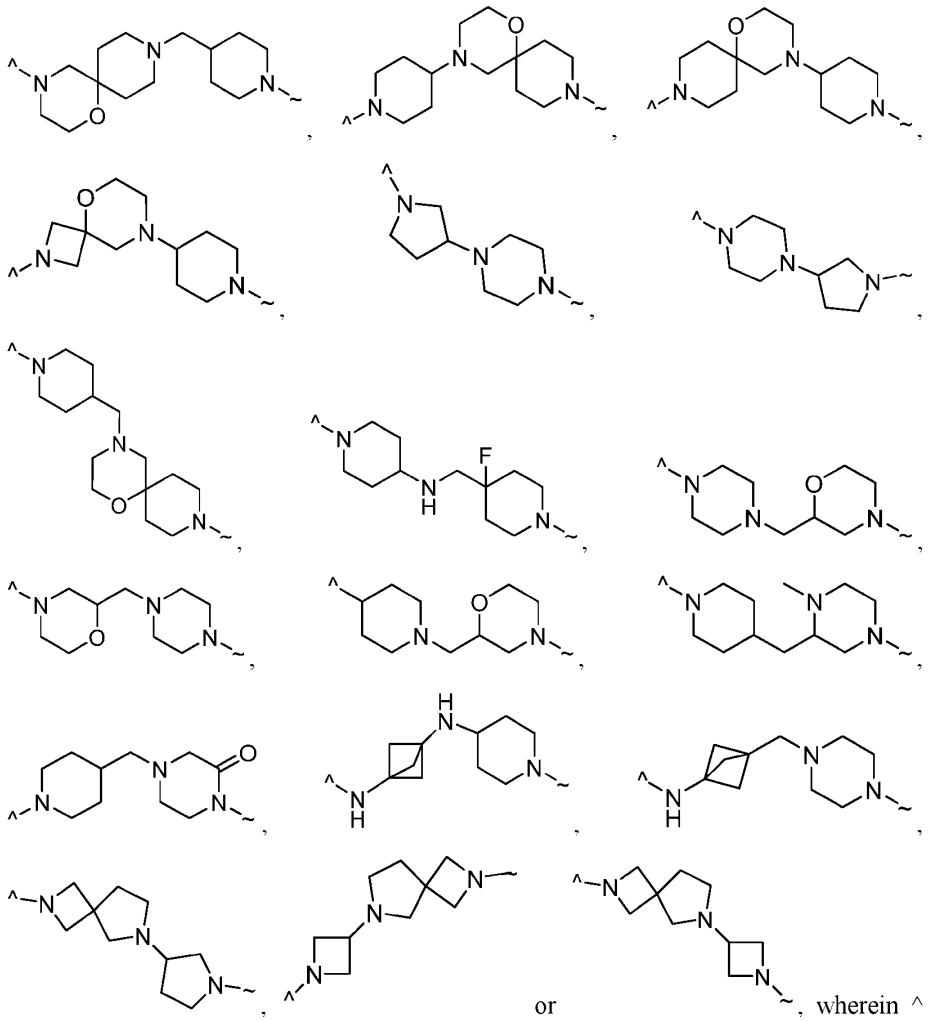
or a pharmaceutically acceptable salt thereof, **r** and **s**, for each instance, are each 2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0069] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **v** is 0. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **v** is 1. In yet another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **v** is 2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

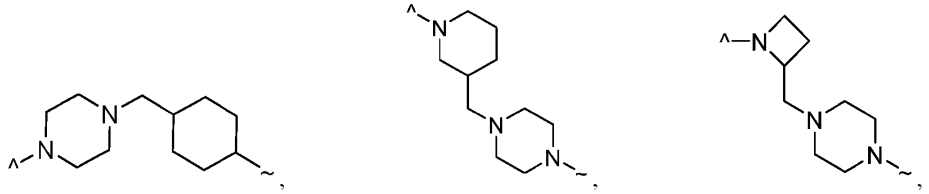
[0070] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **w** is 0. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **w** is 1. In yet another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **w** is 2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

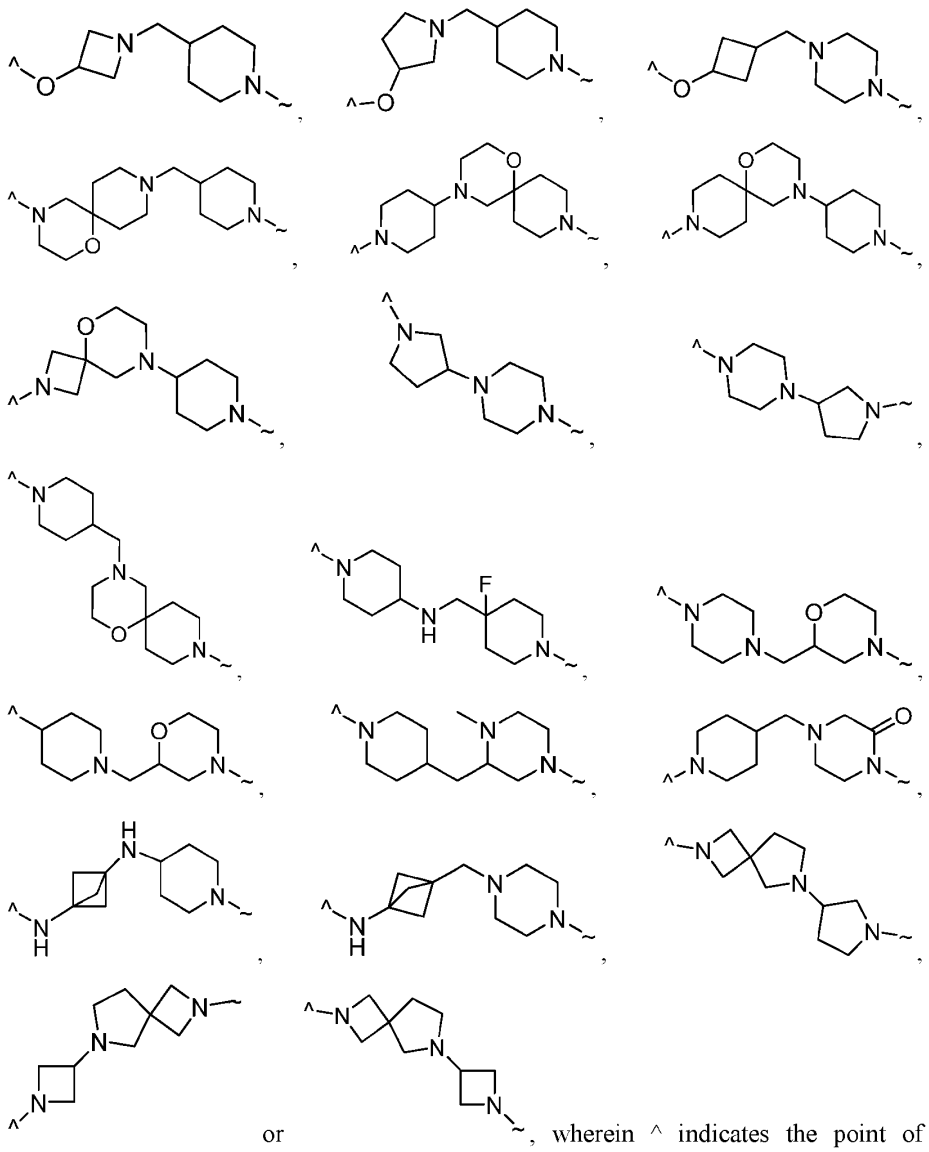
[0071] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **t** and **u** are each 1. In another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **t** is 1 and **u** is 2; or **t** is 2 and **u** is 1. In yet another embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **t** and **u** are each 2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

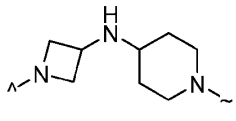
[0072] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **L** is , , , , , , .

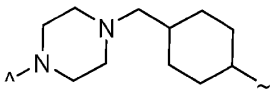
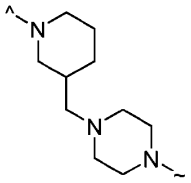
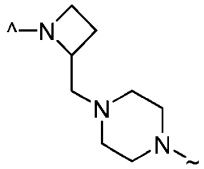
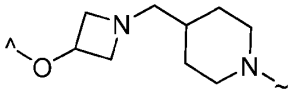
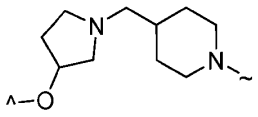
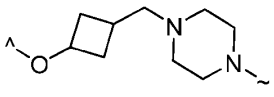
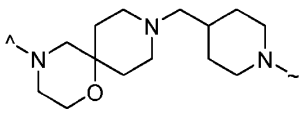


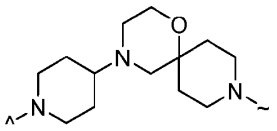
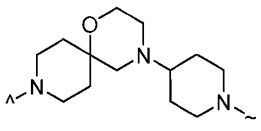
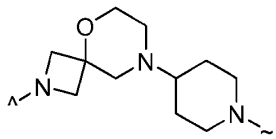
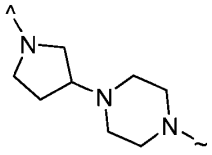
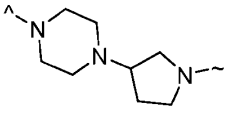
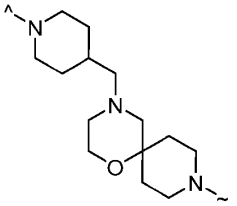
indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **L** is

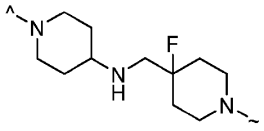
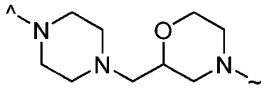
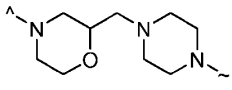
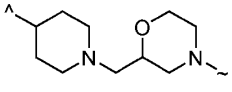
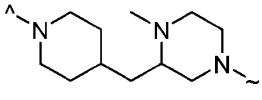
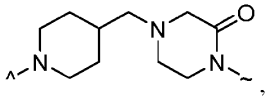
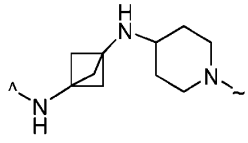
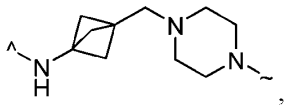


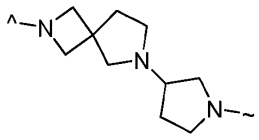
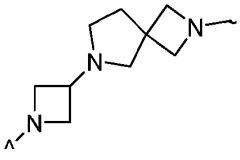
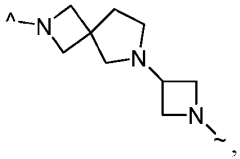


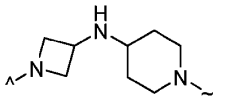
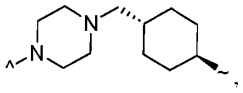
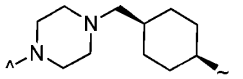
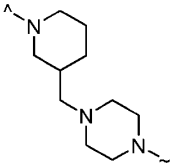
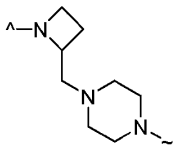
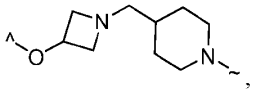
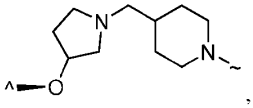
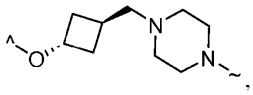
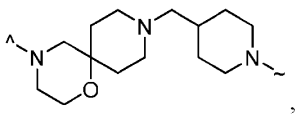
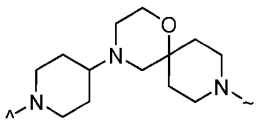
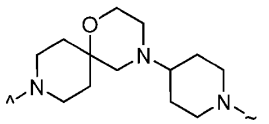
or , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. In one

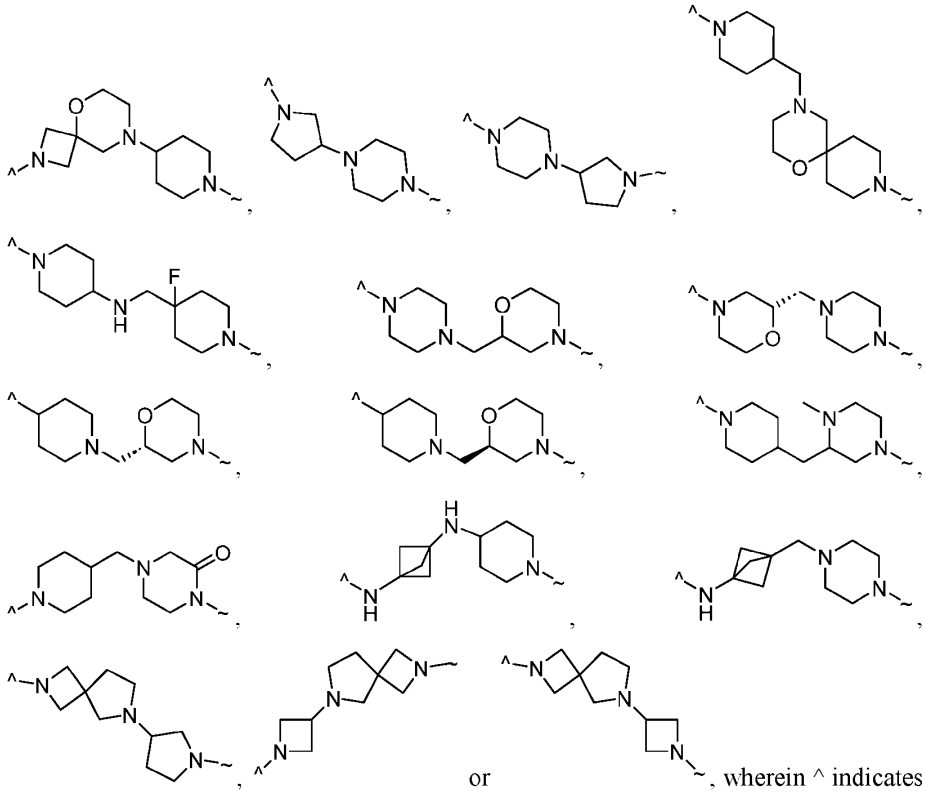
embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is

optionally substituted with **R²**. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with **R²**. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with **R²**. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with **R²**. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with **R²**. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with **R²**. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with **R²**. In one embodiment, **L** is

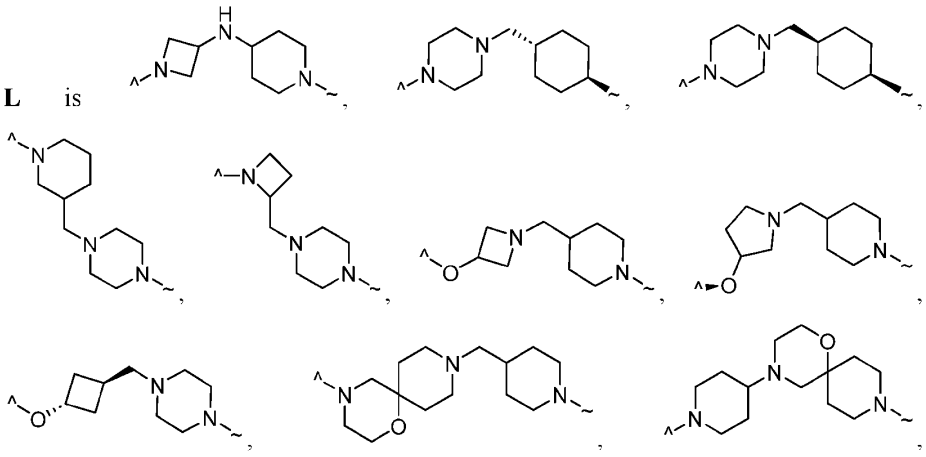

, wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally

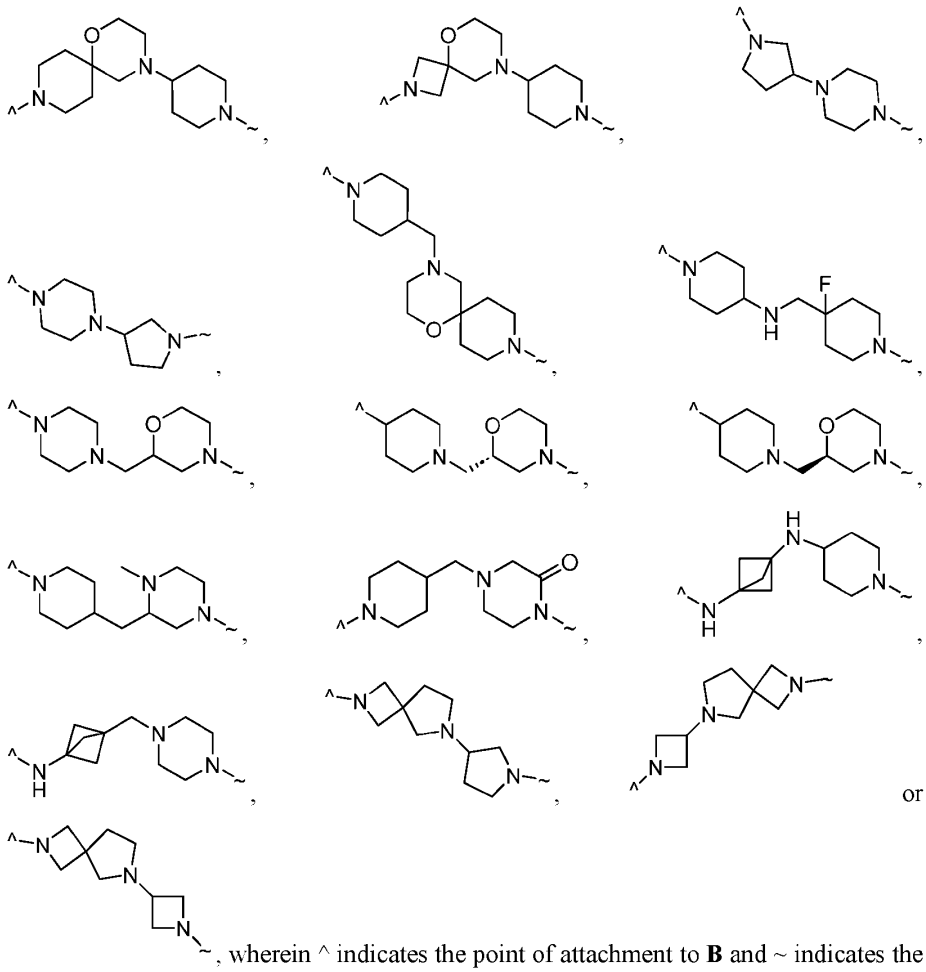
substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2.

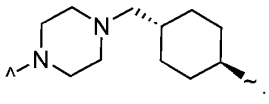
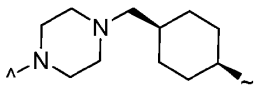
[0073] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **L** is , , , , , , , , , , .

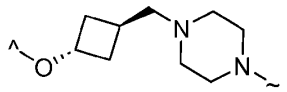
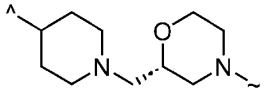
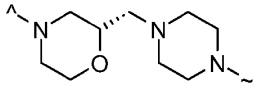
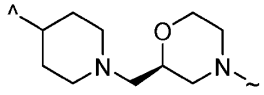


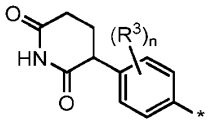
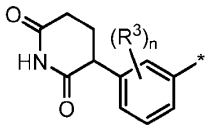
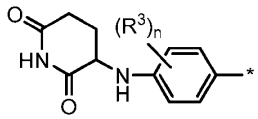
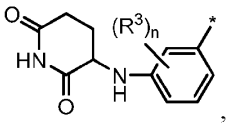
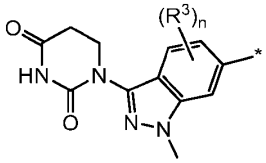
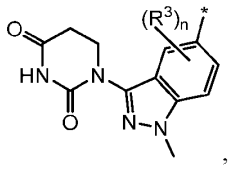
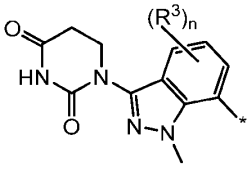
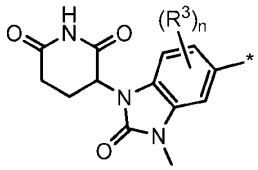
or , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

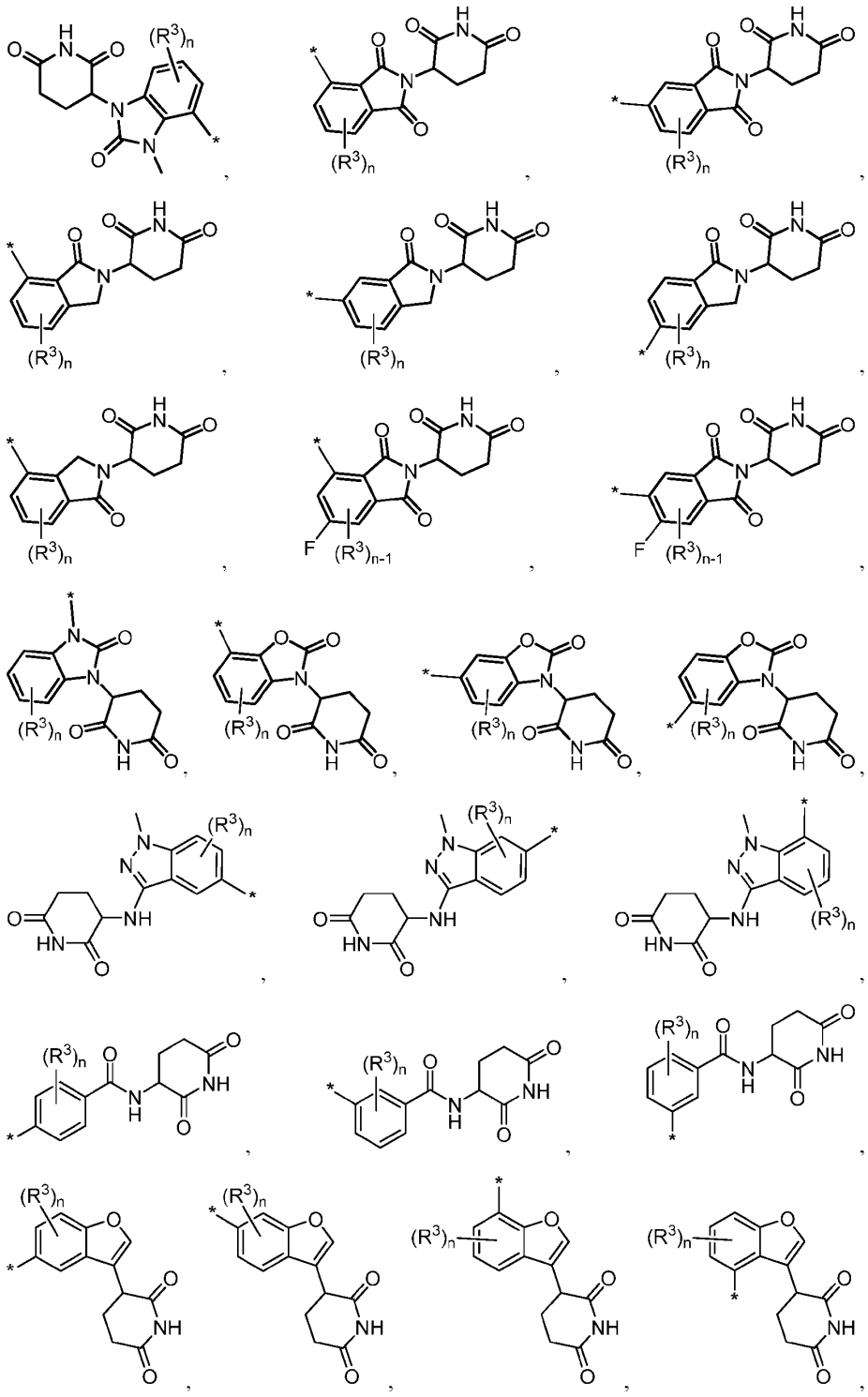
L is 

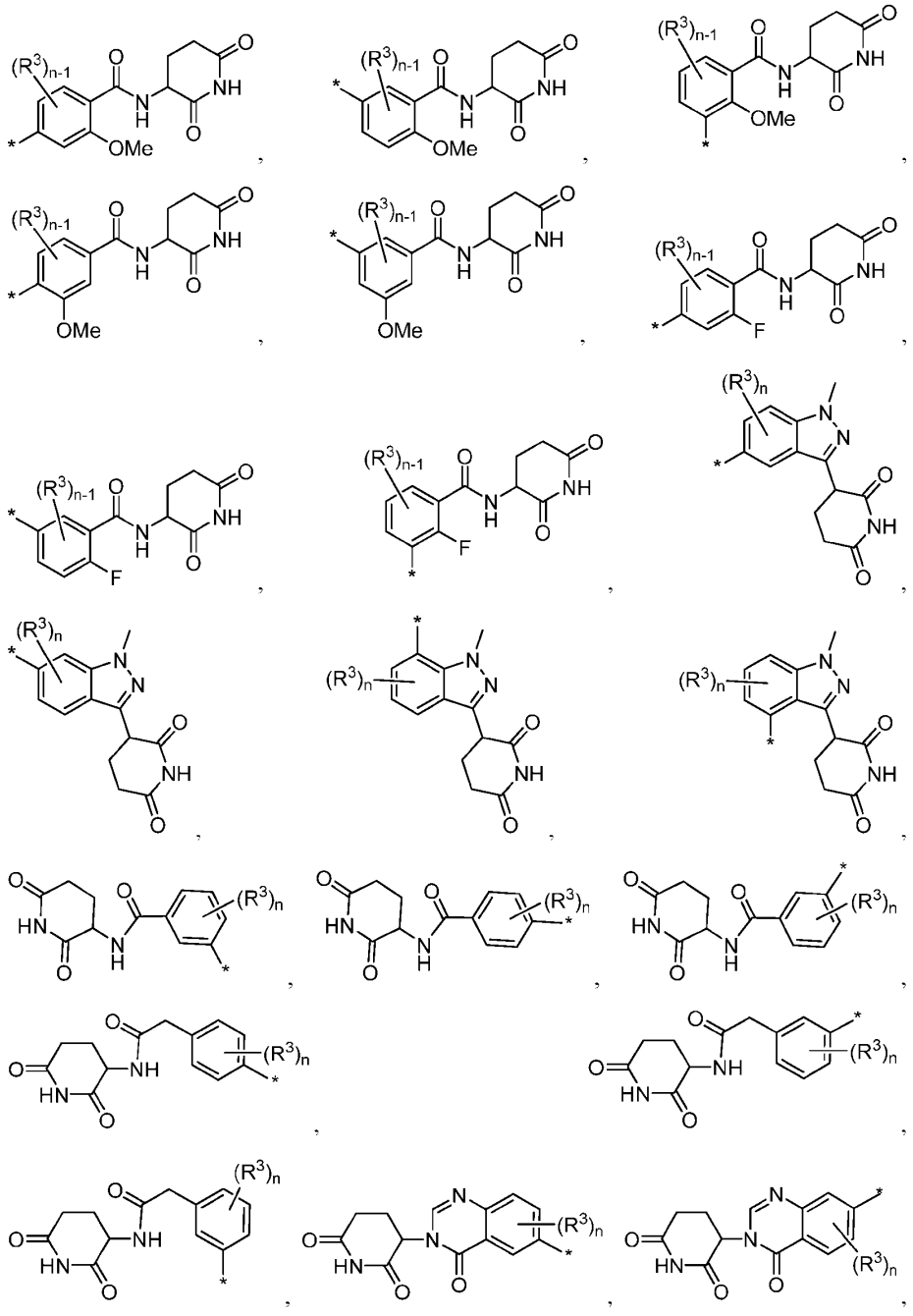


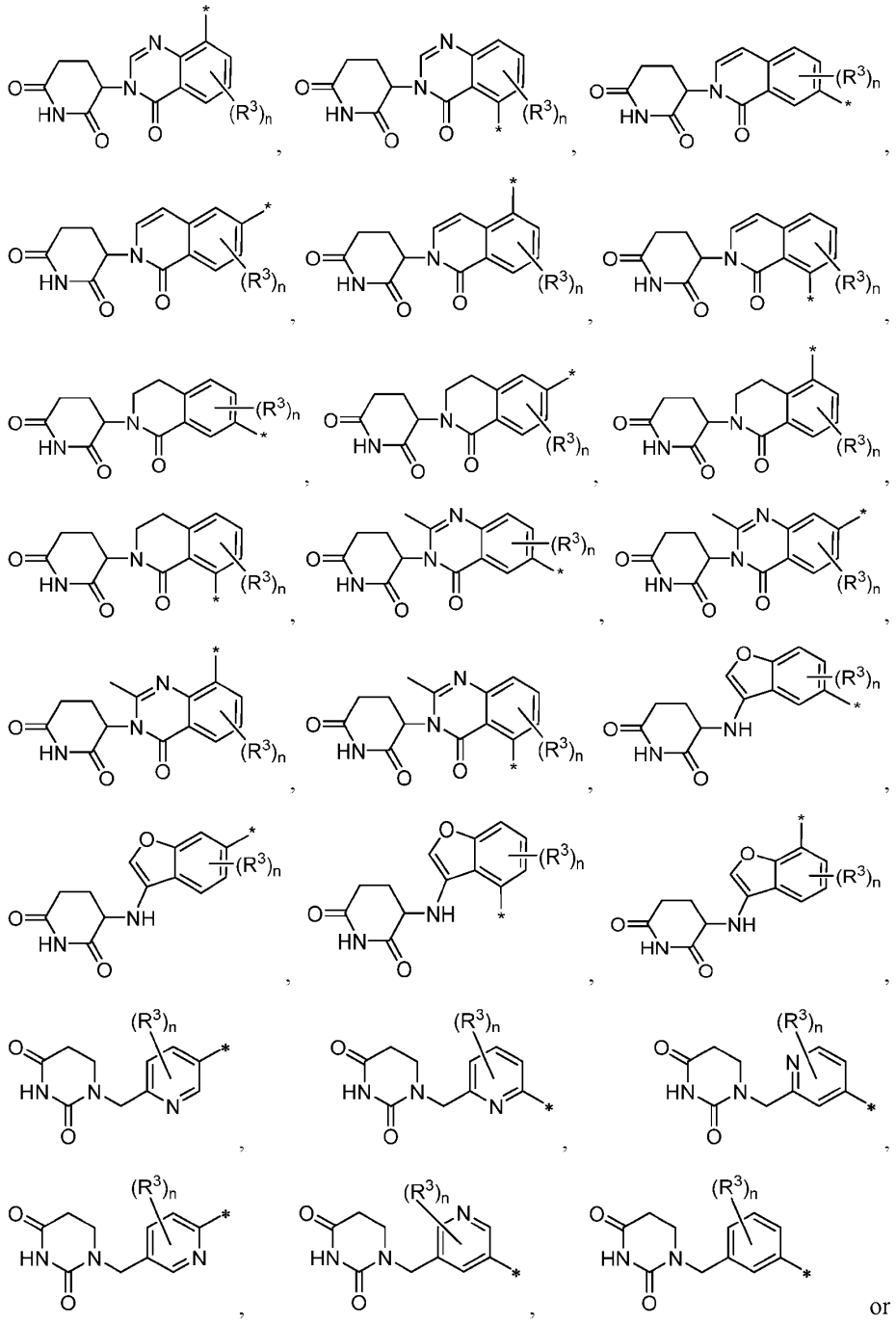
, wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments. In one embodiment, **L** is . wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. In one embodiment, **L** is . wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$. In one embodiment, **L** is

. wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is . wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is . wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. In one embodiment, **L** is . wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with R^2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

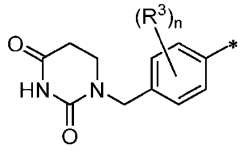
[0074] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is , , , , , , , .



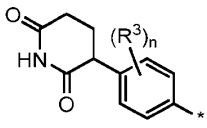
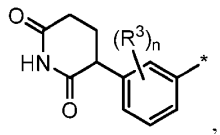
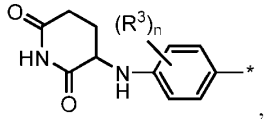
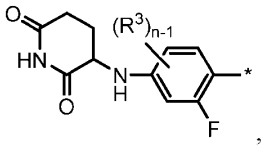
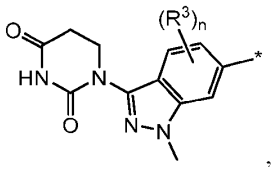
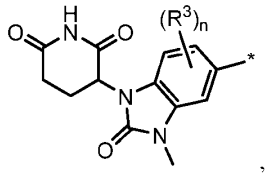
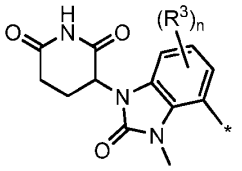
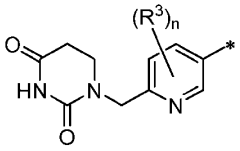
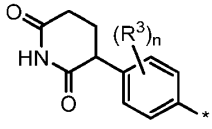
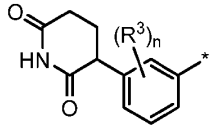
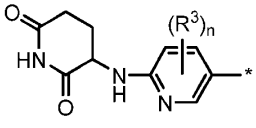


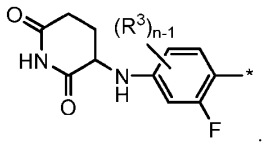
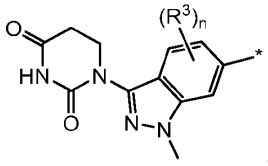
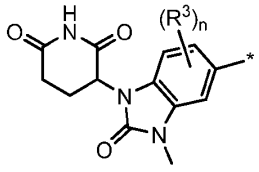
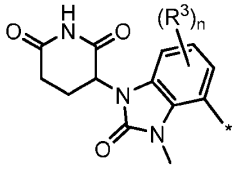
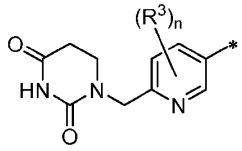


or



. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0075] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is , , , , , , , or . All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

B is  . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is  . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is  . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is  . In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **B** is  . All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0076] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkoxy. As used herein, non-limiting examples of halogen include F, Cl and Br. Non-limiting examples of C_1-C_4 alkyl include methyl, ethyl, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$ and any other branched butyl. Non-limiting examples of C_1-C_4 haloalkyl and C_1-C_4 fluoroalkyl include $-CF_3$, $-CHF_2$, $-CFH_2$ and any C_2-C_4 alkyl substituted with 1, 2, 3, 4 or 5 fluoro atoms. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl or C_1-C_4 alkoxy. non-limiting examples of C_1-C_4 alkoxys include methoxy, ethoxy, *n*-propoxy, iso-propoxy, *n*-butoxy, iso-butoxy, *sec*-butoxy and *tert*-butoxy. In one

embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is F, C_1-C_2 alkyl, C_1-C_2 fluoroalkyl or C_1-C_2 alkoxy. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is F. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0077] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **n**, for each instance, is 0 or 1. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **n**, for each instance, is 0. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **n**, for each instance, is 1. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

[0078] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is C_1-C_4 alkyl or C_1-C_4 haloalkyl. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is C_1-C_4 alkyl or C_1-C_4 fluoroalkyl. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is C_1-C_2 alkyl or C_1-C_2 fluoroalkyl. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is methyl. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is ethyl. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is $-CF_3$. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is $-CHF_2$. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

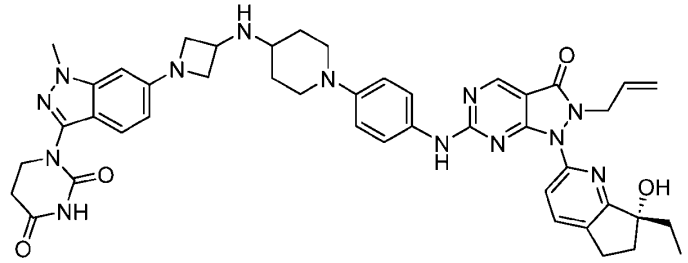
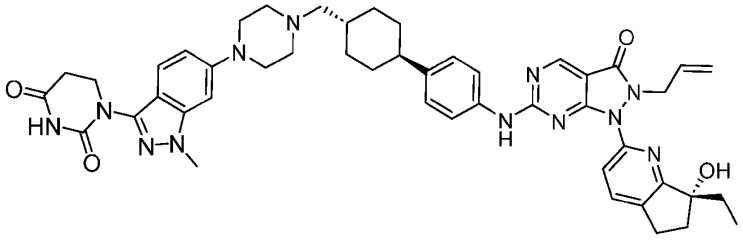
[0079] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is halogen, $-CN$, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is halogen, $-CN$, C_1-C_4 alkyl or C_1-C_4 haloalkyl. non-limiting examples of C_1-C_4 alkyls and C_1-C_4 haloalkyls are described herein. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is methyl, ethyl, *n*-propyl, iso-propyl, *n*-butyl, iso-butyl, *sec*-butyl, *tert*-butyl, $-CF_3$, $-CHF_2$ or $-CH_2F$. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is F, $-CN$, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

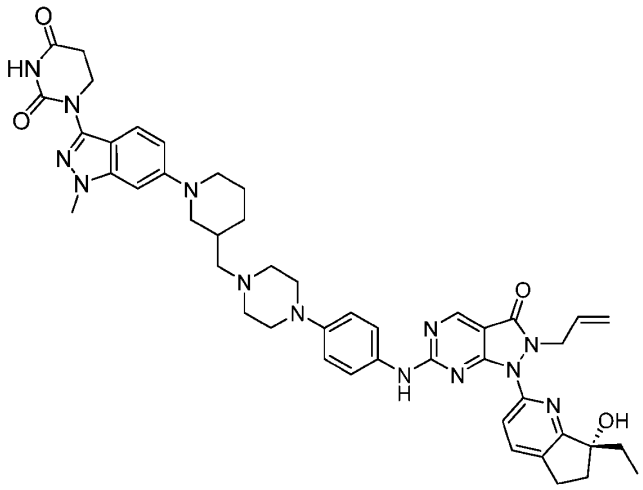
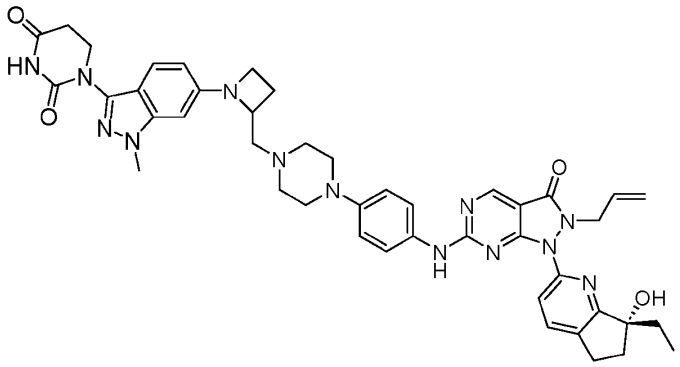
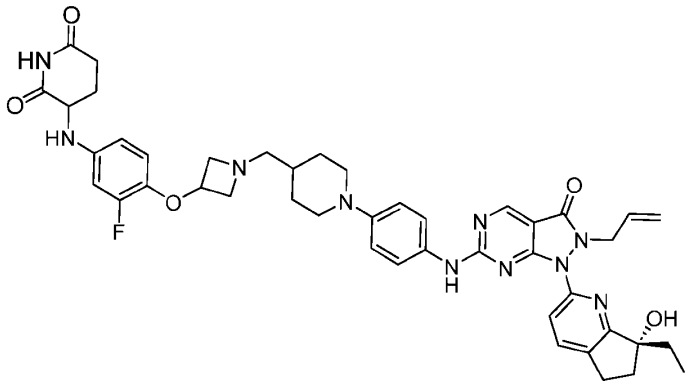
R^2 is F, −CN, C_1-C_2 alkyl or C_1-C_2 fluoroalkyl. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

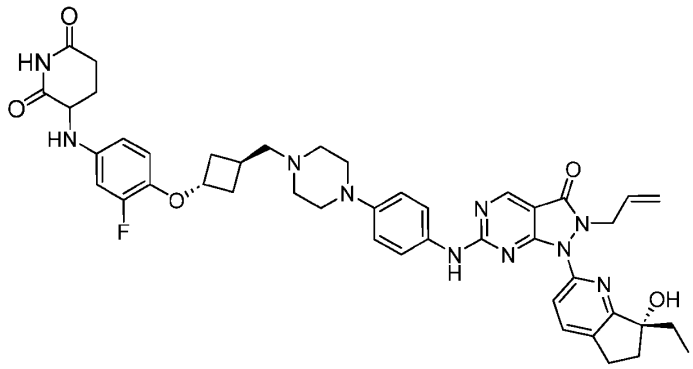
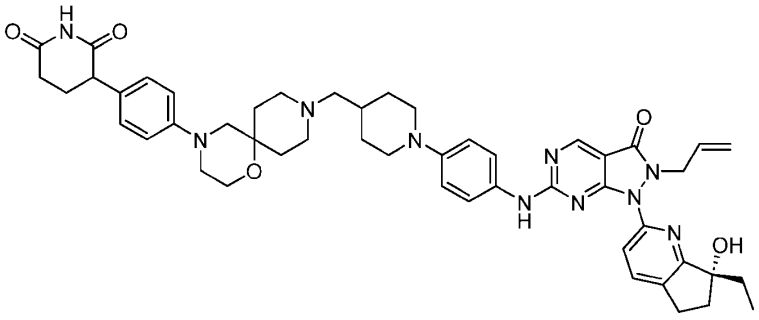
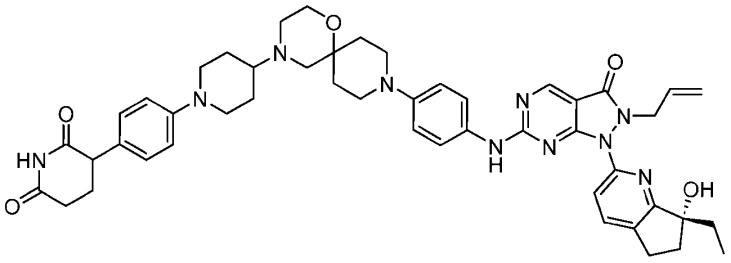
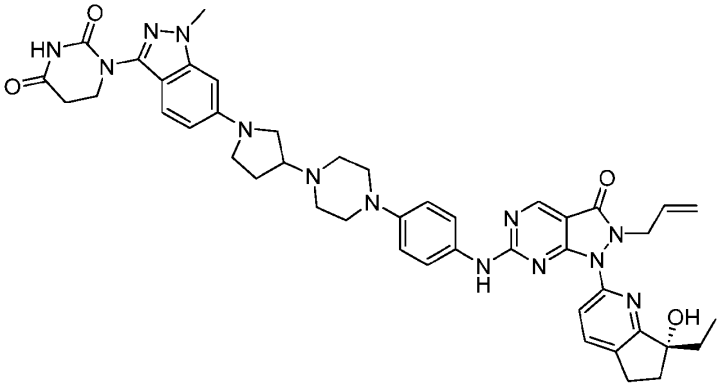
[0080] In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **y** is 0 or 1. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **y** is 1 or 2. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **y** is 0. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **y** is 1. In one embodiment, in a compound of Formula (I), or a pharmaceutically acceptable salt thereof, **y** is 2. All other variables in Formula (I), are as described in any one of the above embodiments and in any one of the following embodiments.

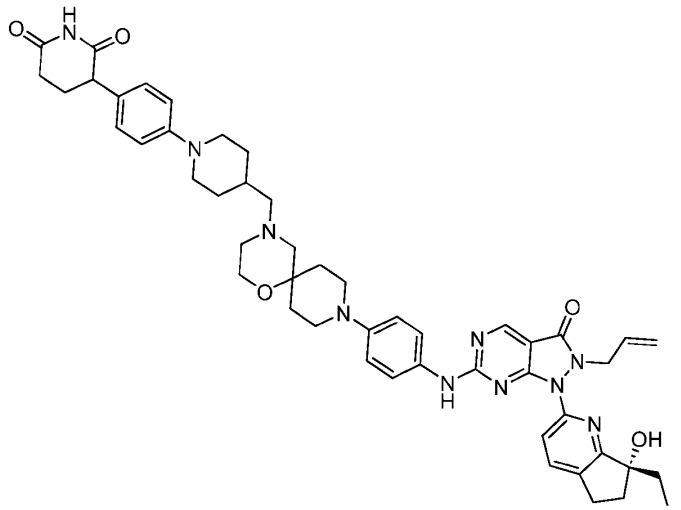
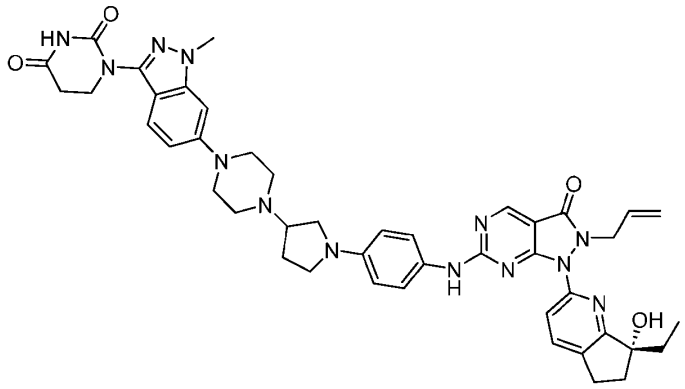
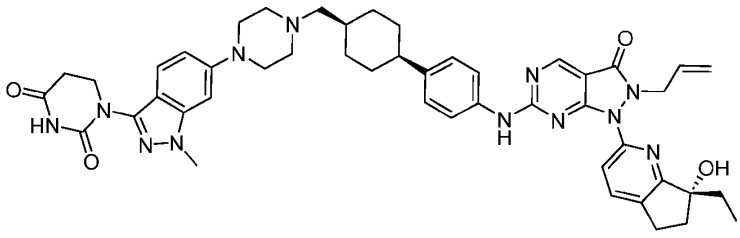
[0081] Various embodiments provide a compound (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, wherein the compound has a structure selected from those of Compound Nos. 1 to 44 as listed in the following Table 1, or a pharmaceutically acceptable salt thereof:

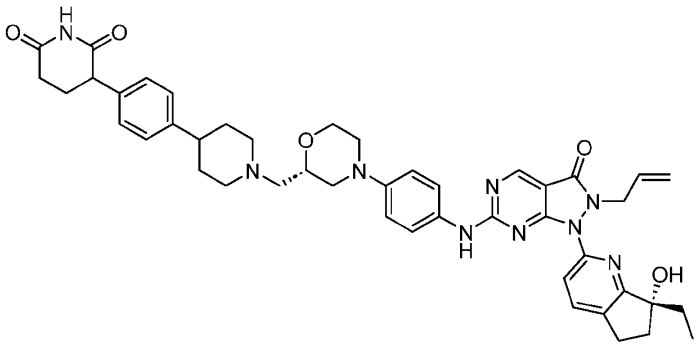
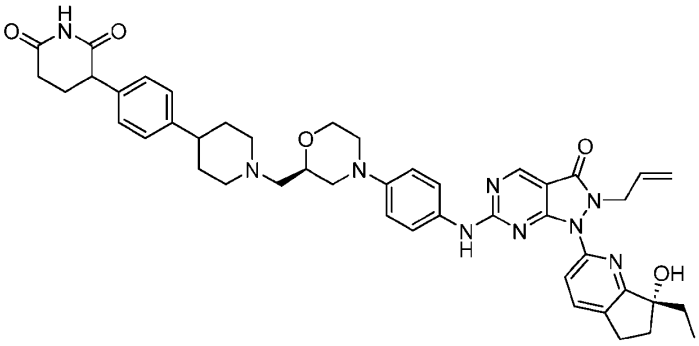
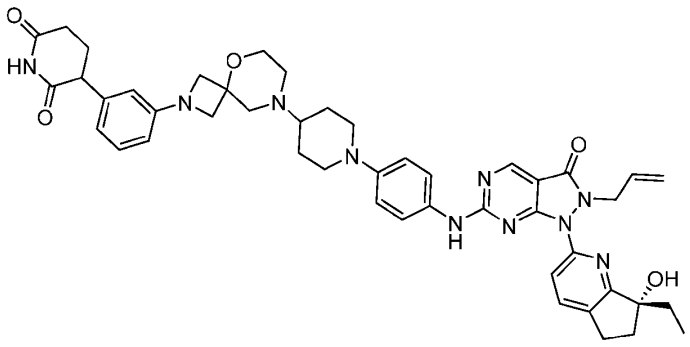
Table 1. Exemplary Compound Nos. 1 to 44.

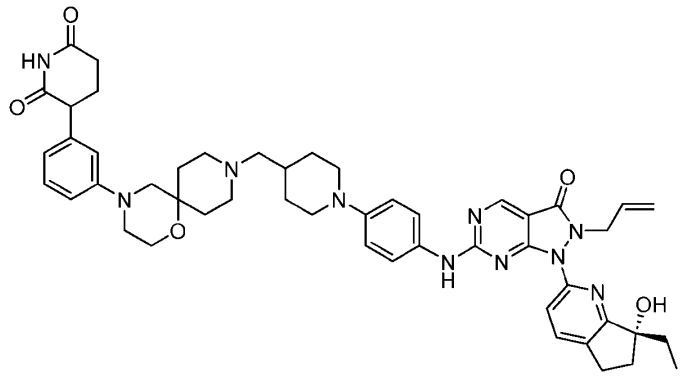
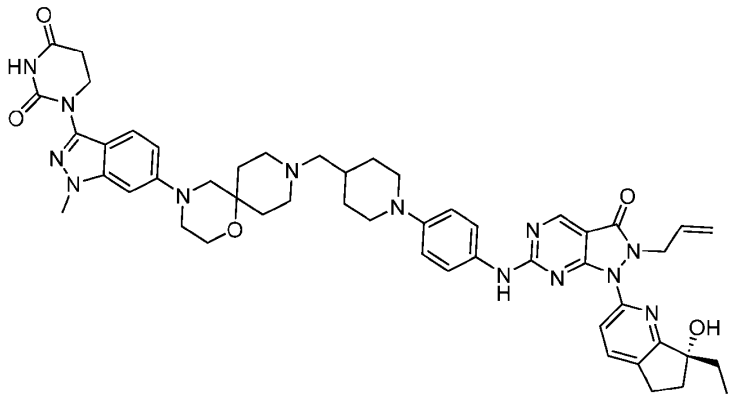
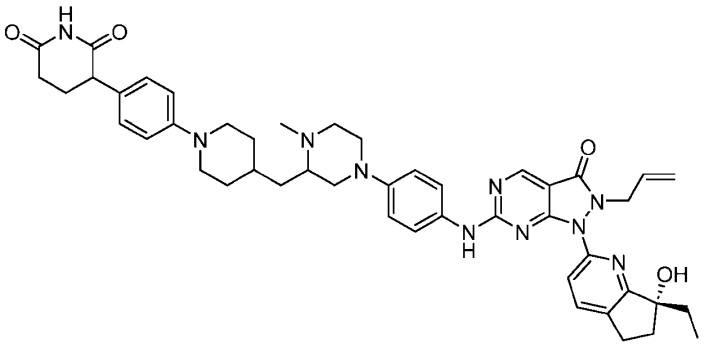
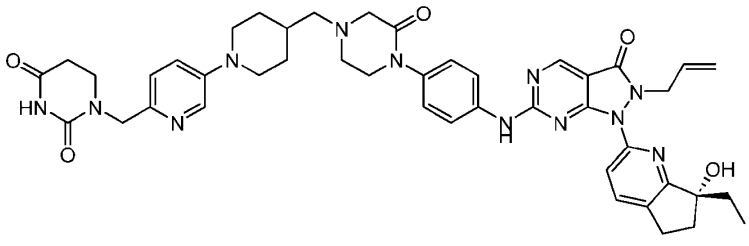
Compound No.	Structure
1	
2	

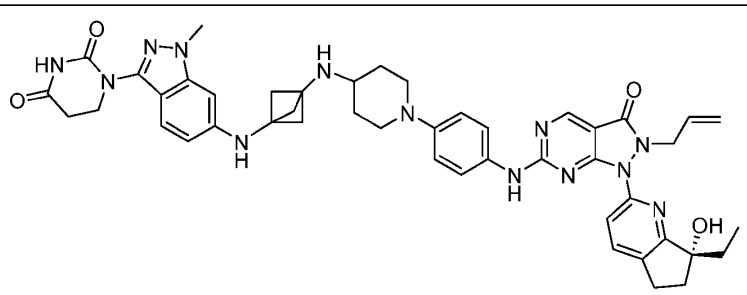
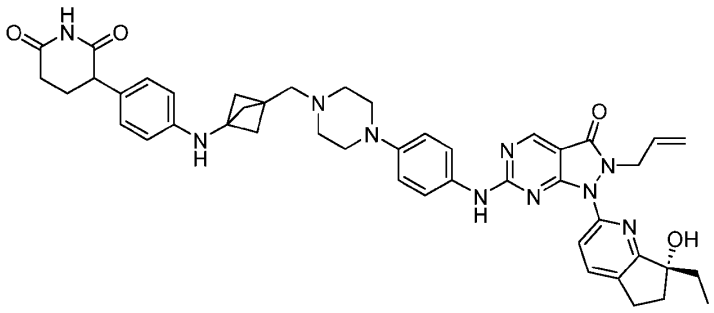
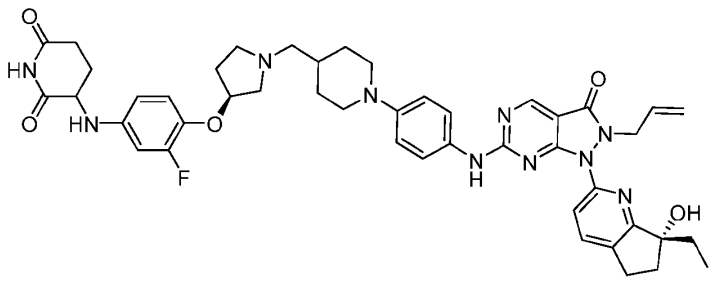
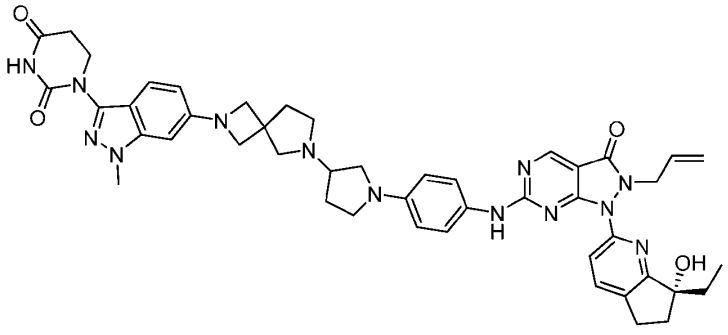
Compound No.	Structure
3	
4	
5	

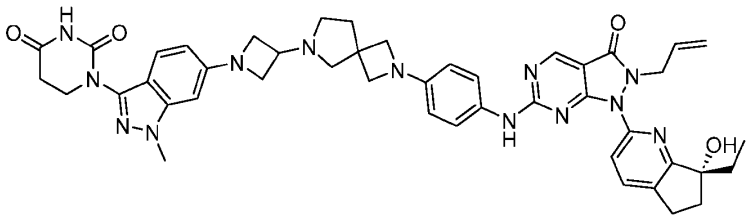
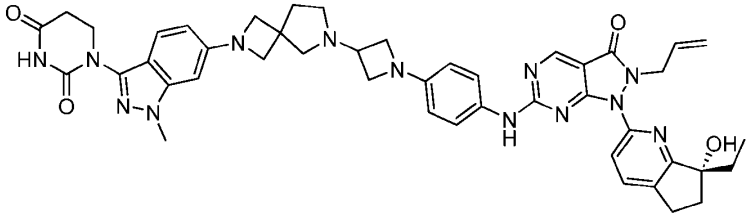
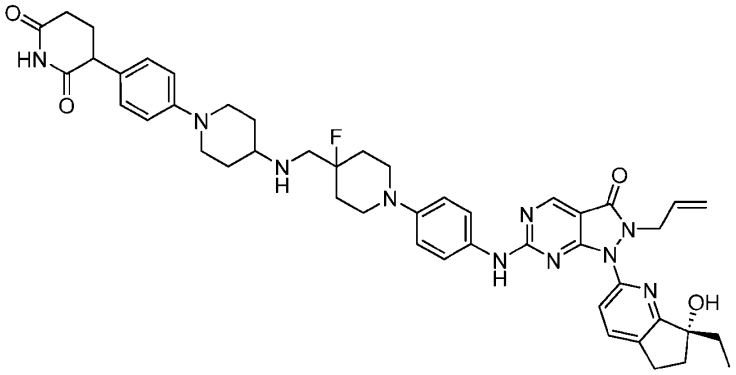
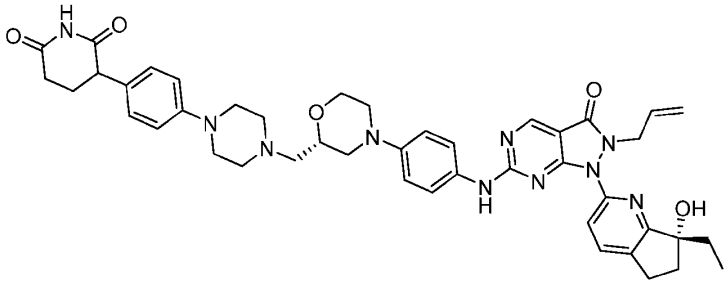
Compound No.	Structure
6	
7	
8	
9	

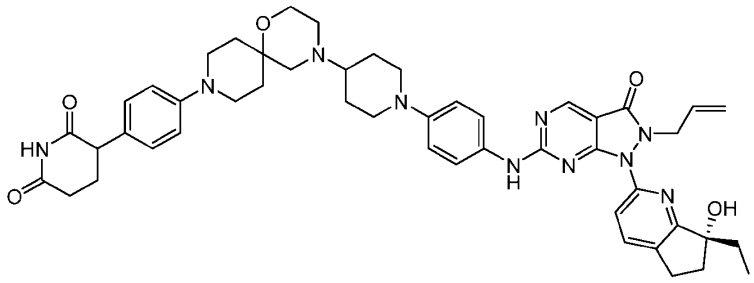
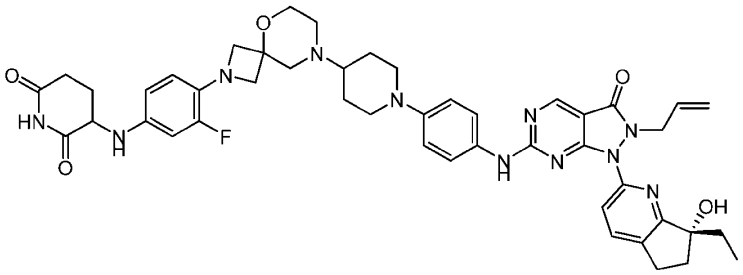
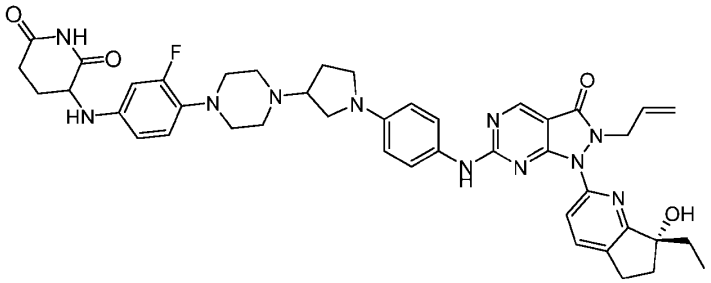
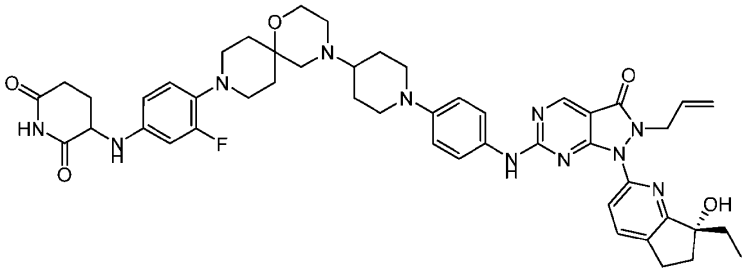
Compound No.	Structure
10	
11	
12	

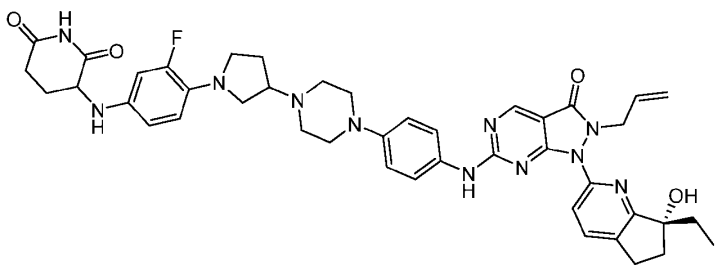
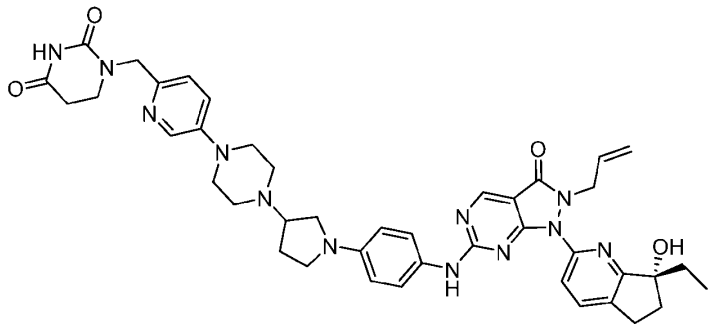
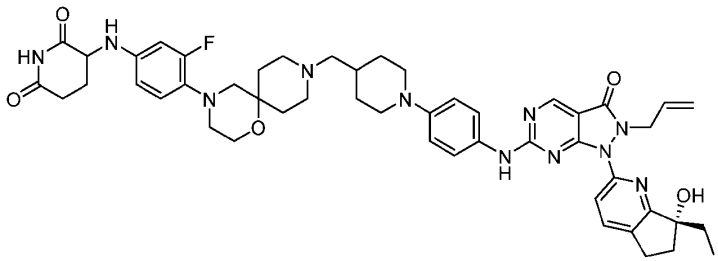
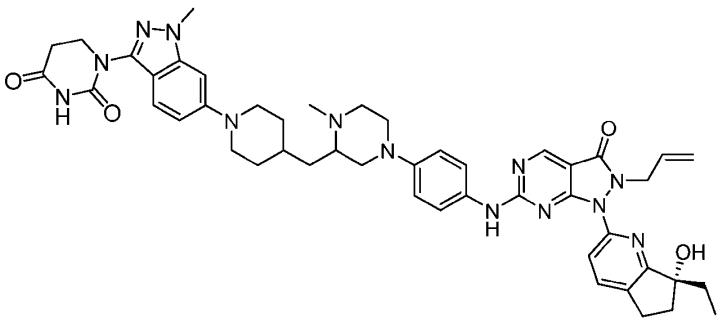
Compound No.	Structure
13	
14	
15	

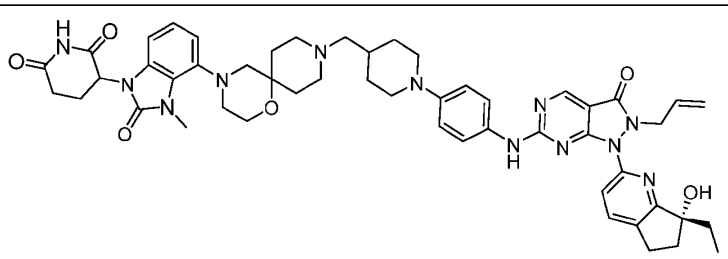
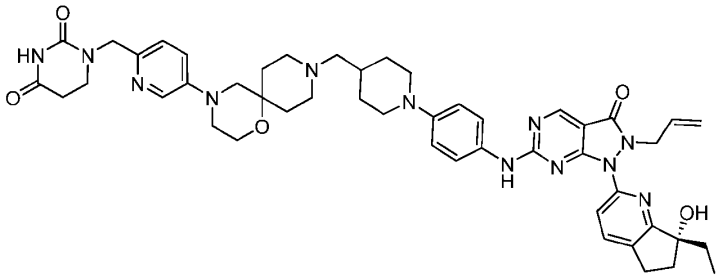
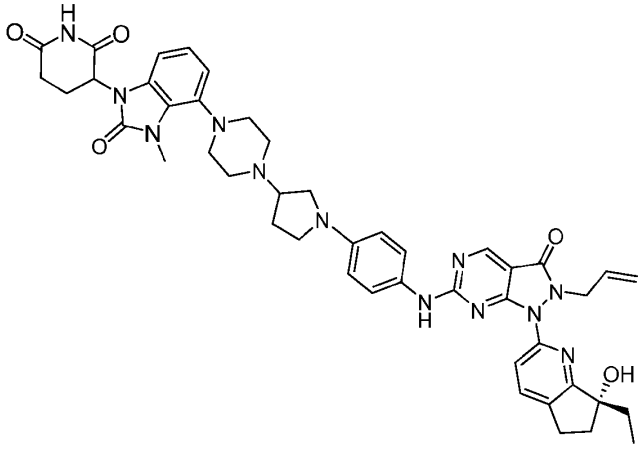
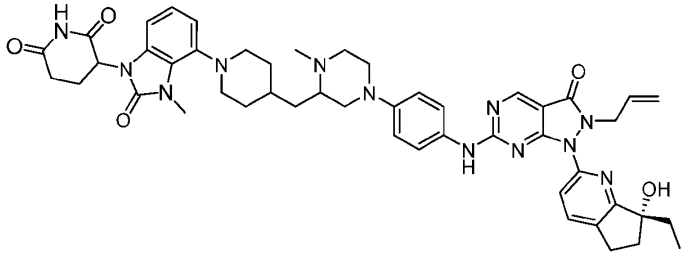
Compound No.	Structure
16	
17	
18	
19	

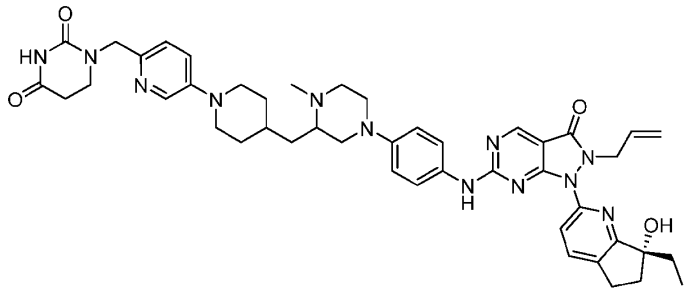
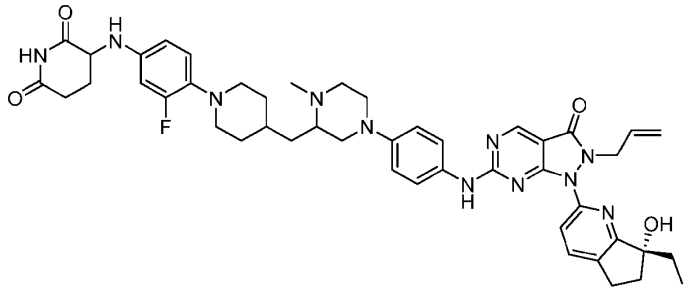
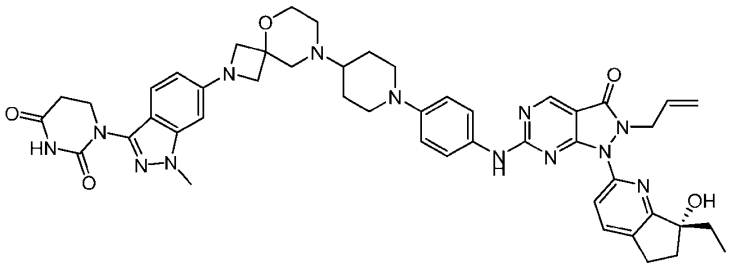
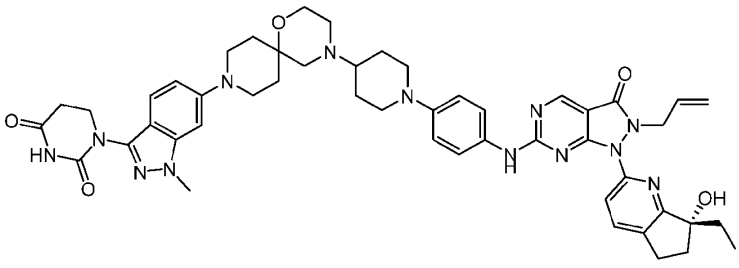
Compound No.	Structure
20	
21	
22	
23	

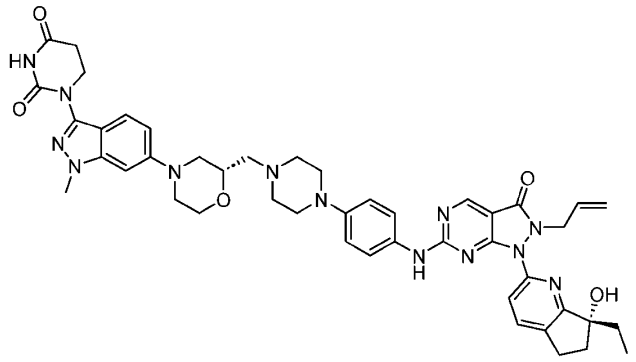
Compound No.	Structure
24	
25	
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27	

Compound No.	Structure
28	
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Compound No.	Structure
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Compound No.	Structure
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Compound No.	Structure
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41	
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43	

Compound No.	Structure
44	

[0082] In one embodiment, in a compound of Formula (I) (including pharmaceutically acceptable salts thereof) in accordance with any one of the foregoing embodiments and in any one of Compound Nos. 1 to 44, any one or more hydrogen atoms in the compound is substituted with deuterium.

Synthesis

[0083] Compounds of the Formula (I), or pharmaceutically acceptable salts thereof, can be made in various ways by those skilled using known techniques as guided by the detailed teachings provided herein, including the Examples provided below. For example, in an embodiment, compounds of the Formula (I) are prepared in accordance with the procedures illustrated in General Scheme A provided herein. Any preliminary reaction steps required to form starting compounds or other precursors, can be carried out by those skilled in the art, for example by appropriate adjustment of the reagents and conditions described in the Examples. In General Scheme A, the variables including, **L**, **B**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, **n**, **p**, **q**, **r**, **s**, **t**, **u**, **v**, **w** and **y**, can be as described elsewhere herein, taking into consideration the synthetic conversions involved as understood by those of skill in the art.

Pharmaceutical Compositions

[0084] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt

thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0085] The term "pharmaceutical composition" refers to a mixture of one or more compounds and/or salts disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0086] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound nor cause appreciable damage or injury to an animal to which delivery of the composition is intended.

[0087] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0088] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks appreciable pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the pH and isotonicity of human blood.

[0089] As used herein, an "excipient" refers to an essentially inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. For example, stabilizers such as anti-oxidants and metal-chelating agents are excipients. In an embodiment, the pharmaceutical composition comprises an anti-oxidant and/or a metal-chelating agent. A "diluent" is a type of excipient.

[0090] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or

combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0091] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0092] Multiple techniques of administering a compound, salt and/or composition exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection, infusion and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered orally.

[0093] One may also administer the compound, salt and/or composition in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory disease or condition may be desirable.

[0094] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound and/or salt

described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Uses and Methods of Treatment

[0095] Some embodiments described herein relate to a method for ameliorating and/or treating a cancer described herein that can include administering an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating and/or treating a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for use in ameliorating and/or treating a cancer described herein.

[0096] Some embodiments described herein relate to a method for inhibiting replication of a malignant growth or a tumor that can include contacting the growth or the tumor with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), wherein the malignant growth or tumor is due to a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or

tumor is due to a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for use in inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein.

[0097] Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include contacting a malignant growth or a tumor with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating or treating a cancer that can include contacting a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for use in ameliorating or treating a cancer that can include contacting a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein.

[0098] Some embodiments described herein relate to a method for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described

herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a cancer cell from a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for use in inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Some embodiments described herein relate to a method for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) that can include administering an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to subject suffering from a cancer described herein. Other embodiments described herein relate to a method for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) that can include contacting a cancer cell from a cancer described herein with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described

herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), and thereby inhibiting the activity of WEE1.

[0099] Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) using an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating or treating a cancer described herein by inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for use in ameliorating or treating a cancer described herein by inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include contacting a cancer cell with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), wherein the compound inhibits the activity of WEE1 (for example, inhibiting the activity

of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells).

[0100] Some embodiments disclosed herein relate to a method for inhibiting the activity of WEE1 that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject having a cancer described herein or a cancer cell from a cancer described herein. Other embodiments disclosed herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting the activity of WEE1. Still other embodiments disclosed herein relate to a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for use in inhibiting the activity of WEE1.

[0101] Examples of suitable cancers include, but are not limited to: brain cancers, cervicocerebral cancers, esophageal cancers, thyroid cancers, small cell cancers, non-small cell cancers, breast cancers, lung cancers (for example non-small cell lung cancer and small cell lung cancer), stomach cancers, gallbladder/bile duct cancers, liver cancers, pancreatic cancers, colon cancers, rectal cancers, ovarian cancers, choriocarcinomas, uterus body cancers, uterocervical cancers, renal pelvis/ureter cancers, bladder cancers, prostate cancers, penis cancers, testicular cancers, fetal cancers, Wilms' cancer, skin cancers, malignant melanoma, neuroblastomas, osteosarcomas, Ewing's tumors, soft part sarcomas, acute leukemia, chronic lymphatic leukemias, chronic myelocytic leukemias, polycythemia vera, malignant lymphomas, multiple myeloma, Hodgkin's lymphomas and non-Hodgkin's lymphomas.

[0102] As described herein, a cancer can become resistant to one or more anti-cancer agents. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a

pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a cancer that has become resistant to one or more anti-cancer agents (such as one or more WEE1 inhibitors). Examples of anti-cancer agents that a subject may have developed resistance to include, but are not limited to, WEE1 inhibitors (such as AZD1775). In some embodiments, the cancer that has become resistant to one or more anti-cancer agents can be a cancer described herein.

[0103] Several known WEE1 inhibitors can cause one or more undesirable side effects in the subject being treated. Examples of undesirable side effects include, but are not limited to, thrombocytopenia, neutropenia, anemia, diarrhea, vomiting, nausea, abdominal pain and constipation. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can decrease the number and/or severity of one or more side effects associated with a known WEE1 inhibitor. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a severity of a side effect (such as one of those described herein) that is 25% less than compared to the severity of the same side effect experienced by a subject receiving a known WEE1 inhibitor (such as AZD1775, formally known as MK1775 (CAS No.: 955365-80-7, 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(4-(4-methylpiperazin-1-yl)phenylamino)-1,2-dihydropyrazolo[3,4-*d*]pyrimidin-3-one)). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is 25% less than compared to the number of side effects experienced by a subject receiving a known WEE1 inhibitor (for example, AZD1775). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a severity of a side effect (such as one of those described herein) that is less in the range of about 10% to about 30% compared to the severity of the same side effect experienced by a subject receiving a known WEE1 inhibitor (such as AZD1775). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is in the range of about 10% to about 30% less than compared to the number of side effects experienced by a subject receiving a known WEE1 inhibitor (for example, AZD1775).

[0104] The one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used to treat, ameliorate and/or inhibit the growth of a

cancer wherein inhibiting the activity of WEE1 is beneficial is provided in any of the embodiments described under the heading titled "Compounds" above.

[0105] As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human. In some embodiments, the subject can be a child (*i.e.*, $\geq$ 1 year and < 18 years old) and/or an infant (*i.e.*, < 1 year old), for example, a child or infant with a fever. In other embodiments, the subject can be an adult (*i.e.*, $\geq$ 18 years old).

[0106] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of the disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject's overall feeling of well-being or appearance.

[0107] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound, salt or composition can be the amount needed to prevent, alleviate or ameliorate symptoms of the disease or condition, or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease or condition being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0108] For example, an effective amount of a compound, or radiation, is the amount that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the

tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor. In the treatment of lung cancer (such as non-small cell lung cancer) a therapeutically effective amount is that amount that alleviates or eliminates cough, shortness of breath and/or pain. As another example, an effective amount, or a therapeutically effective amount of an WEE1 inhibitor and/or degrader is the amount which results in the reduction in WEE1 activity and/or phosphorylation (such as phosphorylation of CDC2). The reduction in WEE1 activity is known to those skilled in the art and can be determined by the analysis of WEE1 intrinsic kinase activity and downstream substrate phosphorylation.

[0109] The amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature and/or symptoms of the disease or condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the dosage ranges described herein in order to effectively and aggressively treat particularly aggressive diseases or conditions.

[0110] In general, however, a suitable dose will often be in the range of from about 0.05 mg/kg to about 10 mg/kg. For example, a suitable dose may be in the range from about 0.10 mg/kg to about 7.5 mg/kg of body weight per day, such as about 0.15 mg/kg to about 5.0 mg/kg of body weight of the recipient per day, about 0.2 mg/kg to 4.0 mg/kg of body weight of the recipient per day, or any amount in between. The compound may be administered in unit dosage form; for example, containing 1 to 500 mg, 10 to 100 mg, 5 to 50 mg or any amount in between, of active ingredient per unit dosage form.

[0111] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

[0112] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, the mammalian species treated, the particular compounds employed and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels

necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, *in vivo* studies and *in vitro* studies. For example, useful dosages of a compound of Formula (I), or pharmaceutically acceptable salts thereof, can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Such comparison can be done by comparison against an established drug, such as cisplatin and/or gemcitabine.

[0113] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vivo* and/or *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0114] It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the disease or condition to be treated and to the route of administration. The severity of the disease or condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0115] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, dogs or monkeys,

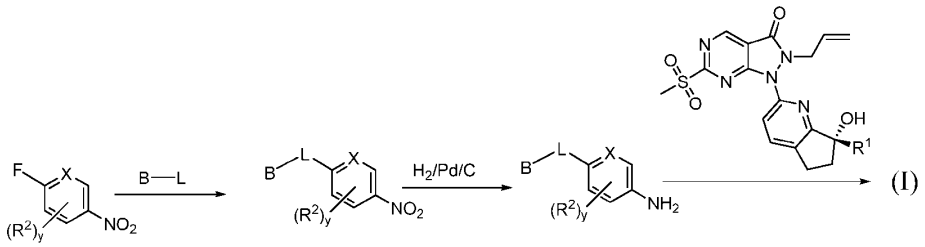
may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

EXAMPLES

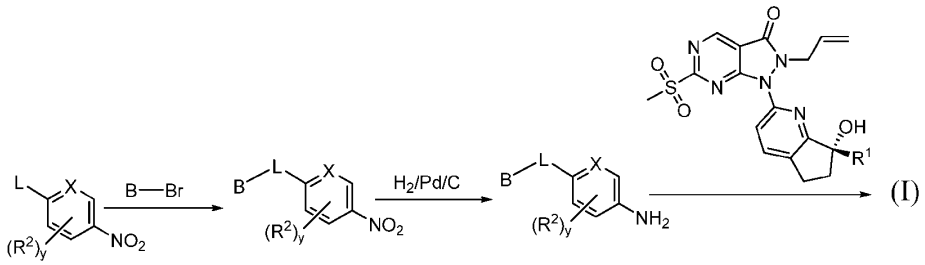
[0116] The compounds of Formula (I) and Compounds No. 1 to 44 as described herein are prepared using General Scheme A below.

General Scheme A

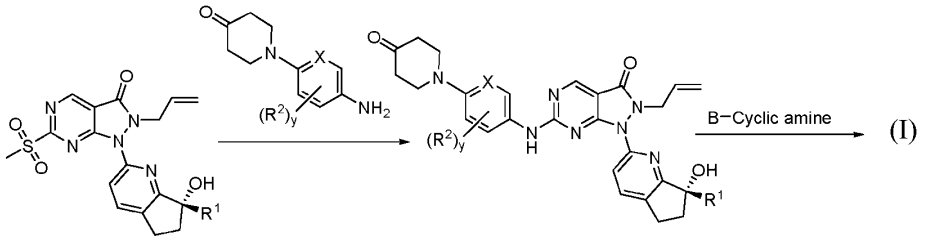
Method 1



Method 2



Method 3

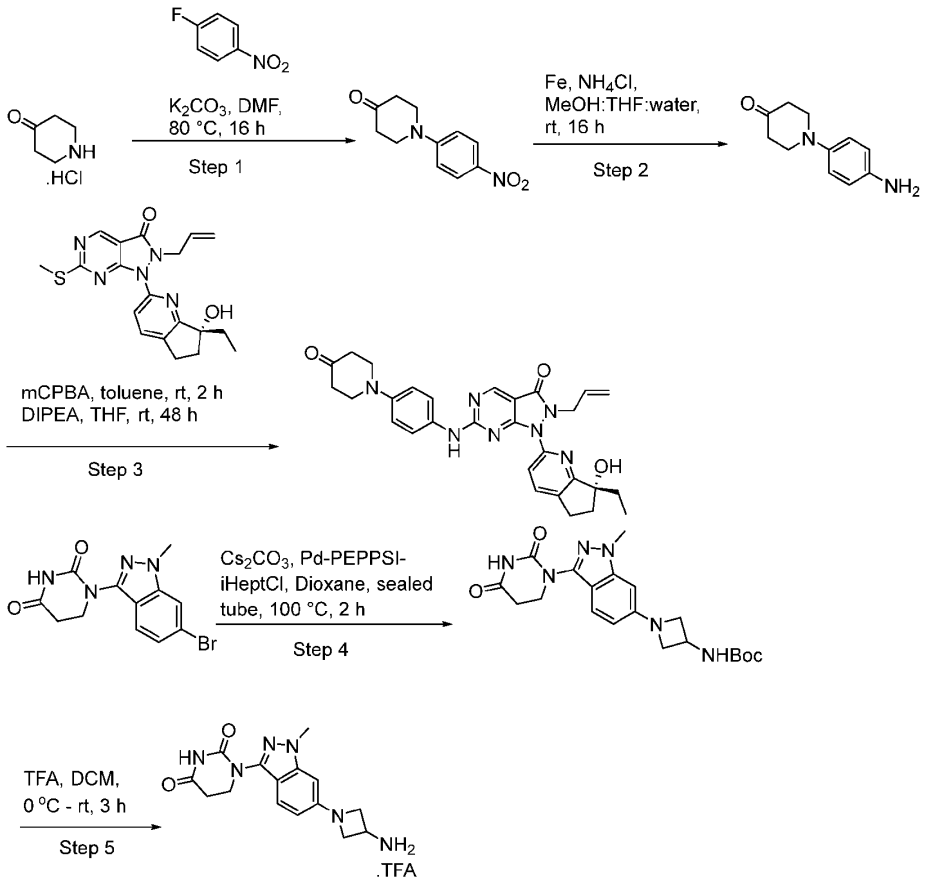


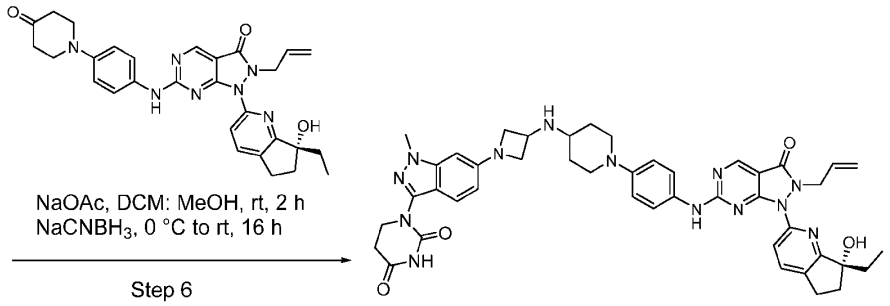
[0117] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims. Numbers in bold and within parentheses immediately ensuing a titular compound IUPAC name in each example corresponds to the Compound No. as indicated in Table 1.

Example 1

(*R*)-1-(6-(3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)azetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

(1)





Step 1: 1-(4-nitrophenyl)piperidin-4-one

[0118] To a stirred solution of HCl salt of piperidin-4-one (5 g, 37.023 mmol) and 1-fluoro-4-nitrobenzene (5.22 g, 37.023 mmol) in DMF (50 mL) at room temperature (rt), K_2CO_3 (12.79 g, 92.558 mmol) was added, and the mixture was stirred at 80 °C for 16 h. After completion of the reaction, the reaction was quenched with water (200 mL) and resulting precipitate was filtered through a Buchner funnel, washed with water (100 mL), and dried under vacuum to afford 1-(4-nitrophenyl)piperidin-4-one (6 g, 73%), which was directly used for next step without further purification. MS (LCMS) *m/z* 221.20 $[M+H]^+$.

Step 2: 1-(4-aminophenyl)piperidin-4-one

[0119] To a stirred solution of 1-(4-nitrophenyl)piperidin-4-one (2.0 g, 9.081 mmol) in a mixture of methanol (20 mL), THF (20 mL) and water (20 mL) at rt, NH_4Cl (3.4 g, 63.570 mmol) and Fe (3.55 g, 63.570 mmol) were added, and the mixture was stirred at rt for 16 h. After completion of the reaction, the mixture was filtered through a celite bed, and washed with 10% MeOH in DCM (150 mL). From the filtrate, the organic and aqueous layer were separated. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude. The crude was purified by flash chromatography (silica gel; 60% EtOAc in petroleum ether) to afford pure 1-(4-aminophenyl)piperidin-4-one (0.8 g, 46%). MS (LCMS) *m/z* 191.16 $[M+H]^+$.

Step 3: (*R*)-2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-((4-(4-oxopiperidin-1-yl)phenyl)amino)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one

[0120] To a stirred solution of (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (0.5 g, 1.304 mmol) in toluene (10 mL) at 0 °C, mCPBA (0.45 g, 2.608 mmol) was added. The mixture was allowed to stir at rt for 2 h. To this mixture, DIPEA (1.14 mL, 6.519 mmol) and a solution of 1-(4-aminophenyl)piperidin-4-one

(0.372 g, 1.956 mmol) in THF (10 mL) were added. The mixture was stirred at rt for 48 h. After completion of the reaction, the reaction was quenched with water (100 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford crude. The crude was purified by flash chromatography (silica gel; 3% MeOH in DCM) to afford (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-((4-(4-oxopiperidin-1-yl)phenyl)amino)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (0.6 g, 87%). MS (LCMS) *m/z* 526.50 $[M+H]^+$.

Step 4: *tert*-butyl (1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)azetidin-3-yl)

[0121] To a stirred solution of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.5 g, 1.547 mmol) and *tert*-butyl azetidin-3-ylcarbamate (0.799 g, 4.642 mmol) in dioxane (10 mL), cesium carbonate (2.521 g, 7.736 mmol) was added and the mixture degassed with nitrogen gas for 15 minutes. To this mixture, Pd-PEPPSI-iHeptCl (0.151 g, 0.155 mmol) was added and stirred the mixture at 100 °C for 2 h. After completion of reaction, the reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with brine solution (5 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford crude as brown liquid. The crude was purified by flash chromatography (silica gel; 50 to 60% EtOAc in petroleum ether) to afford pure *tert*-butyl (1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)azetidin-3-yl)carbamate (0.18 g, 28%). MS *m/z* 415.40 $[M+H]^+$.

Step 5: 1-(6-(3-aminoazetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0122] To a stirred solution of *tert*-butyl (1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)azetidin-3-yl)carbamate (0.18 g, 0.434 mmol) in DCM (1.8 mL) at 0 °C, trifluoroacetic acid (0.9 mL, 2.389 mmol) was added and the mixture was allowed to stir at rt for 3 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure and the crude was triturated with diethyl ether (10 mL) to afford the TFA salt of 1-(6-(3-aminoazetidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.15 g, 100%). The product was directly used for the next step without further purification. MS *m/z* 315.40 $[M+H]^+$.

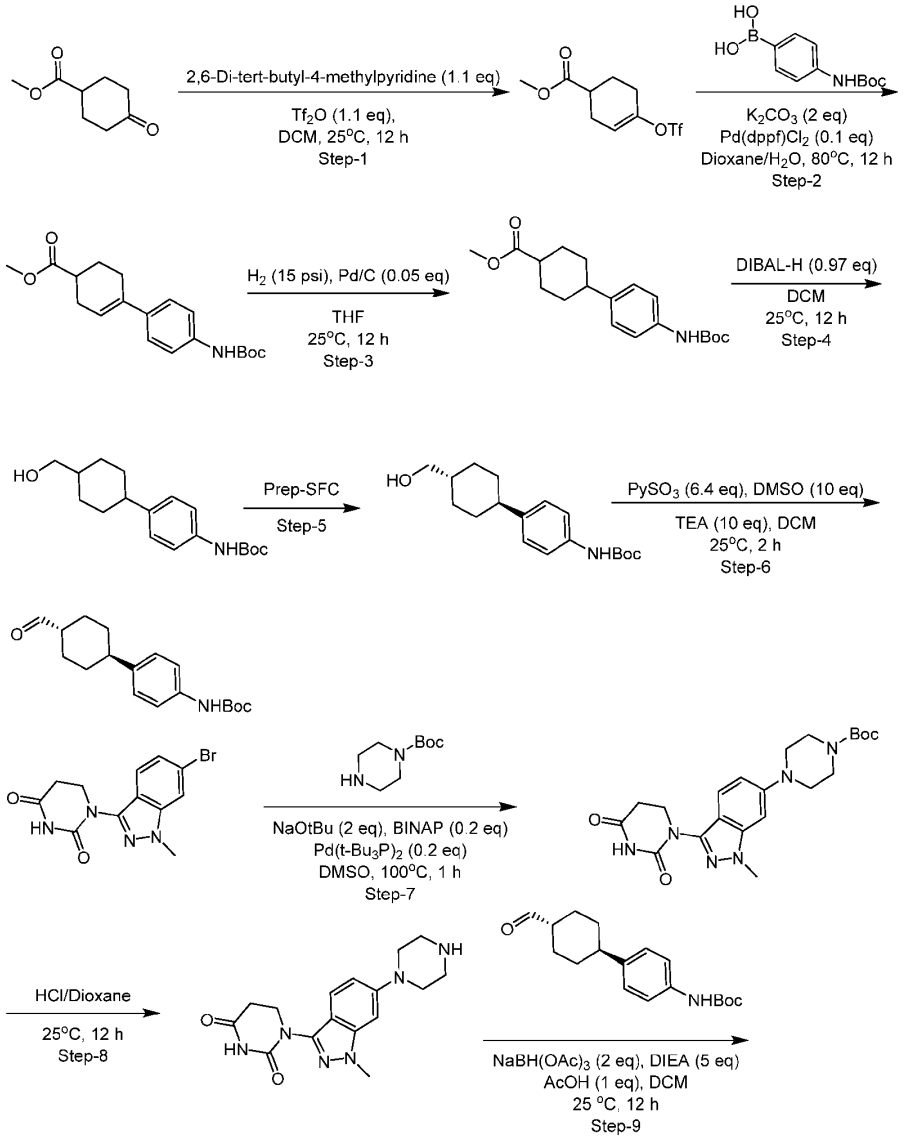
Step 6: (*R*)-1-(6-(3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)azetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

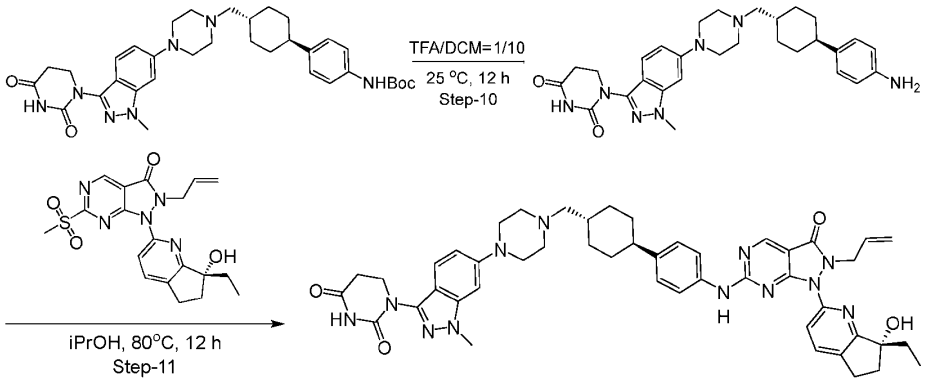
[0123] To a stirred solution of the TFA salt of 1-(6-(3-aminoazetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.15 g, 0.477 mmol) and (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-((4-(4-oxopiperidin-1-yl)phenyl)amino)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (0.125 g, 0.239 mmol) in MeOH (3.0 mL) and DCM (3.0 mL), Sodium acetate (0.196 g, 2.386 mmol) was added and the resulting mixture was stirred at rt for 3 h. To this mixture, sodium cyanoborohydride (0.09 g, 1.432 mmol) was added and the resulting mixture was stirred at rt for 16 h. Progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the reaction was quenched with water (10 mL) and extracted with 5% MeOH:DCM (2 × 15 mL). The combined organic layer was washed with brine solution (5 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford the crude. The crude was dissolved in 10% MeOH In DCM (5 mL) and to this was added Et_2O (10 mL) to obtain a precipitate, which was filtered to afford crude (*R*)-1-(6-(3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)azetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.16 g). The crude was purified by prep-HPLC (Column/dimensions: DIACEL DCPAK (30*250mm) 5µm, Mobile phase A: ACN:MeOH:0.2% Methanolic ammonia, Flow: 17 mL/min, Solubility: THF+ MeOH) to afford pure (*R*)-1-(6-(3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)azetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.05 g, 16%). ^{1}H NMR (400 MHz, DMSO-*d*6): δ 10.50 (br s, 1H), 10.10 (br s, 1H), 8.81 (s, 1H), 7.93 (d, *J* = 6.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.62-7.49 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.37 (dd, *J* = 8.8, 1.2 Hz, 1H), 6.32 (s, 1H), 5.76 – 5.58 (m, 1H), 5.04 (s, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.91-4.68 (m, 2H), 4.61-4.47 (m, 1H), 4.15 (t, *J* = 7.2 Hz, 2H), 3.94-3.87 (m, 3H), 3.84 (s, 3H), 3.60 (d, *J* = 12.4 Hz, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.03-2.91 (m, 1H), 2.83-2.64 (m, 5H), 2.63-2.54 (m, 1H), 2.28-2.14 (m, 1H), 2.07-1.98 (m, 1H), 1.93-1.79 (m, 3H),

1.78-1.64 (m, 1H), 1.62-1.57 (m, 1H), 1.51-1.32 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). MS m/z 824.43 $[M+H]^+$.

Example 2

1-(6-(4-(((1*R*,4*R*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**2**)





Step 1: methyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate

[0124] To a solution of methyl 4-oxocyclohexane-1-carboxylate (5.00 g, 32.01 mmol) in DCM (50 mL) and were added 2,6-di-*tert*-butyl-4-methylpyridine (7.23 g, 35.22 mmol) and trifluoromethanesulfonic anhydride (9.94 g, 35.22 mmol, 5.81 mL) at 25°C. The reaction was stirred at 25°C for 12 h. TLC showed the starting material consumed and a new spot was detected. The mixture was concentrated under reduced pressure at 40°C to give methyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate (5 g, 17.35 mmol, 54%), which was used to next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.90 (br s, 1H), 3.64-3.60 (m, 3H), 2.71-2.60 (m, 1H), 2.47-2.25 (m, 4H), 2.09-2.00 (m, 1H), 1.87-1.75 (m, 1H).

Step 2: methyl 4'-((*tert*-butoxycarbonyl)amino)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate

[0125] To a solution of methyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate (4.00 g, 13.88 mmol) in dioxane (20 mL) and H_2O (2 mL) were added (4-((*tert*-butoxycarbonyl)amino)phenyl) boronic acid (3.29 g, 13.88 mmol), K_2CO_3 (3.84 g, 27.75 mmol) and Pd(dppf)Cl_2 (1.02 g, 1.39 mmol) at 25°C under N_2. The was stirred at 80°C for 12 h. LCMS showed the reaction was completed. The mixture was diluted with water (20 mL) and extracted with EA (3 × 20 mL). The organic combined organic layers were washed with brine (3 × 20 mL) and dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (eluted with PE:EA=100:1 to 10:1) to give methyl 4'-((*tert*-butoxycarbonyl)amino)-2,3,4,5-tetrahydro-[1,1'-biphenyl] -4-carboxylate (2.50 g, 54%). MS (ESI+): m/z = 330.0 $[M-H]^-$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51 (s, 1H), 7.44-7.34 (m, 2H), 7.29 (d, J = 8.8 Hz, 2H), 6.06 (br s, 1H), 3.63 (s, 3H), 2.60 (m, 1H), 2.47-2.29 (m, 4H), 2.11-2.01 (m, 1H), 1.76-1.65 (m, 1H), 1.47 (s, 9H).

Step 3: methyl 4-(4-((*tert*-butoxycarbonyl)amino)phenyl) cyclohexane-1-carboxylate

[0126] To a solution of methyl 4'-((*tert*-butoxycarbonyl)amino)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (2.50 g, 7.54 mmol) in THF (25 mL) were added Pd/C (401.40 mg, 377.18 μmol, 10% purity) at 25°C. The reaction was stirred at 25 °C under H_2 (15 psi) for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filter cake was washed with THF (50 mL). The collected filtrate was concentrated to give methyl 4-(4-((*tert*-butoxycarbonyl)amino)phenyl) cyclohexane-1-carboxylate (2.50 g, 85% yield, 86% purity). MS (ESI+): m/z = 332.2 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.20 (br s, 1H), 7.33 (br d, J = 8.1 Hz, 2H), 7.12-7.01 (m, 2H), 3.69-3.61 (m, 3H), 2.72 (br s, 1H), 2.45-2.28 (m, 1H), 2.08 (br d, J = 11.1 Hz, 1H), 1.98 (br d, J = 9.3 Hz, 1H), 1.84-1.72 (m, 3H), 1.68-1.56 (m, 3H), 1.46 (s, 9H).

Step 4: *tert*-butyl(4-(4-(hydroxymethyl)cyclohexyl)phenyl) carbamate

[0127] To a solution of methyl 4-(4-((*tert*-butoxycarbonyl)amino)phenyl)cyclohexane-1-carboxylate (1.80 g, 4.64 mmol) in DCM (50 mL) and DIBAL-H (1 M, 4.50 mL) at -65°C. The reaction was stirred at 25°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was quenched by addition of sat. aq. NH_4Cl solution and extracted with DCM (20 mL). The combined organic layer dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure to give *tert*-butyl(4-(4-(hydroxymethyl)cyclohexyl)phenyl) carbamate (1.7 g, 95%), which was purified by prep-SFC. MS (ESI+): m/z = 304.3 $(M-H)^-$.

Step 5: *tert*-butyl (4-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)phenyl) carbamate

[0128] *tert*-Butyl (4-(4-(hydroxymethyl)cyclohexyl)phenyl)carbamate (1.70 g, 79.89% purity) was purified by prep-SFC (IH_MeOH_MNH_3_10_50_34_35_4min) to give *tert*-butyl (4-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)phenyl) carbamate (0.30 g). LCMS (ESI+): m/z = 304.1 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H), 7.33 (br d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 4.38 (t, J = 5.3 Hz, 1H), 3.24 (t, J = 5.8 Hz, 2H), 2.36 (br t, J = 12.2 Hz, 1H), 1.79 (br t, J = 14.8 Hz, 4H), 1.46 (s, 9H), 1.42-1.30 (m, 3H), 1.08-0.93 (m, 2H).

Step 6: *tert*-butyl (4-((1*R*,4*R*)-4-formylcyclohexyl)phenyl)carbamate

[0129] To a solution of *tert*-butyl (4-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)phenyl)carbamate (0.30 g, 982.28 μmol) in DCM (10 mL) were added pyridine•sulfur trioxide (1.00 g, 6.29 mmol), DMSO (767.49 mg, 9.82 mmol)

and TEA (993.96 mg, 9.82 mmol) at 0°C. The reaction was stirred at 25°C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40°C to give the crude product, which was purified by column chromatography on silica gel (eluted with PE: EA=100:1 to 10:1) to give *tert*-butyl (4-((1*R*,4*R*)-4-formylcyclohexyl)phenyl)carbamate (0.20 g, 57% yield, 85% purity). MS (ESI^+): *m/z* = 302.0 $[M-H]^-$.

Step 7: *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1 (2*H*)-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carboxylate

[0130] To a solution of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.00 g, 3.09 mmol) in DMSO (20 mL) were added tert-butyl piperazine-1-carboxylate (576.37 mg, 3.09 mmol), NaO^tBu (594.80 mg, 6.19 mmol), BINAP (385.38 mg, 618.92 μmol) and $Pd(^tBu_3P)_2$ (316.30 mg, 618.92 μmol) at 25°C. The reaction was stirred at 100°C for 1 h. LCMS showed the reaction was completed. The crude product was purified by triturated in EA:PE=5:1 (30 mL) and the solid was collected by suction filtration and dried in vacuum to give *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1 (2*H*)-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carboxylate (1.10 g, 38% yield, 47% purity). MS (ESI+): m/z = 429.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.48 (d, *J* = 8.9 Hz, 1H), 6.93 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.88 (s, 1H), 3.95-3.84 (m, 5H), 3.50 (br s, 4H), 3.25-3.14 (m, 4H), 2.73 (t, *J* = 6.6 Hz, 2H), 1.43 (s, 9H).

Step 8: 1-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0131] A solution of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperazine-1-carboxylate (1.10 g, 2.57 mmol) in HCl/dioxane (11 mL) was stirred at 25°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give 1-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.60 g, 57.65% yield, 81% purity). MS (ESI+): m/z = 329.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 7.51 (d, *J* = 9.5 Hz, 1H), 7.01-6.89 (m, 2H), 3.91 (s, 3H), 3.91-3.86 (m, 2H), 3.55-3.40 (m, 4H), 3.25 (br s, 4H), 2.74 (t, *J* = 6.8 Hz, 2H).

Step 9: *tert*-butyl (4-((1*R*,4*R*)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol- 6-yl)piperazin-1-yl)methyl)cyclohexyl)phenyl)carbamate

[0132] To a solution of 1-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*, 3*H*)-dione (204.42 mg, 560.33 μmol, HCl salt) in DCM (10 mL) were added *tert*-butyl (4-((1*R*,4*R*)-4-formylcyclohexyl)phenyl)carbamate (0.20 g, 560.33 μmol), DIEA (362.08 mg, 2.80 mmol), AcOH (33.65 mg, 560.33 μmol) and $NaBH(OAc)_3$ (237.51 mg, 1.12 mmol) at 25°C. The reaction was stirred at 25°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give *tert*-butyl (4-((1*R*,4*R*)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)cyclohexyl)phenyl)carbamate (0.20 g, 49% yield, 86% purity). MS (ESI^+): *m/z* = 616.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 9.19 (s, 1H), 7.45 (d, *J* = 9.1 Hz, 1H), 7.33 (br d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.92 (dd, *J* = 9.3, 1.7 Hz, 1H), 6.82 (s, 1H), 3.89 (br s, 1H), 3.89-3.85 (m, 3H), 3.23 (br s, 4H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.60-2.51 (m, 4H), 2.40 (br t, *J* = 12.0 Hz, 1H), 2.24-2.15 (m, 2H), 1.91 (br s, 1H), 1.89 (s, 2H), 1.78 (br d, *J* = 10.7 Hz, 2H), 1.68-1.52 (m, 1H), 1.46 (s, 9H), 1.44-1.33 (m, 2H), 1.09-0.93 (m, 2H).

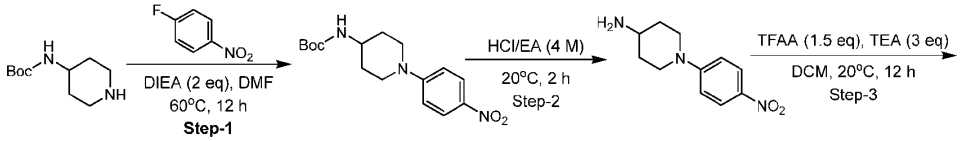
Step 10: 1-(6-(4-(((1*R*,4*R*)-4-(4-aminophenyl)cyclohexyl)methyl) piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

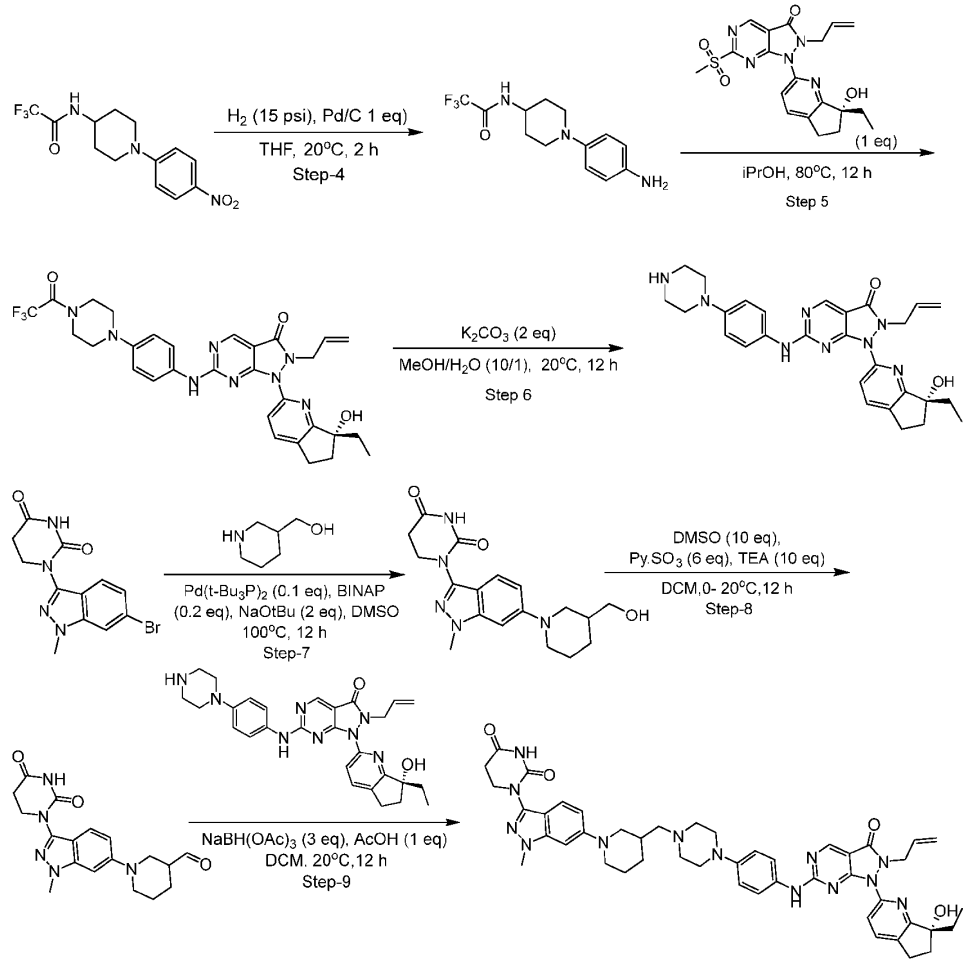
[0133] A solution of *tert*-butyl (4-((1*R*,4*R*)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)cyclohexyl)phenyl)carbamate (0.20 g, 324.80 μmol) in TFA/DCM=1/10 (5 mL) was stirred at 25°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give the residue. The residue was purified by prep-HPLC (NH_3H_2O Condition) to afford 1-(6-(4-(((1*R*,4*R*)-4-(4-aminophenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (70 mg, 39% yield, 95% purity). MS (ESI^+): *m/z* = 516.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 7.53 (d, *J* = 9.4 Hz, 1H), 7.42-7.31 (m, 2H), 7.30-7.22 (m, 2H), 7.07-6.90 (m, 2H), 3.96 (br s, 1H), 3.92 (s, 3H), 3.90 (s, 1H), 3.64 (br d, *J* = 9.2 Hz, 2H), 3.33-3.06 (m, 6H), 2.78-2.70 (m, 2H), 2.60-2.50 (m, 4H), 2.49-2.47 (m, 1H), 1.97-1.89 (m, 3H), 1.85 (br d, *J* = 11.9 Hz, 2H), 1.55-1.43 (m, 2H), 1.26-1.18 (m, 2H).

Step 11: 1-(6-(4-(((1*R*,4*R*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0134] To a solution of (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (78.96 mg, 190.05 μmol) in *i*PrOH (2 mL) was added 1-(6-(4-(((1*R*,4*R*)-4-(4-aminophenyl)cyclohexyl)methyl) piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.07 g, 135.75 μmol) at 25 °C. The reaction was stirred at 80°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filtrate was concentrated to give the residue. The residue was purified by prep-HPLC (NH_4HCO_3 Condition) to afford 1-(6-(4-(((1*R*,4*R*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (20.00 mg, 17% yield, 99.46% purity). MS (ESI^+): *m/z* = 851.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*6): δ 10.52 (br s, 1H), 10.36-10.12 (m, 1H), 8.87 (s, 1H), 7.94 (br d, *J* = 8.1 Hz, 1H), 7.77-7.55 (m, 3H), 7.45 (d, *J* = 9.1 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.92 (br d, *J* = 9.2 Hz, 1H), 6.83 (s, 1H), 5.67 (tdd, *J* = 16.8, 10.6, 5.9 Hz, 1H), 5.07 (s, 1H), 5.00 (d, *J* = 10.3 Hz, 1H), 4.85 (br d, *J* = 17.2 Hz, 1H), 4.76 (br d, *J* = 16.3 Hz, 1H), 4.56 (br dd, *J* = 15.9, 6.1 Hz, 1H), 3.91 (s, 2H), 3.89-3.86 (m, 3H), 3.24 (br s, 4H), 3.03-2.92 (m, 1H), 2.84-2.70 (m, 3H), 2.53 (br s, 4H), 2.45 (br s, 1H), 2.26-2.14 (m, 3H), 2.02 (ddd, *J* = 13.4, 8.3, 5.3 Hz, 1H), 1.90 (td, *J* = 13.6, 6.8 Hz, 3H), 1.82 (br d, *J* = 11.4 Hz, 2H), 1.76-1.57 (m, 2H), 1.55-1.39 (m, 2H), 1.03 (q, *J* = 11.6 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H).

Example 3
1-[6-[3-[[4-[4-[[2-allyl-3-oxo-1-[*rac*-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]piperazin-1-yl]methyl]-1-piperidyl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (**3**)





Step 1: *tert*-butyl N-[1-(4-nitrophenyl)-4-piperidyl]carbamate

[0135] To a solution of *tert*-butyl *N*-(4-piperidyl)carbamate (17.03 g, 85.05 mmol) in DMF (100 mL) were added 1-fluoro-4-nitro-benzene (10.00 g, 70.87 mmol, 7.52 mL) and DIEA (18.32 g, 141.74 mmol, 24.69 mL) at 20°C, and the mixture was stirred at 60 °C for 12 h. LCMS showed the starting material consumed and the desired compound was detected. The mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with EA (EA) (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give *tert*-butyl *N*-[1-(4-nitrophenyl)-4-piperidyl]carbamate (20.00 g, 87.81%).

Step 2: 1-(4-nitrophenyl)piperidin-4-amine

[0136] A mixture *tert*-butyl *N*-[1-(4-nitrophenyl)-4-piperidyl]carbamate (20.00 g, 62.23 mmol) in HCl/EtOAc (200 mL) was stirred at 20°C for 2 h. TLC

(petroleum ether (PE):EA = 3:1) showed the starting material was consumed and a new spot was detected. The mixture was concentrated under reduced pressure to give 1-(4-nitrophenyl)piperidin-4-amine (10.41 g, 72.62%, HCl salt), which was used to next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (br s, 2H), 8.05 (d, J = 9.3 Hz, 2H), 7.05 (d, J = 9.4 Hz, 2H), 4.09 (br d, J = 13.5 Hz, 2H), 3.32 (br dd, J = 4.6, 9.7 Hz, 1H), 3.06 (br t, J = 12.2 Hz, 2H), 2.12-1.93 (m, 2H), 1.63-1.45 (m, 2H).

Step 3: 2,2,2-trifluoro-*N*-[1-(4-nitrophenyl)-4-piperidyl]acetamide

[0137] To a solution of 1-(4-nitrophenyl)piperidin-4-amine (10.41 g, 40.39 mmol) and TFAA (12.73 g, 60.59 mmol, 8.42 mL) in DCM (200 mL) was added TEA (12.26 g, 121.18 mmol, 16.87 mL) at 20°C. The mixture was stirred at 20°C for 12 h. LCMS showed the reaction was completed. The mixture was diluted with water (10 mL) concentrated under reduced pressure to give 2,2,2-trifluoro-*N*-[1-(4-nitrophenyl)-4-piperidyl]acetamide (5.00 g, 39.02%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (br d, J = 7.6 Hz, 1H), 8.05 (d, J = 9.3 Hz, 2H), 7.05 (d, J = 9.5 Hz, 2H), 4.11-4.04 (m, 3H), 3.15-3.06 (m, 2H), 1.92-1.77 (m, 2H), 1.66-1.46 (m, 2H).

Step 4: *N*-[1-(4-aminophenyl)-4-piperidyl]-2,2,2-trifluoro-acetamide

[0138] To a solution of 2,2,2-trifluoro-*N*-[1-(4-nitrophenyl)-4-piperidyl]acetamide (4) (5.00 g, 15.76 mmol) in THF (50 mL) was added Pd/C (16.77 g, 15.76 mmol, 10% purity). Then the reaction was stirred at 20°C under H_2 (15 psi) for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered through celite and the filter cake was washed with THF (50 mL). The collected filtrate was concentrated to give *N*-[1-(4-aminophenyl)-4-piperidyl]-2,2,2-trifluoro-acetamide (3.30 g, 72.89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (br d, J = 7.6 Hz, 1H), 6.70 (br d, J = 8.5 Hz, 2H), 6.49 (br d, J = 8.5 Hz, 2H), 4.62 (br s, 2H), 3.79-3.67 (m, 1H), 3.36 (br d, J = 12.3 Hz, 2H), 2.57 (br t, J = 11.4 Hz, 2H), 1.80-1.76 (m, 2H), 1.74-1.60 (m, 2H).

Step 5: 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl] -6-[4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]anilino]pyrazolo[3,4-*d*]pyrimidin-3-one

[0139] To a mixture of 1-[4-(4-aminophenyl)piperazin-1-yl]-2,2,2-trifluoro-ethanone (723.48 mg, 2.65 mmol) in PrOH (10 mL) was added 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-methylsulfonyl-pyrazolo[3,4-*d*]pyrimidin-3-one (1 g, 2.41 mmol) at 20°C and the reaction was stirred at 80 °C for 12 h under N_2. LCMS showed the starting material was consumed and the desired compound was detected. The mixture was poured into H_2O (10 mL). The mixture was extracted with

DCM (3 × 30 mL). The combined organic was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, PE:EA = 0:1) to give 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-[4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]anilino]pyrazolo[3,4-*d*]pyrimidin-3-one (1.0 g, 68.26% yield, 94.60% purity). MS (ESI^+): *m/z* = 609.3 $[M+H]^+$.

Step 6: 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydro-cyclopenta[*b*]pyridin-2-yl]-6-(4-piperazin-1-ylanilino)pyrazolo[3,4-*d*]pyrimidin-3-one

[0140] To a mixture of 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-[4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]anilino]pyrazolo[3,4-*d*]pyrimidin-3-one (1.0 g, 777.18 umol, 94.60% purity) in MeOH (10 mL) and H_2O (1 mL) was added K_2CO_3 (214.83 mg, 1.55 mmol) at 20 °C and the mixture was stirred at 20 °C for 12 h. LCMS showed the starting material was consumed and the desired compound was detected. The mixture was poured into H_2O (10 mL). The mixture was extracted with DCM (3 × 30 mL). The combined organic was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to obtained 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydro-cyclopenta[*b*]pyridin-2-yl]-6-(4-piperazin-1-ylanilino)pyrazolo[3,4-*d*]pyrimidin-3-one (0.7 g, 83.11%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.29-9.96 (m, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 7.3 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.58 (br d, *J* = 2.8 Hz, 2H), 6.90 (br d, *J* = 8.8 Hz, 2H), 5.73-5.58 (m, 1H), 5.13-5.03 (m, 1H), 5.02-4.95 (m, 1H), 4.83 (s, 1H), 4.81-4.69 (m, 1H), 4.56 (br dd, *J* = 5.3, 15.4 Hz, 1H), 3.29-3.22 (m, 1H), 3.07-2.91 (m, 5H), 2.87-2.72 (m, 5H), 2.20 (ddd, *J* = 5.7, 8.3, 13.5 Hz, 1H), 2.01 (ddd, *J* = 5.3, 8.4, 13.4 Hz, 1H), 1.94-1.83 (m, 1H), 1.70 (dd, *J* = 7.3, 13.6 Hz, 1H), 0.93-0.80 (m, 3H).

Step 7: 1-[6-[3-(hydroxymethyl)-1-piperidyl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione

[0141] To a solution of 1-(6-bromo-1-methyl-indazol-3-yl)hexahydropyrimidine-2,4-dione (0.6 g, 1.86 mmol) and 3-piperidylmethanol (320.77 mg, 2.79 mmol) in DMSO (12 mL) were added NaO^tBu (356.88 mg, 3.71 mmol), BINAP (231.23 mg, 371.35 μmol) and $Pd(^tBu_3P)_2$ (91.78 mg, 186.35 μmol) at 20°C under N_2. Then the reaction was stirred at 100 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was quenched with water (30 mL) and extracted with DCM (30 mL). The combined organic layer was dried over

Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography (PE:EA = 100:1, 0:1)) to give 1-[6-[3-(hydroxymethyl)-1-piperidyl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (300 mg, 40.69%). MS (ESI^+): m/z = 358.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.43 (d, J = 8.9 Hz, 1H), 6.88 (br d, J = 9.2 Hz, 1H), 6.78 (s, 1H), 3.88 (s, 3H), 3.77 (br d, J = 10.7 Hz, 1H), 3.69 (br d, J = 12.0 Hz, 1H), 3.60 (br t, J = 6.2 Hz, 2H), 3.43-3.28 (m, 2H), 2.82-2.62 (m, 4H), 1.73 (br s, 1H), 1.65-1.52 (m, 1H), 1.32-1.19 (m, 2H), 1.18-1.04 (m, 1H).

Step 8: 1-[3-(2,4-dioxohexahydropyrimidin-1-yl)-1-methyl-indazol-6-yl] piperidine-3-carbaldehyde

[0142] To a solution of 1-[6-[3-(hydroxymethyl)-1-piperidyl]-1-methyl-indazol-3-yl]hexahydr opyrimidine-2,4-dione (200 mg, 559.59 μmol) and DMSO (437.22 mg, 5.60 mmol) in DCM (5 mL) were added pyridine•sulfur trioxide (534.39 mg, 3.36 mmol) and TEA (566.24 mg, 5.60 mmol) at 0°C. The reaction was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (10 mL) and extracted with DCM (3 × 10 mL). The organic combined organic layers were washed with brine (3 × 10 mL) and dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give 1-[3-(2,4-dioxohexahydropyrimidin-1-yl)-1-methyl-indazol-6-yl]piperidine-3-carbaldehyde (100 mg, 50.28%), which was used to next step without further purification. MS (ESI^+): m/z = 356.2 $[M+H]^+$.

Step 9: 1-[6-[3-[[4-[4-[[2-allyl-3-oxo-1-[*rac*-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]piperazin-1-yl]methyl]-1-piperidyl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione

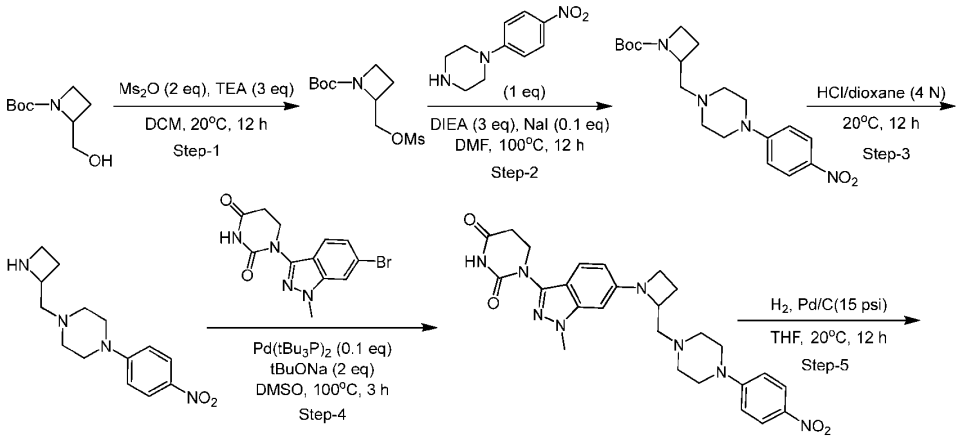
[0143] To a solution of 1-[3-(2,4-dioxohexahydropyrimidin-1-yl)-1-methyl-indazol-6-yl]piperidine-3 -carbaldehyde (59.43 mg, 117.05 μmol) and 2-allyl-6-(4-piperazin-1-ylanilino)-1-[*rac*-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-3-one (60 mg, 117.05 μmol) in DCM (1.2 mL) was added AcOH (7.03 mg, 117.05 μmol) and $NaBH(OAc)_3$ (74.42 mg, 351.15 μmol) at 0 °C. Then the mixture was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (10 mL) and extracted with DCM (3 × 10 mL). The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product,

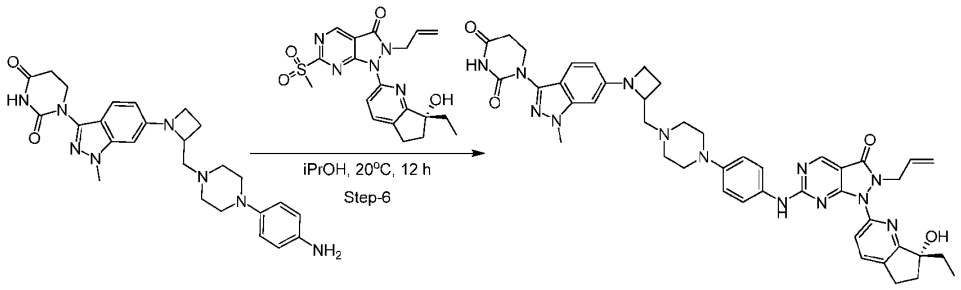
which was purified by prep-HPLC (NH_4HCO_3 condition) to give 1-[6-[3-[[4-[4-[[2-allyl-3-oxo-1-[*rac*-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]piperazin-1-yl]methyl]-1-piperidyl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (25.0 mg, 23.82%). MS (ESI^+): *m/z* = 852.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.49 (br s, 1H), 10.13 (br s, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 6.3 Hz, 1H), 7.70 (br d, *J* = 8.1 Hz, 1H), 7.59 (br s, 2H), 7.44 (br d, *J* = 9.0 Hz, 1H), 6.99-6.85 (m, 3H), 6.77 (s, 1H), 5.67 (tdd, *J* = 16.7, 10.9, 5.7 Hz, 1H), 5.12-5.03 (m, 1H), 5.00 (br d, *J* = 10.3 Hz, 1H), 4.86 (br d, *J* = 17.1 Hz, 1H), 4.74 (br s, 1H), 4.57 (br d, *J* = 11.3 Hz, 1H), 3.98-3.88 (m, 2H), 3.88-3.82 (m, 3H), 3.74 (br d, *J* = 11.4 Hz, 1H), 3.66 (br d, *J* = 11.8 Hz, 1H), 3.14 (br s, 4H), 2.97 (td, *J* = 14.7, 7.5 Hz, 1H), 2.89-2.76 (m, 2H), 2.75-2.69 (m, 2H), 2.65-2.51 (m, 5H), 2.40-2.31 (m, 1H), 2.28-2.16 (m, 2H), 2.07-1.97 (m, 1H), 1.97-1.79 (m, 3H), 1.78-1.56 (m, 3H), 1.23-1.08 (m, 1H), 0.87 (br t, *J* = 7.2 Hz, 3H).

Example 4

1-(6-(2-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)azetidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

(**4**)





Step 1: *tert*-butyl 2-(methylsulfonyloxymethyl)azetidine-1-carboxylate

[0144] To a solution of *tert*-butyl 2-(hydroxymethyl)azetidine-1-carboxylate (0.6 g, 3.20 mmol) in DCM (5 mL) was added methanesulfonic anhydride (1.12 g, 6.41 mmol) and TEA (972.79 mg, 9.61 mmol) at 20°C. Then the reaction was stirred at 20°C for 12 h. LCMS showed all starting material remained and no desired product was detected. The reaction was cooled to 0 °C and quenched (diluted) with saturated $NaHCO_3$ solution (10 mL) at 0°C and extracted with EA (3 × 50 mL). The filtrate was concentrated under reduced pressure to give *tert*-butyl 2-(methylsulfonyloxymethyl)azetidine-1-carboxylate (0.5 g, 52.93% yield, 90% purity). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 4.44-4.35 (m, 2H), 4.30-4.22 (m, 1H), 3.77-3.61 (m, 2H), 3.21 (s, 3H), 2.33-2.22 (m, 1H), 2.12-2.01 (m, 1H), 1.38 (s, 9H).

Step 2: *tert*-butyl 2-[[4-(4-nitrophenyl)piperazin-1-yl]methyl]azetidine-1-carboxylate

[0145] To a solution of *tert*-butyl 2-(methylsulfonyloxymethyl)azetidine-1-carboxylate (297.30 mg, 1.12 mmol) and 1-(4-nitrophenyl) piperazine (215 mg, 933.75 μmol) in DMF (1.5 mL) was added NaI (14.00 mg, 93.38 μmol) and DIEA (362.04 mg, 2.80 mmol) at 20°C. Then the reaction was stirred at 100°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was cooled to 0°C and quenched with saturated H_2O (1 mL) to precipitate out the solid. The mixture was filtered and the filter cake was collected by suction filtration and dried in vacuum to give *tert*-butyl 2-[[4-(4-nitrophenyl)piperazin-1-yl]methyl]azetidine-1-carboxylate (0.2 g, 56.90%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.04 (br d, *J* = 9.3 Hz, 2H), 7.05-7.00 (m, 2H), 4.33-4.22 (m, 1H), 3.81-3.65 (m, 2H), 3.47-3.37 (m, 4H), 3.32-3.24 (m, 2H), 2.63-2.52 (m, 4H), 2.34-2.23 (m, 1H), 2.01-1.90 (m, 1H), 1.41-1.34 (m, 9H).

Step 3: 1-(azetidin-2-ylmethyl)-4-(4-nitrophenyl)piperazine

[0146] A mixture of *tert*-butyl 2-[[4-(4-nitrophenyl)piperazin-1-yl]methyl]azetidine-1-carboxylate (0.2 g, 531.28 μmol) in HCl/dioxane (4 N, 3 mL) was stirred at 20°C for 12 h. LCMS showed all starting material remained and no desired

product was detected. The mixture was concentrated under reduced pressure at 40°C to give 1-(azetidin-2-ylmethyl)-4-(4-nitrophenyl)piperazine (0.1 g, 61.30% yield, 90% purity). MS (ESI^+): m/z = 277.2 $[M+H]^-$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, J = 9.4 Hz, 2H), 7.01 (d, J = 9.4 Hz, 2H), 3.98-3.87 (m, 1H), 3.42 (br t, J = 5.0 Hz, 4H), 3.21 (br s, 1H), 3.19-3.12 (m, 1H), 2.48 (br s, 4H), 2.47 (br s, 2H), 2.24-2.13 (m, 1H), 1.96-1.84 (m, 1H).

Step 4: 1-[1-methyl-6-[2-[[4-(4-nitrophenyl)piperazin-1-yl]methyl]azetidin-1-yl]indazol-3-yl] hexahydropyrimidine-2,4-dione

[0147] To a solution of 1-(azetidin-2-ylmethyl)-4-(4-nitrophenyl)piperazine (102.62 mg, 371.35 µmol) and 1-(6-bromo-1-methyl-indazol-3-yl)hexahydropyrimidine-2,4-dione (0.100 g, 309.46 µmol) in DMSO (3 mL) was added palladium;tri*tert*-butylphosphane (15.81 mg, 30.95 µmol) and ^{t}BuONa (59.48 mg, 618.92 µmol) at 20 °C. Then the reaction was stirred at 100 °C for 3 h. LCMS showed all starting material remained and no desired product was detected. The mixture was filtered and the filter cake was washed with DMSO (3 mL), the collected filtrate was purified by prep-HPLC (NH_4HCO_3 condition) to give 1-[1-methyl-6-[2-[[4-(4-nitrophenyl)piperazin-1-yl]methyl]azetidin-1-yl]indazol-3-yl]hexahydropyrimidine-2,4-dione (0.07 g, 39.26% yield, 90% purity). MS (ESI^+): m/z = 519.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (br s, 1H), 8.05 (d, J = 9.3 Hz, 2H), 7.43 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 9.4 Hz, 2H), 6.61 (d, J = 8.8 Hz, 1H), 6.53 (s, 1H), 4.31-4.22 (m, 1H), 4.02-3.94 (m, 1H), 3.90-3.85 (m, 2H), 3.85-3.81 (m, 3H), 3.66-3.58 (m, 1H), 3.50 (br t, J = 4.6 Hz, 4H), 2.93-2.85 (m, 1H), 2.74-2.71 (m, 2H), 2.64 (br s, 3H), 2.63-2.60 (m, 2H), 2.44-2.31 (m, 1H), 2.26-2.15 (m, 1H).

Step 5: 1-[6-[2-[[4-(4-aminophenyl)piperazin-1-yl]methyl]azetidin-1-yl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione

[0148] To a solution of 1-[1-methyl-6-[2-[[4-(4-nitrophenyl)piperazin-1-yl]methyl]azetidin-1-yl]indazol-3-yl]hexahydropyrimidine-2,4-dione (80 mg, 154.27 µmol) in THF (3 mL) was added Pd/C (16.42 mg, 15.43 µmol, 10% purity) under N_2 at 20 °C. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 12 h. LCMS showed all starting material remained and no desired product was detected. The mixture was filtered and the filter cake was washed with THF (3 mL), the collected filtrate was concentrated to give 1-[6-[2-[[4-(4-aminophenyl)piperazin-1-yl]methyl]azetidin-1-yl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (70 mg, 78.01% yield, 84% purity). MS (ESI^+): m/z =

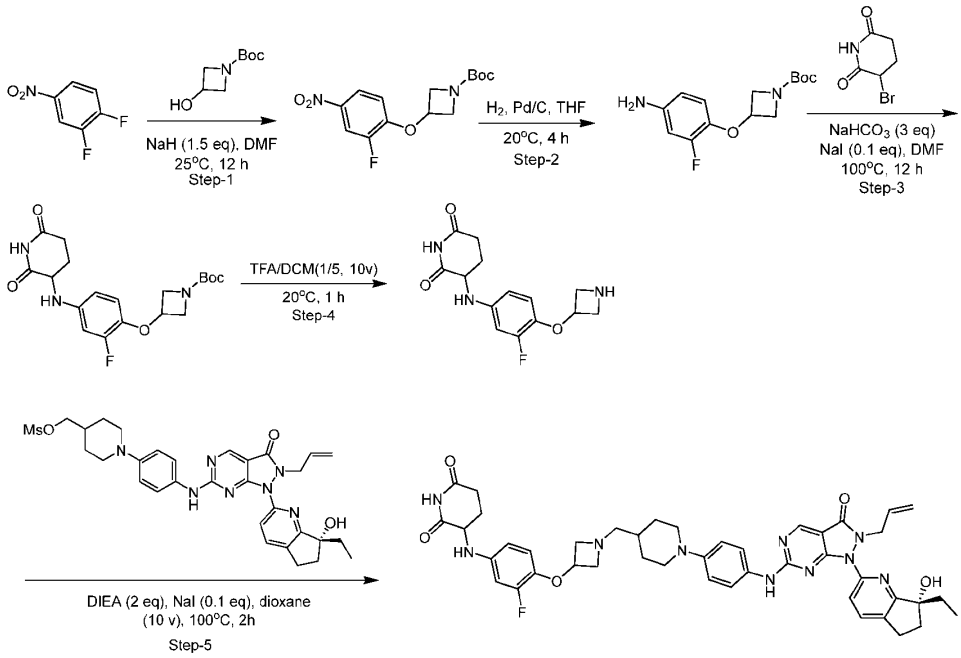
489.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.73-6.66 (m, 2H), 6.65-6.55 (m, 2H), 6.53-6.43 (m, 2H), 4.56 (s, 2H), 4.24 (quin, J = 6.3 Hz, 1H), 4.01-3.91 (m, 1H), 3.90-3.84 (m, 2H), 3.84-3.80 (m, 3H), 3.62 (s, 1H), 3.00-2.91 (m, 4H), 2.91-2.84 (m, 1H), 2.72 (s, 2H), 2.67 (br d, J = 1.8 Hz, 2H), 2.58 (br dd, J = 12.6, 5.2 Hz, 3H), 2.41-2.33 (m, 1H), 2.18 (s, 1H).

Step 6: 1-[6-[2-[[4-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-3-oxo-pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]piperazin-1-yl]methyl]azetidin-1-yl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione

[0149] A solution of 1-[6-[2-[[4-(4-aminophenyl)piperazin-1-yl]methyl]azetidin-1-yl] -1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (60 mg, 122.80 μmol) and 2-allyl-1-[(7R)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-methylsulfonyl-pyrazolo[3,4-*d*]pyrimidin-3-one (51.02 mg, 122.80 μmol) in ^{i}PrOH (0.6 mL) was stirred at 50 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filter cake was washed with ^{i}PrOH (3 mL), the collected filtrate was concentrated to give the crude product, which was purified by prep-HPLC (NH_4HCO_3 condition) to give 1-[6-[2-[[4-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-3-oxo-pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]piperazin-1-yl]methyl]azetidin-1-yl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (30 mg, 29.65% yield, 100% purity). MS (ESI^+): m/z = 824.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H), 10.28-9.96 (m, 1H), 8.82 (s, 1H), 7.93 (br d, J = 7.3 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.59 (br s, 2H), 7.42 (d, J = 8.8 Hz, 1H), 6.94 (br d, J = 9.0 Hz, 2H), 6.62 (dd, J = 8.9, 1.6 Hz, 1H), 6.59 (s, 1H), 5.67 (tdd, J = 16.9, 10.5, 5.9 Hz, 1H), 5.05 (s, 1H), 5.00 (dd, J = 10.3, 1.1 Hz, 1H), 4.86 (dd, J = 17.1, 1.0 Hz, 1H), 4.76 (br d, J = 11.9 Hz, 1H), 4.57 (br dd, J = 15.8, 5.3 Hz, 1H), 4.26 (quin, J = 6.3 Hz, 1H), 3.97 (dt, J = 7.8, 3.6 Hz, 1H), 3.87 (t, J = 6.8 Hz, 2H), 3.83 (s, 3H), 3.62 (q, J = 7.9 Hz, 1H), 3.16 (br s, 4H), 3.01-2.87 (m, 2H), 2.83-2.76 (m, 1H), 2.72 (br t, J = 6.7 Hz, 4H), 2.67-2.58 (m, 3H), 2.43-2.34 (m, 1H), 2.25-2.14 (m, 2H), 2.01 (ddd, J = 13.4, 8.4, 5.4 Hz, 1H), 1.95-1.84 (m, 1H), 1.76-1.66 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H).

Example 5

3-((4-((1-((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)oxy)-3-fluorophenyl)amino)piperidine-2,6-dione (**5**)



Step 1: *tert*-butyl 3-(2-fluoro-4-nitrophenoxy) azetidine-1-carboxylate

[0150] To a solution of 1,2-difluoro-4-nitrobenzene (2 g, 12.57 mmol, 1.39 mL) and *tert*-butyl 3-hydroxyazetidine-1-carboxylate (2.18 g, 12.57 mmol) in DMF (25 mL) was added NaH (1.3 g, 18.86 mmol, 60% purity) at 0 °C under N_2 atmosphere. Then the reaction was stirred at 25 °C for 12 h. TLC (PE:EA = 1:1) showed the starting material consumed and a new spot was detected. The reaction was quenched with saturated NH_4Cl solution (80 mL) at 0 °C, and extracted with EA (80 mL). The organic layer was washed with brine (3 × 50 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel; PE:EA = 100:1 to 1:100) to afford *tert*-butyl 3-(2-fluoro-4-nitrophenoxy) azetidine-1-carboxylate (3.35 g, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.10-7.99 (m, 2H), 6.74 (t, *J* = 8.6 Hz, 1H), 5.07-4.98 (m, 1H), 4.37 (dd, *J* = 10.0, 6.5 Hz, 2H), 4.10 (dd, *J* = 10.1, 3.9 Hz, 2H), 1.46 (s, 9H).

Step 2: *tert*-butyl 3-(4-amino-2-fluorophenoxy) azetidine-1-carboxylate

[0151] To a solution of *tert*-butyl 3- (2-fluoro-4-nitrophenoxy) azetidine-1-carboxylate (1 g, 3.20 mmol) in THF (30 mL) was added Pd/C (340.77 mg, 320.21 μmol, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 4 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filter cake was washed with THF (20 mL). The collected filtrate was concentrated to give *tert*-butyl 3-(4-amino-2-fluorophenoxy) azetidine-1-carboxylate (0.90 g, 99%). ^{1}H NMR (400 MHz, Methanol-d_4): δ 6.68 (t, J = 9.0 Hz, 1H), 6.51 (dd, J = 13.1, 2.6 Hz, 1H), 6.44-6.37 (m, 1H), 4.83 (br s, 1H), 4.27-4.14 (m, 2H), 3.92 (br dd, J = 9.4, 3.3 Hz, 2H), 1.45 (s, 9H)

Step 3: *tert*-butyl 3-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenoxy)azetidine-1-carboxylate

[0152] To a solution of *tert*-butyl 3-(4-amino-2-fluorophenoxy)azetidine-1-carboxylate (0.9 g, 3.19 mmol) and 3-bromopiperidine-2,6-dione (918.19 mg, 4.78 mmol) in DMF (10 mL) was added $NaHCO_3$ (803.44 mg, 9.56 mmol) and NaI (47.79 mg, 318.80 μmol) at 20 °C. Then the reaction was stirred at 100 °C for 12 h. LCMS showed one major peak with desired MS was detected. Silica gel was added to the reaction solution and the mixture stirred for 20 min, then filtered and the filter cake was washed with THF. The collected filtrate was concentrated to give the crude product, which was purified by column chromatography (silica gel; PE:EA = 100:0 to 30:70) to give *tert*-butyl 3-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenoxy)azetidine-1-carboxylate (0.5 g, 40%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 6.75 (t, J = 9.3 Hz, 1H), 6.60 (dd, J = 14.1, 2.4 Hz, 1H), 6.40 (dd, J = 8.9, 1.6 Hz, 1H), 5.86 (d, J = 7.7 Hz, 1H), 4.89-4.74 (m, 1H), 4.34-4.04 (m, 3H), 3.79 (br d, J = 6.2 Hz, 2H), 3.30 (s, 1H), 2.80-2.63 (m, 1H), 2.08 (td, J = 4.2, 8.6 Hz, 1H), 1.93-1.76 (m, 1H), 1.38 (s, 9H)

Step 4: 3-((4-(azetidin-3-yloxy)-3-fluorophenyl)amino) piperidine-2,6-dione

[0153] A solution of tert-butyl 3-(4-((2,6-dioxopiperidin-3-yl) amino)-2-fluorophenoxy) azetidine-1-carboxylate (0.51 g, 1.96 mmol) in TFA/DCM (1 mL/5 mL) was stirred at 20 °C for 1 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 25 °C to give 3-((4-(azetidin-3-yloxy)-3-fluorophenyl)amino)piperidine-2,6-dione (0.3 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.79 (s, 1H), 9.00 (br d, J = 1.9 Hz, 1H), 8.79 (br s, 1H), 6.79 (t, J = 9.2 Hz, 1H), 6.61 (dd, J = 14.2, 2.6 Hz, 1H), 6.41 (dd, J = 8.8, 1.9 Hz,

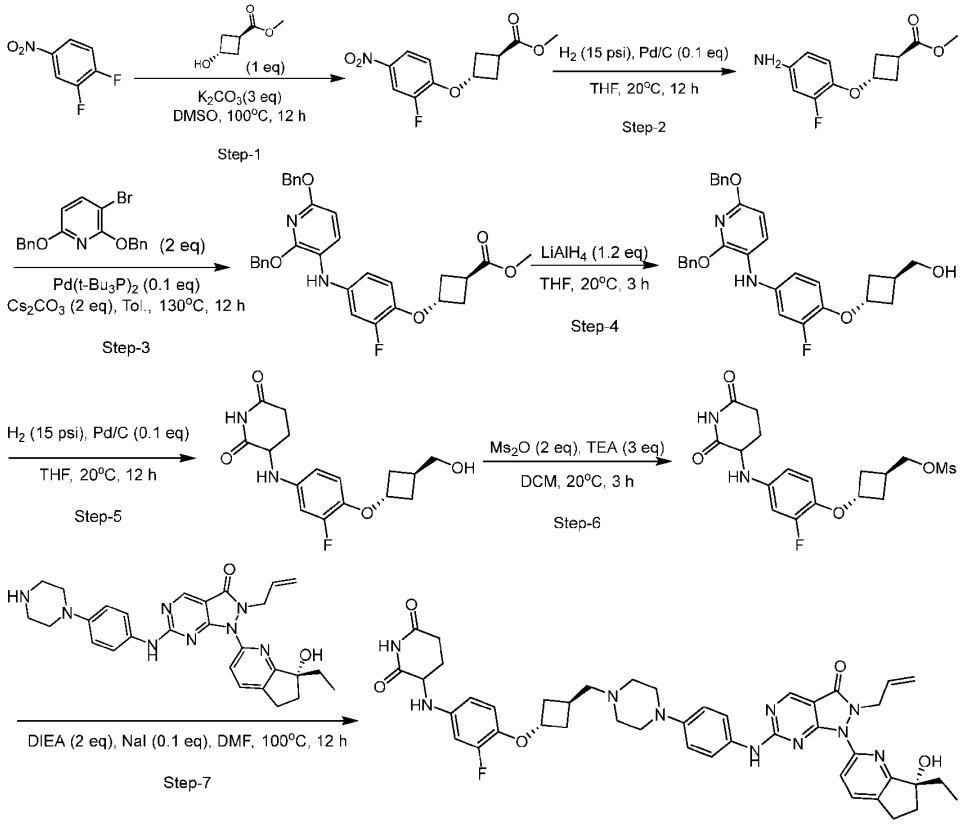
1H), 4.90 (t, *J* = 5.5 Hz, 1H), 4.42-4.31 (m, 2H), 4.27 (dd, *J* = 11.5, 4.8 Hz, 1H), 4.08-3.89 (m, 2H), 2.80-2.65 (m, 1H), 2.61-2.53 (m, 1H), 2.13-2.02 (m, 1H), 1.92-1.78 (m, 1H).

Step 5: 3-((4-((1-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)oxy)-3-fluorophenyl)amino)piperidine-2,6-dione

[0154] To a mixture of 3-((4-(azetidin-3-yloxy)-3-fluorophenyl) amino) piperidine-2,6-dione (0.3 g, 242.04 μmol,) in dioxane (3 mL) were added (*R*)-(1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl methane sulfonate (141.98 mg, 484.08 μmol), DIEA (62.56 mg, 484.08 μmol) and NaI (3.63 mg, 24.20 μmol) at 20 °C, and the mixture was stirred at 100 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filtrate was concentrated to give the residue. The residue was purified by reverse-phase prep-HPLC to afford 3-((4-((1-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)oxy)-3-fluorophenyl) amino) piperidine-2,6-dione (42.2 mg, 14%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80-10.74 (m, 1H), 10.04-9.96 (m, 1H), 8.79-8.74 (m, 1H), 7.92-7.85 (m, 1H), 7.72-7.66 (m, 1H), 7.60-7.38 (m, 2H), 6.79 (br d, *J* = 3.3 Hz, 1H), 6.58 (dd, *J* = 2.3, 14.1 Hz, 1H), 6.49 (br d, *J* = 8.8 Hz, 2H), 6.41-6.35 (m, 1H), 5.84-5.78 (m, 1H), 5.72-5.57 (m, 1H), 5.06-4.95 (m, 2H), 4.91-4.80 (m, 1H), 4.79-4.69 (m, 1H), 4.66-4.50 (m, 2H), 4.29-4.16 (m, 1H), 3.70-3.63 (m, 2H), 3.39 (br t, *J* = 8.2 Hz, 1H), 3.29-3.16 (m, 2H), 3.01-2.90 (m, 3H), 2.87-2.65 (m, 3H), 2.62-2.51 (m, 3H), 2.28-2.15 (m, 2H), 2.12-1.96 (m, 3H), 1.93-1.78 (m, 2H), 1.74-1.65 (m, 1H), 1.62-1.55 (m, 1H), 1.50-1.38 (m, 2H), 0.91-0.82 (m, 3H). MS (ESI$^+$): *m/z* = 817.3 $[M+H]^+$.

Example 6

3-((4-((1*r*,3*r*)-3-((4-(4-((2-allyl-1-((*R*)-7-ethyl -7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)cyclobutoxy)-3-fluorophenyl)amino)piperidine-2,6-dione (**6**)



Step 1: methyl (1*r*,3*r*)-3-(2-fluoro-4-nitrophenoxy)cyclobutane-1-carboxylate

[0155] To a solution of 1,2-difluoro-4-nitrobenzene (2.20 g, 13.83 mmol) and methyl 3-hydroxycyclobutanecarboxylate (1.5 g, 11.53 mmol) in DMSO (50 mL) was added K_2CO_3 (4.78 g, 34.58 mmol) at 20 °C. The reaction was stirred at 100 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was quenched with water (30 mL) and extracted with DCM (30 mL). The combined organic layer was dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel; PE:EA = 60:1 to 0:1) to give methyl (1*r*,3*r*)-3-(2-fluoro-4-nitrophenoxy) cyclobutane-1-carboxylate (1.2 g, 33%). MS (ESI^-): *m/z* =270.7 $[M+H]^+$.

Step 2: methyl (1*r*,3*r*)-3-(4-amino-2-fluorophenoxy)cyclobutane-1-carboxylate

[0156] To a solution of methyl 3-(2-fluoro-4-nitro-phenoxy)cyclobutanecarboxylate (1 g, 3.71 mmol, 85% purity) in THF (20 mL) was added Pd/C (395.28 mg, 371.44 μmol, 10% purity) under N_2 at 20 °C. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered through celite, and the filtrate was concentrated under reduced pressure at 40 °C to give methyl 3-(4-amino-2-fluoro-phenoxy) cyclobutanecarboxylate (0.8 g, 86%). MS (ESI^+): *m/z* =240.0 $[M+H]^+$.

Step 3: methyl (1*r*,3*r*)-3-(4-((2,6-bis(benzyloxy) pyridin-3-yl)amino)-2-fluorophenoxy)cyclobutane-1-carboxylate

[0157] To a solution of methyl 3-(4-amino-2-fluoro-phenoxy)cyclobutanecarboxylate (0.8 g, 3.34 mmol, 95% purity) and 2,6-dibenzyloxy-3-bromo-pyridine (2.48 g, 6.69 mmol) in toluene (16 mL) was added Cs_2CO_3 (2.18 g, 6.69 mmol) and $Pd(t\text{-}Bu_3P)_2$ (170.89 mg, 334.39 μmol) at 20 °C. The reaction was stirred at 130 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was quenched with water (30 mL) and extracted with DCM (30 mL). The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel; PE:EA = 50:1 to 0:1) to give methyl 3-[4-[(2,6-dibenzyloxy-3-pyridyl)amino]-2-fluoro-phenoxy] cyclobutanecarboxylate (0.7 g, 36%). MS (ESI^+): *m/z* =529.3 $[M+H]^+$.

Step 4: ((1*r*,3*r*)-3-(4-((2,6-bis(benzyloxy)pyridin-3-yl)amino)-2-fluorophenoxy)cyclobutyl)methanol

[0158] To a solution of methyl (1*r*,3*r*)-3-(4-((2,6-bis(benzyloxy)pyridin-3-yl)amino)-2- fluorophenoxy)cyclobutane-1-carboxylate (0.7 g, 1.19 mmol, 90% purity) in THF (14 mL) was added $LiAlH_4$ (2.5 M, 1.43 mmol, 572.11 μL) at 0 °C. Then the reaction was stirred at 20 °C for 3 h. LCMS showed the reaction was completed and the desired product was detected. After the reaction is completed, the mixture is cooled to -10 °C, then water (1 mL), 10 mL 15% sodium hydroxide solution and water (10 mL) were added in sequence slowly to quench the reaction. Then the mixture was stirred for 15 min and extracted with DCM (30 mL). The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give [3-[4-[(2,6-dibenzyloxy-3-pyridyl) amino]-2-fluoro-phenoxy]cyclobutyl]methanol (0.5 g, 74% yield,

88% purity). which was used to next step without further purification. MS (ESI^+): *m/z* = 501.3 $[M+H]^+$.

Step 5: 3-((3-fluoro-4-((1*r*,3*r*)-3-(hydroxymethyl) cyclobutoxy)phenyl)amino)piperidine-2,6-dione.

[0159] To a solution of [3-[4-[(2,6-dibenzyloxy-3-pyridyl)amino]-2-fluoro-phenoxy]cyclobutyl] methanol (0.5 g, 998.88 μmol) in THF (12 mL) was added Pd/C (106.30 mg, 99.89 μmol, 10% purity) under N_2 at 20 °C. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give 3-((3-fluoro-4-((1*r*,3*r*)-3-(hydroxymethyl)cyclobutoxy)phenyl)amino)piperidine-2,6-dione (0.3 g, 75%). MS (ESI^+): *m/z* = 323.2 $[M+H]^+$.

Step 6: ((1*r*,3*r*)-3-(4-((2,6-dioxopiperidin-3-yl) amino)-2-fluorophenoxy)cyclobutyl)methyl methanesulfonate

[0160] To a solution of 3-[3-fluoro-4-[3-(hydroxymethyl)cyclobutoxy]anilino]piperidine-2,6-dione (0.15 g, 465.36 μmol) in DCM (6 mL) at 0 °C, was added TEA (141.27 mg, 1.40 mmol) and methanesulfonic anhydride (162.13 mg, 930.72 μmol). Then the reaction was stirred at 20 ° C for 3 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was quenched with water (30 mL) and extracted with DCM (30 mL). The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by prep-TLC (silica gel; PE:EA = 0:1, Rf=0.5) to give [3-[4-[(2,6-dioxo-3-piperidyl)amino]-2-fluoro-phenoxy]cyclobutyl]methyl methanesulfonate (60 mg, 32%). MS (ESI^+): *m/z* = 401.1 $[M+H]^+$.

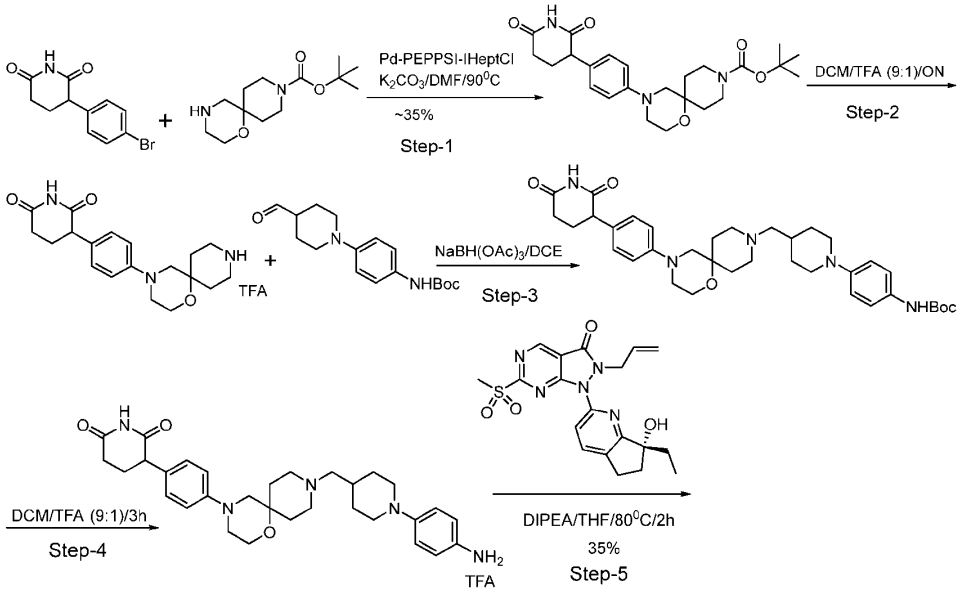
Step 7: 3-((4-((1*r*,3*r*)-3-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)cyclobutoxy)-3-fluorophenyl)amino)piperidine-2,6-dione.

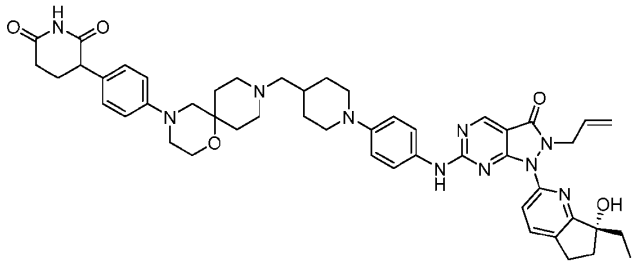
[0161] To a solution of [3-[4-[(2,6-dioxo-3-piperidyl)amino]-2-fluoro-phenoxy]cyclobutyl]methyl methanesulfonate (60.0 mg, 149.84 μmol) and 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-(4-piperazin-1-ylanilino)pyrazolo[3,4-*d*]pyrimidin-3-one (76.81 mg, 149.84 μmol) in DMF (1 mL) at rt, was added DIEA (58.10 mg, 449.53 μmol) and NaI (2.25 mg, 14.98 μmol). Then the

reaction was stirred at 100 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give the crude product, which was purified by reverse-phase prep-HPLC to give 3-[4-[3-[[4-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-3-oxo-pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]piperazin-1-yl]methyl]cyclobutoxy]-3-fluoro-anilino]piperidine-2,6-dione (16 mg, 13%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (br s, 1H), 10.30-9.92 (m, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.66-7.47 (m, 2H), 6.91 (br d, *J* = 8.9 Hz, 2H), 6.75 (t, *J* = 9.3 Hz, 1H), 6.57 (dd, *J* = 14.1, 2.6, Hz, 1H), 6.39 (dd, *J* = 8.8, 1.7 Hz, 1H), 5.76 (d, *J* = 7.6 Hz, 1H), 5.67 (tdd, *J* = 16.8, 10.6, 5.9 Hz, 1H), 5.05 (s, 1H), 5.03-4.95 (m, 1H), 4.85 (br d, *J* = 17.2 Hz, 1H), 4.81-4.72 (m, 1H), 4.71-4.62 (m, 1H), 4.57 (br dd, *J* = 15.4, 5.5 Hz, 1H), 4.28-4.18 (m, 1H), 3.38-3.33 (m, 2H), 3.08 (br s, 4H), 3.02-2.92 (m, 1H), 2.82-2.67 (m, 2H), 2.61-2.57 (m, 1H), 2.57-2.51 (m, 3H), 2.48-2.42 (m, 2H), 2.27-2.17 (m, 2H), 2.17-2.11 (m, 3H), 2.11-1.97 (m, 2H), 1.95-1.78 (m, 2H), 1.76-1.64 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): *m/z* = 817.5 [M+H]$^+$.

Example 7

3-(4-(9-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione (**7**)





Step 1: *tert*-butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate.

[0162] A stirred solution of 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylic acid, 1,1-dimethylethyl ester (250 mg, 0.975 mmol), 3-(4-bromophenyl)piperidine-2,6-dione (261 mg, 0.975 mmol), anhydrous potassium carbonate (270 mg, 1.950 mmol) in DMF (4.88 mL) was heated at 90 °C for 1 h. The mixture was partitioned between DCM/water. The organic layer was separated, dried over Na_2SO_4, concentrated, and was purified by column chromatography (silica gel, 0-10% MeOH in DCM) to afford *tert*-butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (143 mg, 33%). MS (APCI) m/z: 444.2 $[M+H]^+$.

Step 2: 3-(4-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione

[0163] A solution of *tert*-butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (100 mg, 0.225 mmol) in DCM (2.03 mL) and TFA (225 µL) was stirred at rt overnight. The mixture was concentrated to afford 3-(4-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione as a TFA salt (quantitative yield). MS (APCI) m/z: 344.2 $[M+H]^+$.

Step 3: *tert*-butyl (4-(4-((4-(4-(2,6-dioxopiperidin-3-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)piperidin-1-yl)phenyl)carbamate

[0164] To a solution of 3-(4-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione TFA salt (99 mg, 0.225 mmol) in DCE (2.25 mL) at 0 °C, was added *N,N*-diisopropylethylamine (196 µL, 1.125 mmol). To this mixture was added a solution of *tert*-butyl (4-(4-formylpiperidin-1-yl)phenyl)carbamate (68.5 mg, 0.225 mmol) in DCE (0.5 mL) at 0 °C. The mixture was stirred at rt for 1 h. The mixture was cooled to 0 °C then sodium triacetoxyborohydride (95 mg, 0.450 mmol) was added. The resulting mixture was stirred at rt for 1 h. LCMS shows the formation of product. Did the work up with DCM/water. The organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-10% of MeOH in DCM) to afford *tert*-

butyl (4-(4-((4-(4-(2,6-dioxopiperidin-3-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)piperidin-1-yl)phenyl)carbamate (95 mg, 0.150 mmol, 66%). MS (APCI) m/z: 632.40 $[M+H]^+$.

Step 4: 3-(4-(9-((1-(4-aminophenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione.

[0165] A solution of *tert*-butyl (4-(4-((4-(4-(2,6-dioxopiperidin-3-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)piperidin-1-yl)phenyl)carbamate (95 mg, 0.150 mmol) in DCM (2.7 mL) and TFA (301 µL) was stirred at rt for 3 h. The mixture was concentrated under reduced pressure to afford 3-(4-(9-((1-(4-aminophenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione (quantitative yield) as TFA salt. MS (APCI) m/z: 532.4 $[M+H]^+$.

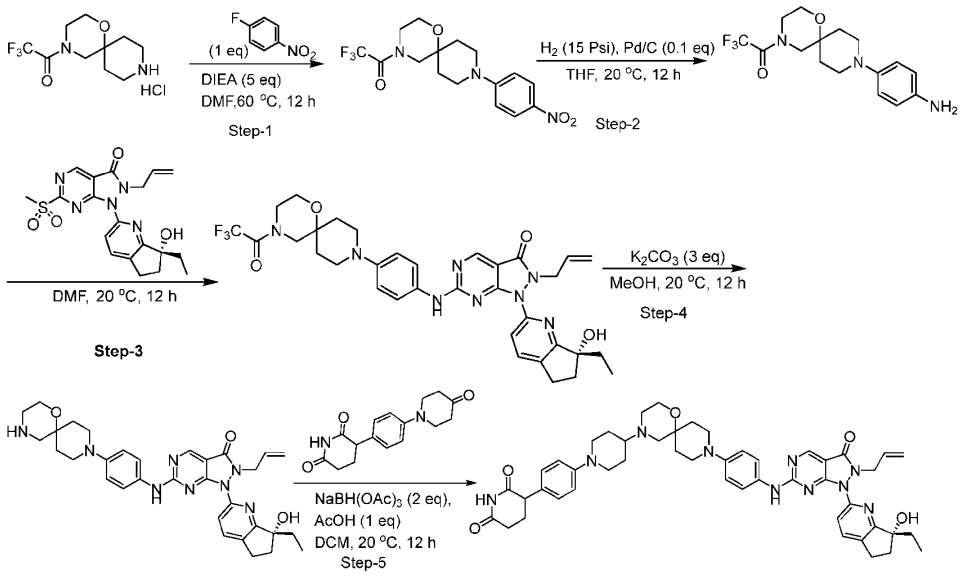
Step 5: 3-(4-(9-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione

[0166] To a solution of 3-(4-(9-((1-(4-aminophenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione TFA salt (80 mg, 0.15 mmol) in THF (3 mL) was added *N*,*N*-Diisopropylethylamine (131 µL, 0.750 mmol) followed by (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (49.9 mg, 0.120 mmol). The mixture was heated at 80 °C for 3 h. The mixture was diluted with DCM/Water. The organic layer was separated, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography (silica gel, 0-70% of 9:1, DCM: MeOH) to afford the impure product. Further purification by reverse-phase preparative HPLC (10-80% acetonitrile (contains 0.1% formic acid) in water (contains 0.1% formic acid)) afforded 3-(4-(9-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione (45 mg, 0.052 mmol, 34%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.73-10.81 (m, 1H), 10.01-10.20 (m, 1H), 8.75-8.86 (m, 1H), 7.87-7.97 (m, 1H), 7.64-7.76 (m, 1H), 7.46-7.64 (m, 2H), 7.00-7.11 (m, 2H), 6.82-6.97 (m, 4H), 5.59-5.74 (m, 1H), 4.92 -5.13 (m, 2H), 4.67-4.92 (m, 2H), 4.50-4.63 (m, 1H), 3.56-3.82 (m, 7H), 2.90-3.09 (m, 5H), 2.70-2.85 (m, 1H), 2.55-2.70 (m, 1H), 2.42-2.67 (m, 4H), 2.07-2.38

(m, 6H), 1.95-2.07 (m, 2H), 1.53-1.95 (m, 8H), 1.10-1.31 (m, 2H), 0.78-0.96 (m, 3H). MS (APCI) m/z: 868.4 $[M+H]^+$.

Example 8

3-(4-(4-(9-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**8**)



Step 1: 2,2,2-trifluoro-1-[9-(4-nitrophenyl)-1-oxa-4,9-diazaspiro[5.5] undecan-4-yl]ethanone

[0167] To a solution of 2,2,2-trifluoro-1-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone (2 g, 6.23 mmol, HCl salt) and 1-fluoro-4-nitrobenzene (879 mg, 6.23 mmol) in DMF (40 mL) was added DIEA (4.03 g, 31.17 mmol) at 20 °C. Then the reaction was stirred at 60 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (50 mL) and extracted with DCM (3 × 50 mL). The organic layer was dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, 0-100% EA in PE) to afford 2,2,2-trifluoro-1-[9-(4-nitrophenyl)-1-oxa-4,9-diazaspiro[5.5] undecan-4-yl]ethanone (2 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (dd, J = 1.3, 9.4 Hz, 2H), 7.02 (d, J = 9.4 Hz, 2H), 3.87-3.79 (m, 1H), 3.78-3.73 (m, 2H), 3.72-3.67 (m, 1H), 3.64-3.57 (m, 2H), 3.54 (s, 1H), 3.48-3.45 (m,

1H), 3.31-3.24 (m, 1H), 3.23-3.13 (m, 1H), 1.89 (br d, J = 13.1 Hz, 1H), 1.81 (br d, J = 13.8 Hz, 1H), 1.67-1.54 (m, 2H). MS (ESI) m/z: 374.1 $[M+H]^+$.

Step 2: 1-[9-(4-aminophenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-2,2,2-trifluoro-ethanone

[0168] To a solution of 2,2,2-trifluoro-1-[9-(4-nitrophenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl] ethanone (2 g, 5.36 mmol) in THF (40 mL) was added Pd/C (570.12 mg, 535.72 μmol, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give 1-[9-(4-aminophenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-2,2,2-trifluoro-ethanone (1.7 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.69 (d, J = 8.7 Hz, 2H), 6.48 (d, J = 8.5 Hz, 2H), 4.56 (br s, 2H), 3.78-3.68 (m, 2H), 3.65-3.60 (m, 2H), 3.53 (s, 1H), 3.47-3.43 (m, 1H), 3.10-3.01 (m, 1H), 3.01-2.93 (m, 1H), 2.90-2.81 (m, 1H), 2.80-2.70 (m, 1H), 1.85 (br d, J = 12.6 Hz, 1H), 1.77 (br s, 1H), 1.69-1.54 (m, 2H). MS (ESI) m/z: 344.2 $[M+H]^+$.

Step 3: 2-allyl-1-[rac-(7R)-7-ethyl-7-hydroxy-5,6- dihydrocyclopenta[*b*]pyridin-2-yl]-6-[4-[4-(2,2,2-trifluoroacetyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]anilino]pyrazolo[3,4-*d*]pyrimidin-3-one

[0169] To a solution of 1-[9-(4-aminophenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-2,2,2- trifluoro-ethanone (595.01 mg, 1.73 mmol) in DMF (6 mL) was added 2-allyl-6-methylsulfonyl-1-[rac-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-3-one (0.6 g, 1.44 mmol) at 20 °C. Then the reaction was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (10 mL) and extracted with DCM (3 × 10 mL). The organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, 0-100% EA in PE) to afford 2-allyl-1-[rac-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-[4-[4-(2,2,2-trifluoroacetyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]anilino]pyrazolo[3,4-*d*]pyrimidin-3-one (0.9 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25-9.97 (m, 1H), 8.82 (s, 1H), 7.95-7.89 (m, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.57 (br s, 2H), 6.93 (br d, J = 8.8 Hz, 2H), 5.67 (tdd, J = 16.8, 10.5, 5.9 Hz, 1H), 5.05 (s, 1H), 4.99 (dd, J = 10.3, 1.0 Hz, 1H), 4.85 (br d, J = 17.0 Hz, 1H), 4.81-4.69 (m, 1H), 4.63-4.51 (m, 1H), 3.79-3.70 (m, 2H), 3.60 (br s, 2H), 3.55 (s, 1H),

3.47 (s, 1H), 3.42-3.34 (m, 1H), 3.29-3.23 (m, 1H), 3.06-2.92 (m, 2H), 2.83-2.75 (m, 1H), 2.25-2.14 (m, 1H), 2.06-2.00 (m, 1H), 1.94-1.85 (m, 2H), 1.85-1.78 (m, 1H), 1.75 (br s, 1H), 1.68-1.57 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: 679.4 $[M+H]^+$.

Step 4: 2-allyl-6-[4-(1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)anilino]-1-[rac-(7R)-7-ethyl-7- hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-3-one

[0170] To a solution of 2-allyl-1-[rac-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-[4-[4-(2,2,2-trifluoroacetyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]anilino]pyrazolo[3,4-*d*]pyrimidin-3-one (0.8 g, 1.18 mmol) in MeOH (16 mL) was added K_2CO_3 (488.72 mg, 3.54 mmol) at 20 °C. Then the reaction was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The organic layer was dried over Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give 2-allyl-6-[4-(1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)anilino]-1-[rac-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-3-one (0.6 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24-9.99 (m, 1H), 8.81 (s, 1H), 7.99-7.88 (m, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.63-7.43 (m, 2H), 6.92 (br d, J = 8.9 Hz, 2H), 5.73-5.59 (m, 1H), 5.05 (s, 1H), 4.99 (br d, J = 10.4 Hz, 1H), 4.85 (br d, J = 17.4 Hz, 1H), 4.81-4.68 (m, 1H), 4.62-4.51 (m, 1H), 3.57-3.51 (m, 2H), 3.27-3.21 (m, 2H), 3.01-2.93 (m, 3H), 2.82-2.75 (m, 1H), 2.67-2.62 (m, 2H), 2.57 (s, 2H), 2.25-2.15 (m, 1H), 2.06-2.00 (m, 1H), 1.96-1.85 (m, 3H), 1.75-1.67 (m, 1H), 1.62-1.52 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS (ESI) m/z: 583.2 $[M+H]^+$.

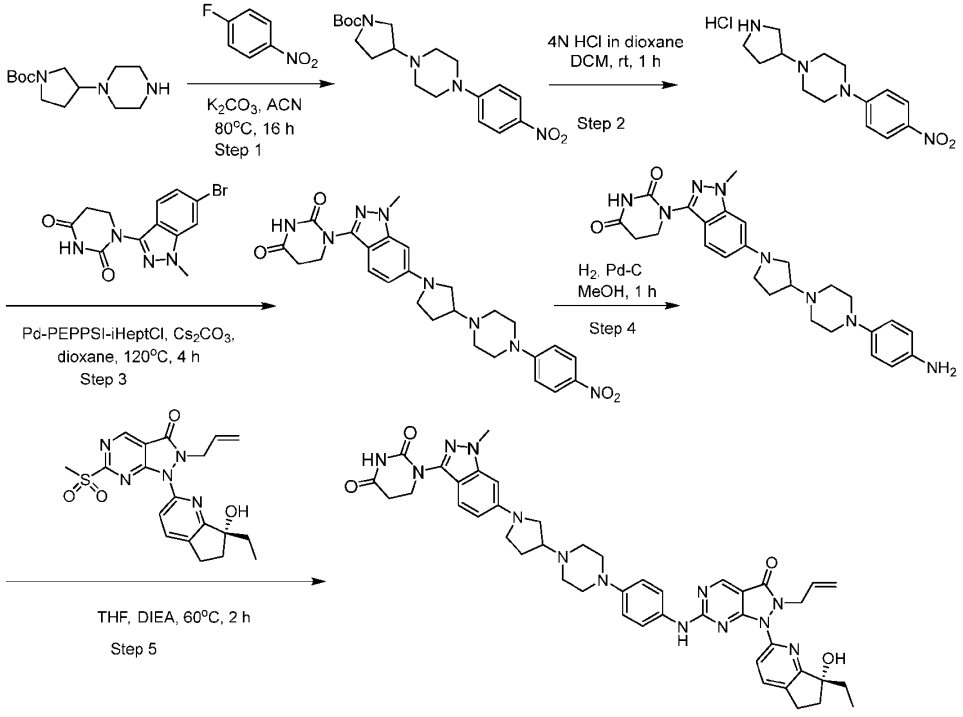
Step 5: 3-(4-(4-(9-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro -5*H*-cyclopenta[*b*]pyridine -2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione

[0171] To a solution of 2-allyl-6-[4-(1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)anilino]-1-[rac-(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]pyrazolo[3,4-*d*]pyrimidin-3-one (0.1 g, 171.62 μmol) and 3-(4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione (98.28 mg, 343.23 μmol) in DCM (1 mL) was added $NaBH(OAc)_3$ (72.75 mg, 343.23 μmol) and AcOH (20.83 mg, 171.62 μmol) at 0 °C. Then the reaction was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give the crude product, which was purified by reverse phase

prep-HPLC to afford 3-(4-(4-(9-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro -5*H*-cyclopenta[*b*]pyridine -2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione (50.0 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 10.25-9.88 (m, 1H), 8.81 (s, 1H), 7.93 (br d, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.56 (br s, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.97-6.81 (m, 4H), 5.67 (tdd, *J* = 16.9, 10.6, 5.9 Hz, 1H), 5.04 (s, 1H), 4.99 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.85 (br d, *J* = 17.2 Hz, 1H), 4.76 (br d, *J* = 14.3 Hz, 1H), 4.56 (br dd, *J* = 15.4, 5.1 Hz, 1H), 3.76-3.60 (m, 5H), 3.28-3.19 (m, 2H), 3.05-2.92 (m, 3H), 2.83-2.73 (m, 1H), 2.71-2.57 (m, 3H), 2.49-2.45 (m, 3H), 2.39 (s, 2H), 2.23 (br s, 1H), 2.23-2.15 (m, 1H), 2.15-2.06 (m, 1H), 2.05-1.96 (m, 2H), 1.81 (br s, 5H), 1.75-1.60 (m, 3H), 1.57-1.44 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). MS (ESI) m/z: 853.5 $[M+H]^+$.

Example 9

1-(6-(3-(4-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)pyrrolidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**9**)



Step 1: *tert*-butyl 3-(4-(4-nitrophenyl)piperazin-1-yl)pyrrolidine-1-carboxylate

[0172] To a solution of 4-nitrofluorobenzene (243 mg, 1.720 mmol) in ACN (5 mL) was added anhydrous potassium carbonate (594 mg, 4.30 mmol) and *tert*-butyl-3-(1-piperazinyl)-1-pyrrolidine-carboxylate (366 mg, 1.433 mmol). The reaction was heated at 80 °C for 4 h. The reaction was diluted with water (50 mL) and EtOAc (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (50 mL × 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (silica gel) 0-100% EtOAc/hexanes to give product *tert*-butyl 3-(4-(4-nitrophenyl)piperazin-1-yl)pyrrolidine-1-carboxylate (458 mg, 1.217 mmol, 85%). MS (APCI) *m/z* 377.2 $[M+1]^+$.

Step 2: 1-(4-nitrophenyl)-4-(pyrrolidin-3-yl)piperazine hydrochloride

[0173] To a solution of *tert*-butyl 3-(4-(4-nitrophenyl)piperazin-1-yl)pyrrolidine-1-carboxylate (458 mg, 1.217 mmol) in DCM (1 mL) was added 4N HCl in dioxane (0.1 mL, 0.8 mmol). The reaction was stirred at 0 °C for 1 h. The resulting product was collected by centrifuge and afforded 1-(4-nitrophenyl)-4-(pyrrolidin-3-yl)piperazine as an HCl salt. MS (APCI) *m/z* 277.2 $[M+1]^+$.

Step 3: 1-(1-methyl-6-(3-(4-(4-nitrophenyl)piperazin-1-yl)pyrrolidin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0174] In a microwave tube (20 mL) was loaded 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (381 mg, 1.179 mmol), 1,4-dioxane (6 mL), 1-(4-nitrophenyl)-4-(pyrrolidin-3-yl)piperazine hydrochloride, and cesium carbonate (768 mg, 2.358 mmol). The mixture was bubbled with nitrogen for 1 min before adding Pd-PEPPSI-iHeptCl (115 mg, 0.118 mmol). The tube was sealed and heated at 120 °C for 4 h. The reaction was diluted with EtOAc (50 mL) and brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (silica gel; 0-10% MeOH/DCM) to afford 1-(1-methyl-6-(3-(4-(4-nitrophenyl)piperazin-1-yl)pyrrolidin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (100 mg, 0.193 mmol, 16%). MS (APCI) *m/z* 489.3 $[M+1]^+$.

Step 4: 1-(6-(3-(4-(4-aminophenyl)piperazin-1-yl)pyrrolidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0175] A solution of 1-(1-methyl-6-(3-(4-(4-nitrophenyl)piperazin-1-yl)pyrrolidin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (100 mg, 0.193 mmol) in MeOH (20 mL) and DCM (10 mL), was bubbled with nitrogen for 1 min. Pd-C (10%) was added. The suspension was bubbled with hydrogen for 1 min and then stirred under hydrogen (1 atmosphere) for 1 h. The catalyst was filtered off and the filtrate was concentrated and dried, to afford 1-(6-(3-(4-(4-aminophenyl)piperazin-1-yl)pyrrolidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (87 mg, 0.178 mmol, 92%). MS (APCI) *m/z* 519.2 [M+1]+.

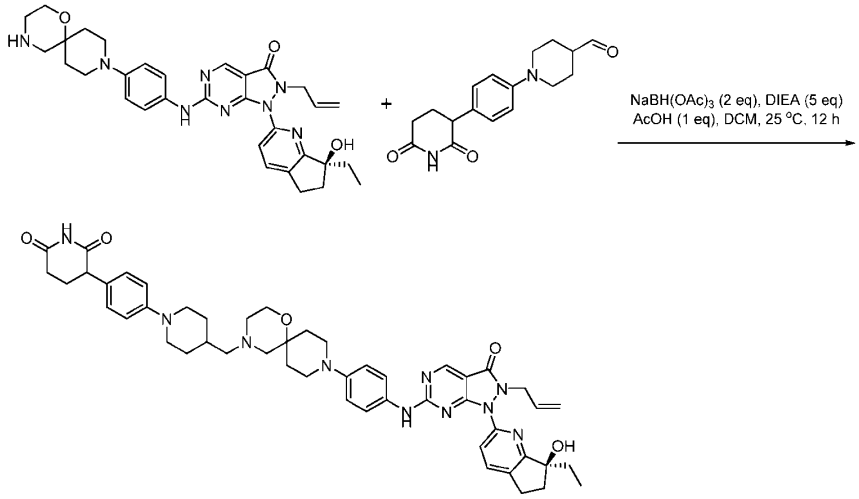
Step 5: 1-(6-(3-(4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)pyrrolidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0176] To a solution of 1-(6-(3-(4-(4-aminophenyl)piperazin-1-yl)pyrrolidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (87 mg, 0.178 mmol) in THF (3 mL) were added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (89 mg, 0.214 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL, 2.87 mmol). The mixture was heated at 60 °C for 2 h. the reaction was quenched with saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, the filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel; 0-10% MeOH in DCM). The product was further purified by reverse-phase prep-HPLC (C18 column eluted with 0-100% MeCN/H_2O (with 0.1% formic acid)). The pure product fractions were combined and concentrated. To the residue was added saturated $NaHCO_3$ and then extracted with EtOAc (100 mL × 3). The combined organic layers was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1-(6-(3-(4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)pyrrolidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (24.6 mg, 0.029 mmol, 16%). MS (APCI) *m/z* 824.4 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.49-10.38 (m, 1H), 10.17-

9.90 (m, 1H), 8.83-8.69 (m, 1H), 7.94-7.76 (m, 1H), 7.68-7.60 (m, 1H), 7.59-7.45 (m, 2H), 7.40-7.32 (m, 1H), 6.95-6.81 (m, 2H), 6.58-6.47 (m, 1H), 6.39-6.24 (m, 1H), 5.71-5.47 (m, 1H), 5.04-4.96 (m, 1H), 4.96-4.88 (m, 1H), 4.85-4.74 (m, 1H), 4.74-4.59 (m, 1H), 4.59-4.32 (m, 1H), 3.86-3.80 (m, 2H), 3.80-3.76 (m, 2H), 3.60-3.49 (m, 1H), 3.47-3.38 (m, 1H), 3.34-3.26 (m, 1H), 3.24-3.20 (m, 1H), 3.17-3.02 (m, 4H), 3.01-2.82 (m, 2H), 2.78-2.70 (m, 1H), 2.70-2.63 (m, 2H), 2.63-2.53 (m, 3H), 2.29-2.07 (m, 2H), 2.00-1.90 (m, 1H), 1.89-1.76 (m, 2H), 1.70-1.57 (m, 1H), 1.27-0.96 (m, 2H), 0.88.

Example 10

3-(4-(4-((9-(4-((2-allyl-1-((*S*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**10**)

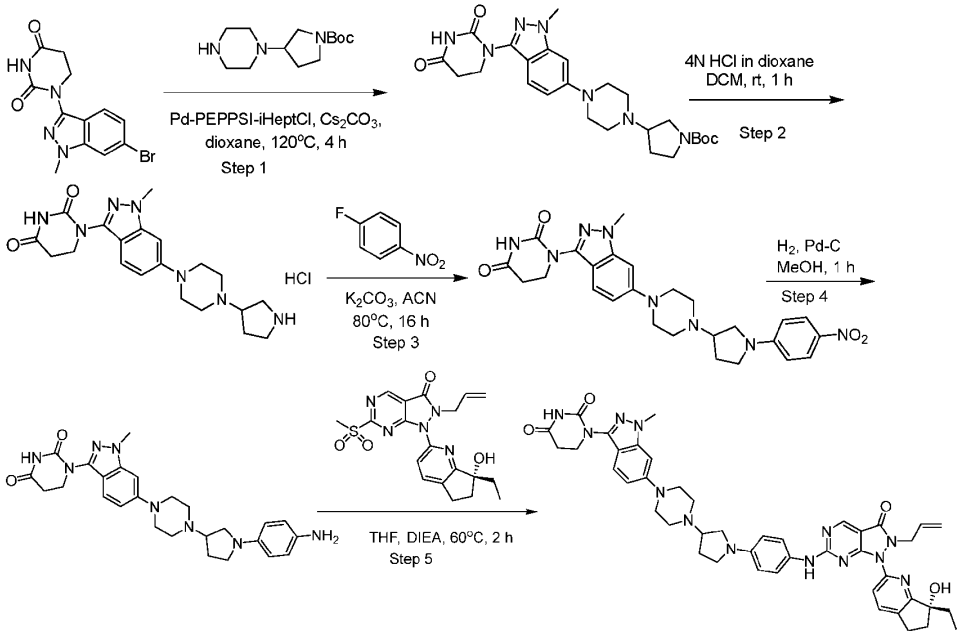


[0177] To a mixture of (*S*)-6-((4-(1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)phenyl)amino)-2-allyl-1-(7 -ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (0.1 g, 171.62 μmol, synthesized as shown in Step-4, Example 8) in DCM (1 mL) were added 1-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperidine-4-carbaldehyde (171.82 mg, 343.23 μmol,), DIEA (110.90 mg, 858.08 μmol), AcOH (10.31 mg, 171.62 μmol) and $NaBH(OAc)_3$ (72.75 mg, 343.23 μmol) at 0 °C, and the mixture was stirred at 25 °C for 1 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filtrate was concentrated to give the residue. The residue was purified by reverse phase preparative HPLC to afford 3-(4-(4-((9-(4-((2-allyl-1-((*S*)-7-ethyl- 7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-

d]pyrimidin-6-yl)amino)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (33.5 mg, 22%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.77 (s, 1H), 10.26-9.96 (m, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.57 (br s, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.97-6.80 (m, 4H), 5.77-5.55 (m, 1H), 5.05 (s, 1H), 4.99 (br d, *J* = 10.1 Hz, 1H), 4.85 (br d, *J* = 17.0 Hz, 1H), 4.76 (br d, *J* = 10.0 Hz, 1H), 4.57 (br dd, *J* = 14.9, 5.0 Hz, 1H), 3.77-3.57 (m, 5H), 3.27 (br d, *J* = 11.7 Hz, 2H), 3.11-2.92 (m, 3H), 2.84-2.70 (m, 1H), 2.69-2.56 (m, 3H), 2.48-2.40 (m, 1H), 2.33 (br s, 2H), 2.28-2.15 (m, 3H), 2.14-2.06 (m, 3H), 2.06-1.84 (m, 5H), 1.82-1.56 (m, 6H), 1.28-1.13 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H). MS (ESI) m/z: 867.5 $[M+H]^+$.

Example 11

1-(6-(4-(1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-*dihydro*-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)pyrrolidin-3-yl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**11**)



Step 1: *tert*-butyl 3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)pyrrolidine-1-carboxylate

[0178] To a solution of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (1470 mg, 4.55 mmol) in 1,4-Dioxane (30 mL), was added *tert*-butyl 3-(piperazin-1-yl)pyrrolidine-1-carboxylate (1162 mg, 4.55 mmol)

and cesium carbonate (3600 mg, 11.05 mmol). The mixture was bubbled with nitrogen for 1 min before adding Pd-PEPPSI-iHeptCl (600 mg, 0.616 mmol). The tube was sealed and the mixture heated at 120 °C for 2 h. The reaction was diluted with EtOAc (50 mL) and brine (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (silica gel; 0-100% EtOAc/Hexanes) to give *tert*-butyl 3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)pyrrolidine-1-carboxylate (640 mg, 1.286 mmol, 28%). MS (APCI) *m/z* 498.2 $[M+1]^+$.

Step 2: 1-(1-methyl-6-(4-(pyrrolidin-3-yl)piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride

[0179] To a solution of *tert*-butyl 3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)pyrrolidine-1-carboxylate (640 mg, 1.286 mmol) in DCM (10 mL) was added 4N HCl in dioxane (3 mL, 12 mmol). The reaction was stirred at rt for 2 h. The resulting product was concentrated under reduced pressure to afford 1-(1-methyl-6-(4-(pyrrolidin-3-yl)piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione as HCl salt. MS (APCI) *m/z* 398.2 [M+1]+.

Step 3: 1-(1-methyl-6-(4-(1-(4-nitrophenyl)pyrrolidin-3-yl)piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0180] To a solution of 1-(1-methyl-6-(4-(pyrrolidin-3-yl)piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride (450 mg, 1.037 mmol) in ACN (50 mL) was added potassium carbonate (430 mg, 3.11 mmol) and 4-nitrofluorobenzene (176 mg, 1.244 mmol). The reaction was heated at 80 °C for 4 h. The reaction was diluted with water (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (silica gel; 0-10% MeOH/DCM) to give 1-(1-methyl-6-(4-(1-(4-nitrophenyl)pyrrolidin-3-yl)piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (450 mg, 0.868 mmol, 84%). MS (APCI) *m/z* 519.2 $[M+1]^+$.

Step 4: 1-(6-(4-(1-(4-aminophenyl)pyrrolidin-3-yl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

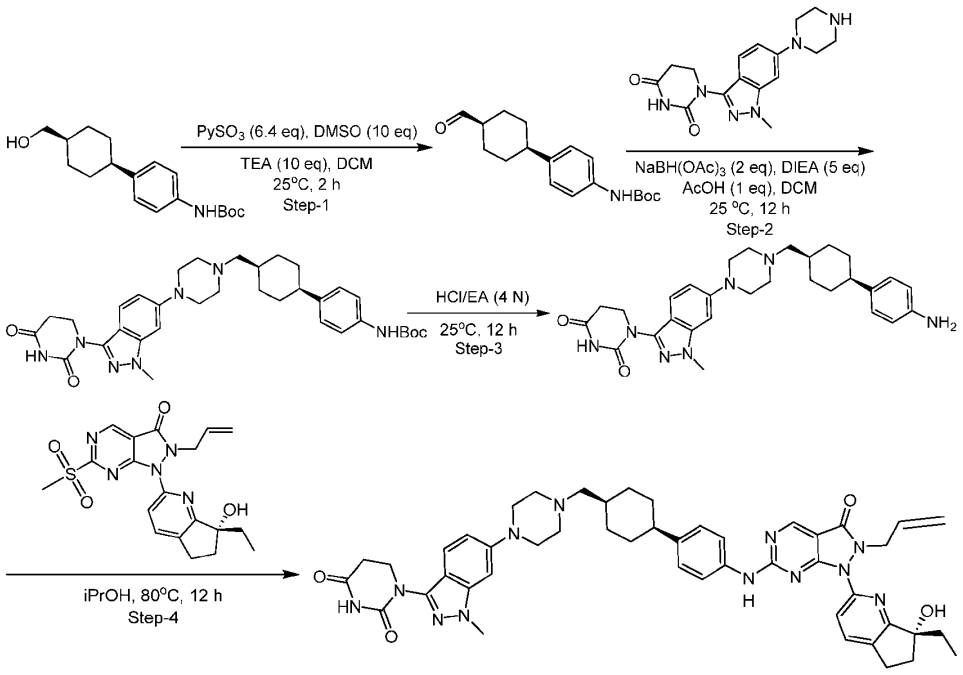
[0181] A solution of 1-(1-methyl-6-(4-(1-(4-nitrophenyl)pyrrolidin-3-yl)piperazin-1-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (450 mg, 0.868

mmol) in MeOH (50 mL) and DCM (50 mL), was bubbled with nitrogen for 1 min before adding Pd-C (10%). The suspension was bubbled with hydrogen for 1 min and then stirred under hydrogen (1 atmosphere) for 1 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford 1-(6-(4-(1-(4-aminophenyl)pyrrolidin-3-yl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (380 mg, 0.778 mmol, 90%). MS (APCI) *m/z* 489.3 [M+1]+.

Step 5: 1-(6-(4-(1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)pyrrolidin-3-yl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0182] To a solution of 1-(6-(4-(1-(4-aminophenyl)pyrrolidin-3-yl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (340 mg, 0.696 mmol) in THF (20 mL) were added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-*5H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (362 mg, 0.871 mmol) and *N*,*N*-diisopropylethylamine (5 mL, 28.7 mmol). The mixture was heated at 80 °C for 2 h. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the solvent was removed *in vacuo*. The product was purified by flash chromatography (silica gel; 0-10% MeOH/DCM). The product was further purified by flash chromatography (silica gel; 0-60% hexanes/EtOAc (containing 10% 7N NH_3 in MeOH)) to afford 1-(6-(4-(1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)pyrrolidin-3-yl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (235.5 mg, 0.281 mmol, 40%). MS (APCI) *m/z* 824.4 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.60-10.44 (m, 1H), 10.17-9.89 (m, 1H), 8.88-8.67 (m, 1H), 8.01-7.80 (m, 1H), 7.77-7.65 (m, 1H), 7.62-7.51 (m, 1H), 7.51-7.37 (m, 2H), 7.03-6.91 (m, 1H), 6.91-6.77 (m, 1H), 6.63-6.45 (m, 2H), 5.78-5.51 (m, 1H), 5.13-5.02 (m, 1H), 5.02-4.93 (m, 1H), 4.93-4.83 (m, 1H), 4.83-4.70 (m, 1H), 4.66-4.50 (m, 1H), 4.00-3.82 (m, 5H), 3.58-3.48 (m, 1H), 3.44-3.36 (m, 1H), 3.28 (br s, 4H), 3.19-3.10 (m, 1H), 3.08-2.90 (m, 2H), 2.85-2.77 (m, 1H), 2.77-2.72 (m, 3H), 2.72-2.60 (m, 4H), 2.31-2.14 (m, 2H), 2.08-1.96 (m, 1H), 1.96-1.81 (m, 2H), 1.79-1.75 (m, 1H), 0.96-0.76 (m, 3H).

Example 12
1-(6-(4-(((1*s*,4*s*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-*hydroxy*-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**12**)



Step 1: *tert*-butyl (4-((1*s*,4*s*)-4-formylcyclohexyl)phenyl) carbamate

[0183] To a solution of *tert*-butyl (4-((1*s*,4*s*)-4-(hydroxymethyl)cyclohexyl)phenyl)carbamate (0.60 g, 1.85 mmol) in DCM (12 mL) were added pyridine•sulfur trioxide (1.88 g, 11.82 mmol) DMSO (1.44 g, 18.47 mmol, 1.44 mL) TEA (1.87 g, 18.47 mmol, 2.57 mL) at 0 °C. The reaction was stirred at 25 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40°C to give the crude product, which was was purified by column chromatography on silica gel (eluted with PE:EA = 100:1 to 10:1) to give *tert*-butyl (4-((1*s*,4*s*)-4-formylcyclohexyl)phenyl)carbamate (0.40 g, 61%). MS (ESI^+): *m/z* = 302.2 $(M-H)^-$

Step 2: *tert*-butyl (4-((1*s*,4*s*)-4-((4-(3-(2,4-dioxotetrahydrop yrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)cyclohexyl)phenyl)carbamate

[0184] To a solution of 1-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H, 3H)-dione (408.85 mg, 1.12 mmol, HCl) in DCM (10 mL) and were added *tert*-butyl (4-((1*s*,4*s*)-4-formylcyclohexyl)phenyl)carbamate (0.40 g, 1.12

mmol) DIEA (724.18 mg, 5.60 mmol, 975.98 μL), AcOH (67.30 mg, 1.12 mmol, 64.15 μL) and $NaBH(OAc)_3$ (475.02 mg, 2.24 mmol) at 25 °C. The reaction was stirred at 25 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give *tert*-butyl (4-((1*s*,4*s*)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)cyclohexyl)phenyl)carbamate (0.20 g, 24%). MS (ESI^+): $m/z = 616.3$ $[M+H]^+$

Step 3: 1-(6-(4-(((1*s*,4*s*)-4-(4-aminophenyl)cyclohexyl)methyl) piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0185] A solution of *tert*-butyl (4-((1*s*,4*s*)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)cyclohexyl)phenyl)carbamate (0.20 g, 272.83 μmol) in HCl/EtOAc (10 mL) was stirred at 25 °C. The reaction was stirred at 25 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C to give the residue. The residue was purified by prep-HPLC to afford 1-(6-(4-(((1*s*,4*s*)-4-(4-aminophenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.10 g, 68%). MS (ESI^+): $m/z = 516.2$ $[M+H]^+$.

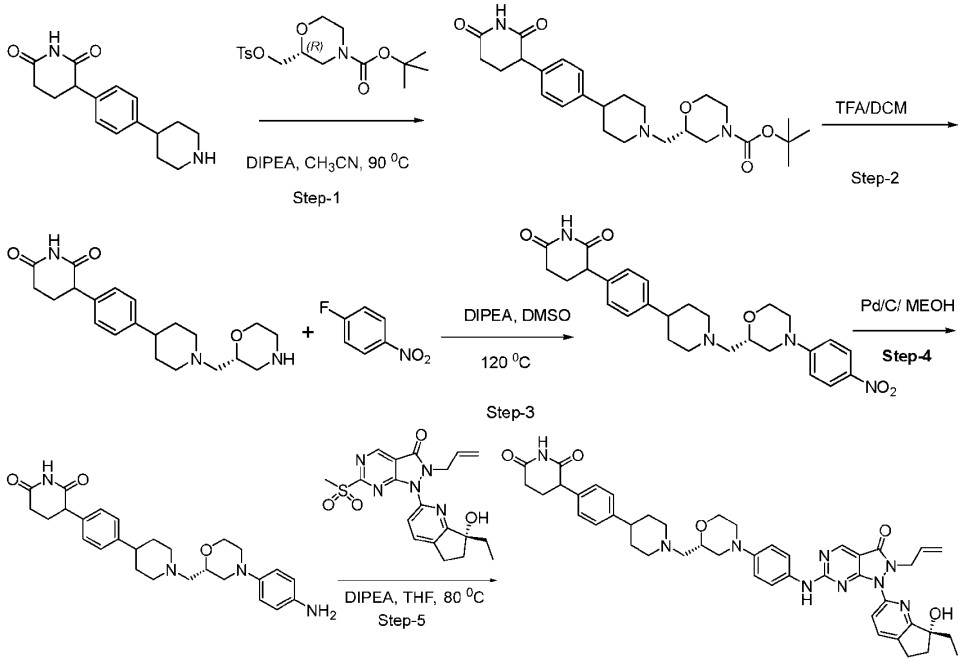
Step 4: 1-(6-(4-(((1*s*,4*s*)-4-(4-((2-allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

[0186] To a solution of (R)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3H-pyrazolo[3,4-*d*]pyrimidin-3-one (89.74 mg, 215.99 μmol,) in *i*PrOH (2 mL) and were added 1-(6-(4-(((1*s*,4*s*)-4-(4-aminophenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.10 g, 154.28 μmol) at 25 °C. The reaction was stirred at 80 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filter was concentrated to give the residue. The residue was purified by prep-HPLC to afford 1-(6-(4-(((1*s*,4*s*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)cyclohexyl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (37.20 mg, 28%). ^1H NMR

(400 MHz, DMSO-d_6): δ 10.50 (br s, 1H), 10.35-10.05 (m, 1H), 8.86 (s, 1H), 7.93 (br d, J = 8.2 Hz, 1H), 7.78-7.57 (m, 3H), 7.45 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.92 (br d, J = 9.2 Hz, 1H), 6.83 (s, 1H), 5.78-5.56 (m, 1H), 5.08-4.95 (m, 2H), 4.86 (br d, J = 17.9 Hz, 1H), 4.80-4.66 (m, 1H), 4.56 (br dd, J = 15.9, 5.7 Hz, 1H), 3.92-3.89 (m, 2H), 3.88 (s, 3H), 3.24 (br s, 4H), 3.04-2.91 (m, 1H), 2.81 (br dd, J = 8.3, 5.5 Hz, 1H), 2.73 (t, J = 6.6 Hz, 2H), 2.57 (br s, 6H), 2.40 (br d, J = 7.6 Hz, 2H), 2.26-2.16 (m, 1H), 2.07-1.94 (m, 2H), 1.90 (br dd, J = 13.7, 7.5 Hz, 1H), 1.76-1.65 (m, 3H), 1.61 (br s, 5H), 0.87 (t, J = 7.4 Hz, 3H). MS (ESI$^+$): m/z = 851.4 $[M+H]^+$.

Example 13

3-(4-(1-(((*S*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (**13**)



Step 1: *tert*-butyl (2*S*)-2-((4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperidin-1-yl)methyl)morpholine-4-carboxylate

[0187] To a solution of 3-(4-(piperidin-4-yl)phenyl)piperidine-2,6-dione (110 mg, 0.403 mmol) in CH_3CN (4 mL) at 0 °C was added *N*,*N*-diisopropylethylamine (491 µL, 2.82 mmol) and stirred for 5 min. To this solution was added *tert*-butyl (*R*)-2-((tosyloxy)methyl)morpholine-4-carboxylate (225 mg, 0.605 mmol) (0.3 mL in CH_3CN).

It was then heated at 100 °C for 15 h. The mixture was partitioned between DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography (silica gel, 0-60% EA in hexane) to afford *tert*-butyl (2*S*)-2-((4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperidin-1-yl)methyl)morpholine-4-carboxylate (125 mg, 0.265 mmol, 65%). MS (APCI) m/z: 472.30 $[M+H]^+$.

Step 2: 3-(4-(1-(((*R*)-morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione

[0188] A solution of *tert*-butyl (2*S*)-2-((4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperidin-1-yl)methyl)morpholine-4-carboxylate (175 mg, 0.371 mmol) in DCM (1.67 mL) and TFA (186 µL) was stirred at rt for 2 h. The mixture was concentrated under reduced pressure to afford 3-(4-(1-(((*R*)-morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (quantitative yield) which was used for next step without further purification. MS (APCI) m/z: 372.20 $[M+H]^+$.

Step 3: 3-(4-(1-(((*S*)-4-(4-nitrophenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione

[0189] To a solution of 3-(4-(1-(((*R*)-morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (137 mg, 0.37 mmol) in DMSO (3.7 mL) at 0 °C, was added *N*,*N*-diisopropylethylamine (516 µL, 2.96 mmol). To this mixture was added 4-nitrofluorobenzene (52 mg, 0.370 mmol) and the mixture was heated at 120 °C for 5 h. The mixture was partitioned between DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated, and was purified by column chromatography (silica gel, 0-10% MeOH in DCM) to afford 3-(4-(1-(((*S*)-4-(4-nitrophenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (89 mg, 0.181 mmol, 48%). MS (APCI) m/z: 493.2 $[M+H]^+$.

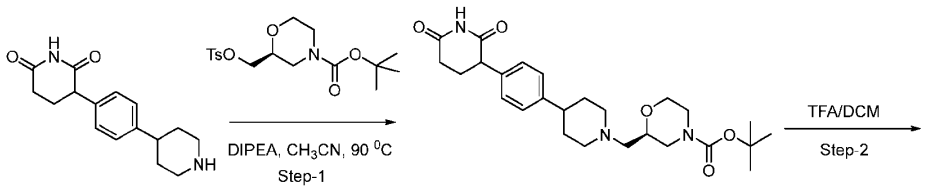
Step 4: 3-(4-(1-(((*S*)-4-(4-aminophenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione

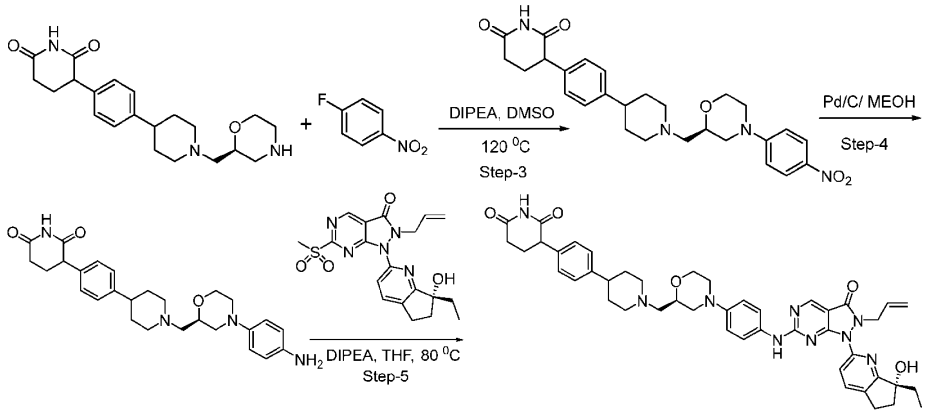
[0190] To a solution of 3-(4-(1-(((*S*)-4-(4-nitrophenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (60 mg, 0.122 mmol) in ethanol (974 µL) and DCM (244 µL) was added Pd/C (10 mg, 0.94 µmol). The mixture was back filled with H_2 multiple times and was stirred under H_2 balloon overnight. LCMS shows the formation of product and minor starting material. The mixture was diluted with DCM and filtered using a celite pad. The filtrate was concentrated to afford crude 3-(4-(1-(((*S*)-4-(4-aminophenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (55 mg, 0.119 mmol, 98%) which was used in next step without further purification. MS (APCI) m/z: 463.30 $[M+H]^+$.

Step 5: 3-(4-(1-(((*S*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione

[0191] To a solution of 3-(4-(1-(((*S*)-4-(4-aminophenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (56.4 mg, 0.122 mmol) in THF (1.22 mL) at 0 °C, was added *N*,*N*-diisopropylethylamine (63.8 µL, 0.366 mmol). To this mixture was added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (35.5 mg, 0.085 mmol) and the mixture was heated at 80 °C for 2 h. The mixture was partitioned between DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated, and was purified by column chromatography (silica gel, 0-10% of MeOH in DCM) to afford slightly impure product. This was further purified by reverse-phase preparative HPLC (10-80% acetonitrile (contains 0.1% formic acid) in water (contains 0.1% formic acid)) to afford 3-(4-(1-(((*S*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (23 mg, 0.029 mmol, 23%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.85-10.79 (m, 1H), 10.24-10.07 (m, 1H), 8.86-8.79 (m, 1H), 7.99-7.86 (m, 1H), 7.73-7.67 (m, 1H), 7.67-7.53 (m, 2H), 7.25-7.18 (m, 2H), 7.18-7.07 (m, 2H), 6.99-6.89 (m, 2H), 5.73-5.61 (m, 1H), 5.10-5.03 (m, 1H), 5.03-4.96 (m, 1H), 4.89-4.69 (m, 2H), 4.62-4.50 (m, 1H), 3.99-3.88 (m, 1H), 3.86-3.70 (m, 2H), 3.70-3.61 (m, 1H), 3.61-3.53 (m, 1H), 3.51-3.42 (m, 1H), 3.12-2.88 (m, 3H), 2.83-2.59 (m, 3H), 2.48-2.32 (m, 4H), 2.26-1.95 (m, 6H), 1.95-1.82 (m, 1H), 1.80-1.58 (m, 5H), 0.92-0.81 (m, 3H). MS (APCI) m/z: 798.40 $[M+H]^+$.

Example 14
3-(4-(1-(((*R*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (**14**)

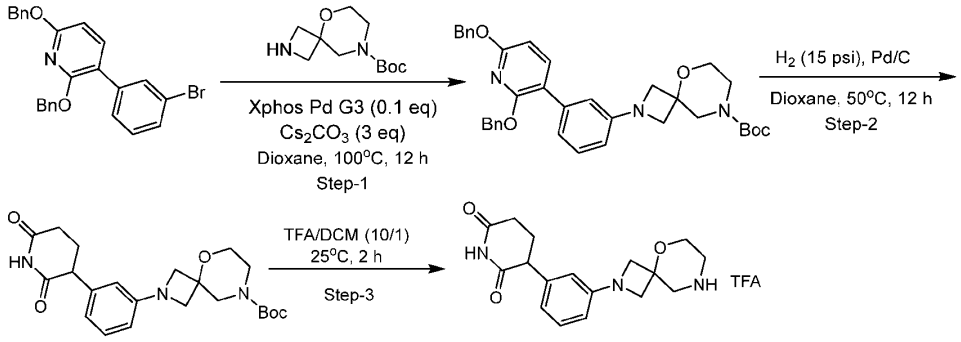


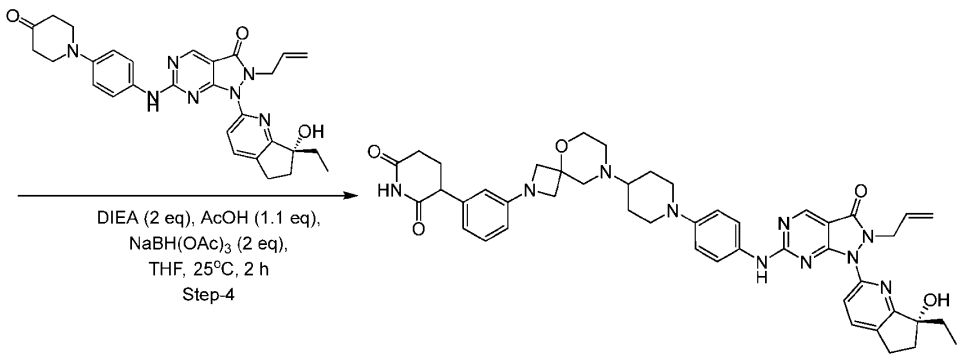


[0192] 3-(4-(1-(((*R*)-4-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione (19% for final step) was synthesized using a similar procedure to that described for the synthesis of Example 13, using *tert*-butyl (*S*)-2-((tosyloxy)methyl)morpholine-4-carboxylate as starting material instead of *tert*-butyl (*R*)-2-((tosyloxy)methyl)morpholine-4-carboxylate used in Example 13. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.87-10.79 (m, 1H), 10.26-10.04 (m, 1H), 8.89-8.77 (m, 1H), 7.99-7.88 (m, 1H), 7.77-7.51 (m, 3H), 7.29-7.09 (m, 4H), 7.01-6.89 (m, 2H), 5.76-5.57 (m, 1H), 5.12-4.93 (m, 2H), 4.93-4.67 (m, 2H), 4.65-4.49 (m, 1H), 3.99-3.89 (m, 1H), 3.87-3.71 (m, 2H), 3.71-3.43 (m, 4H), 3.12-2.88 (m, 3H), 2.84-2.57 (m, 3H), 2.49-2.30 (m, 4H), 2.27-1.83 (m, 7H), 1.81-1.59 (m, 5H), 0.93-0.82 (m, 3H). MS (APCI) m/z: 798.40 $[M+H]^+$.

Example 15

3-(3-(8-(1-(4-((2-allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)phenyl)piperidine-2,6-dione (**15**)





Step 1: *tert*-butyl 2-[3-(2,6-dibenzyloxy-3-pyridyl)phenyl]-5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate

[0193] To a solution of 2,6-dibenzyloxy-3-(3-bromophenyl)pyridine (Core 3A) (1.9 g, 4.26 mmol) and *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate (971.79 mg, 4.26 mmol) in dioxane (20 mL) were added Cs_2CO_3 (4.16 g, 12.77 mmol) and Xphos Pd G3 (360.32 mg, 425.69 μmol) at 25 °C under N_2. The mixture was stirred at 100 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was cooled to 25 °C and poured into water (20 mL). The aqueous phase was extracted with EA (3 × 10 mL). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography on silica gel (eluted with PE:EA = 50: 1 to 10: 1) to give *tert*-butyl 2-[3-(2,6-dibenzyloxy-3-pyridyl)phenyl]-5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate (2.22 g, 84%). MS (ESI^+): m/z = 594.3 $[M+H]^+$.

Step 2: *tert*-butyl 2-[3-(2,6-dioxo-3-piperidyl)phenyl]-5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate

[0194] To a suspension of Pd/C (391.65 mg, 368.02 μmol, 10% purity) in dioxane (80 mL) was added *tert*-butyl 2-[3-(2,6-dibenzyloxy-3-pyridyl)phenyl]-5-oxa-2,8-diazaspiro[3.5]nonane-8 -carboxylate (2.3 g, 3.68 mmol) under Ar. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 50 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The suspension was filtered through a pad of celite and the filter cake was washed with dioxane (3 × 50 mL). The filtrate was concentrated to give *tert*-butyl2-[3-(2,6-dioxo-3-piperidyl)phenyl]-5-oxa-2,8-diazaspiro[3.5]nonane-8-

carboxylate (1.4 g, 71%) which was used for next step directly without further purification. MS (ESI^+): m/z = 416.1 $[M+H]^+$.

Step 3: 3-[3-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)phenyl]piperidine-2,6-dione

[0195] A solution of *tert*-butyl 2-[3-(2,6-dioxo-3-piperidyl)phenyl]-5-oxa-2,8-diazaspiro[3.5]nonane -8-carboxylate (0.2 g, 375.47 μmol) in DCM (2 mL) and TFA (0.2 mL) was stirred at 25 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated to give 3-[3-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl) phenyl]piperidine-2,6-dione (0.16 g, crude, TFA salt), which was used for next step directly without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 9.11 (br s, 1H), 7.15 (br s, 1H), 6.57 (br d, J = 7.6 Hz, 1H), 6.38 (dd, J = 1.8, 7.9 Hz, 1H), 6.31 (s, 1H), 3.95 (dd, J = 3.9, 8.3 Hz, 2H), 3.89-3.80 (m, 2H), 3.76 (dd, J = 5.0, 10.9 Hz, 1H), 3.68 (dd, J = 4.6, 8.3 Hz, 1H), 3.60 (br t, J = 6.4 Hz, 1H), 3.41 (br s, 2H), 3.12 (br s, 2H), 2.70-2.56 (m, 1H), 2.48-2.40 (m, 1H), 2.24-2.09 (m, 1H), 2.07-1.93 (m, 1H), 1.75 (td, J = 3.2, 6.5 Hz, 1H). MS (ESI^+): m/z = 316.2 $[M+H]^+$.

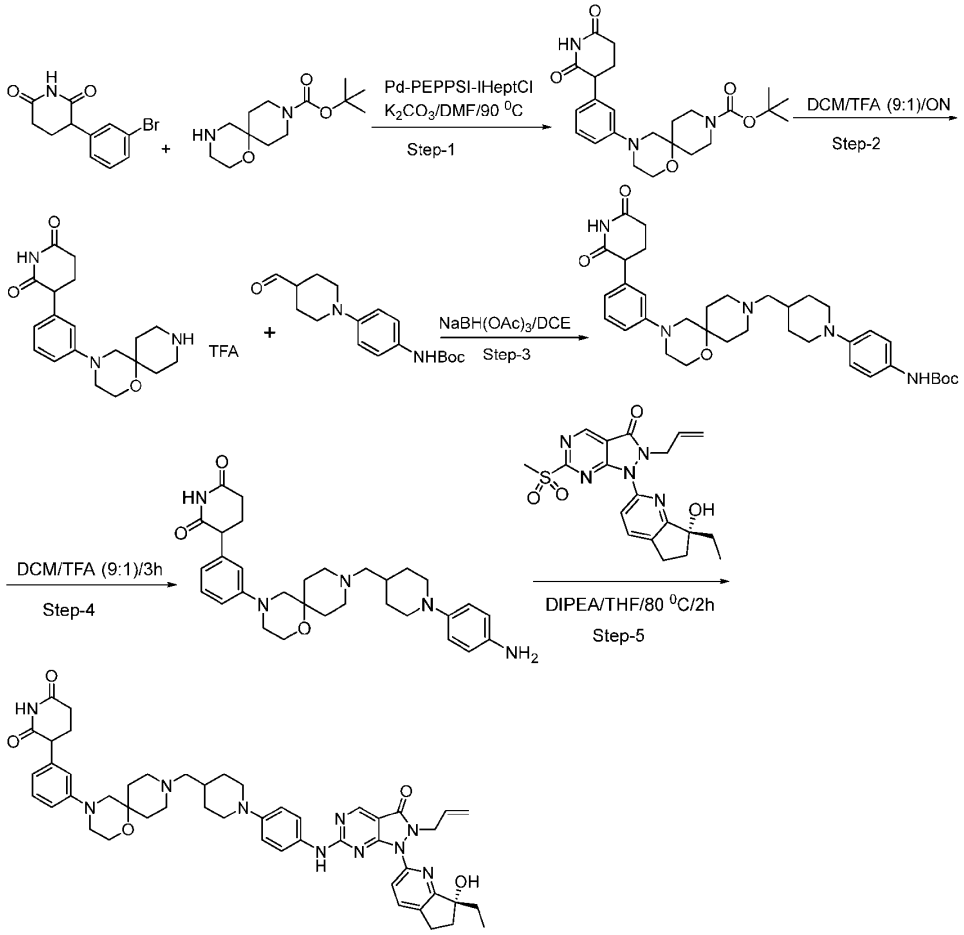
Step 4: 3-[3-[8-[1-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-3-oxo-pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]-4-piperidyl]-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]phenyl]piperidine-2,6-dione

[0196] To a solution of 3-[3-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)phenyl]piperidine-2,6-dione (0.16 g, 372.62 μmol, TFA salt) and 2-allyl-1-[(7R)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridine-2-yl]-6-[4-(4-oxo-1-piperidyl)anilino]pyrazolo[3,4-*d*]pyrimidin-3-one (195.85 mg, 372.62 μmol) in THF (4 mL) were added DIEA (96.32 mg, 745.24 μmol). The mixture was stirred at 25 °C for 10 min. AcOH (24.61 mg, 409.88 μmol) was added and the mixture was stirred at 25 °C for 10 min. Then $NaBH(OAc)_3$ (157.95 mg, 745.24 μmol) was added and the mixture was stirred at 25 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the crude product, which was further purified by prep-HPLC to give 3-[3-[8-[1-[4-[[2-allyl-1-[(7R)-7-ethyl-7-hydroxy- 5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-3-oxo-pyrazolo[3,4-*d*]pyrimidin-6-yl]amino]phenyl]-4-piperidyl]-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]phenyl]piperidine-2,6-dione (0.049 g, 16%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.79 (s, 1H), 10.40-9.84 (m, 1H), 8.81 (s, 1H), 7.92 (br d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.56 (br d, J = 1.2 Hz, 2H), 7.11 (t, J = 7.8 Hz, 1H), 6.92 (br d, J = 9.0 Hz, 2H), 6.52 (d, J = 7.6 Hz, 1H), 6.45-6.33 (m, 1H), 6.31 (s, 1H), 5.67 (tdd, J = 5.9, 10.6, 16.8 Hz, 1H), 5.04 (s, 1H), 4.99 (d, J = 10.3 Hz, 1H),

4.85 (br d, J = 17.1 Hz, 1H), 4.80-4.67 (m, 1H), 4.56 (br dd, J = 5.6, 15.9 Hz, 1H), 3.82-3.70 (m, 3H), 3.70-3.51 (m, 6H), 3.04-2.90 (m, 1H), 2.84-2.73 (m, 1H), 2.72-2.56 (m, 5H), 2.49-2.41 (m, 3H), 2.40-2.29 (m, 1H), 2.26-2.10 (m, 2H), 2.08-1.96 (m, 2H), 1.94-1.81 (m, 3H), 1.76-1.63 (m, 1H), 1.61-1.46 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H). MS (ESI^+): m/z = 825.4 $[M+H]^+$.

Example 16

3-(3-(9-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)phenyl)piperidine-2,6-dione (**16**)

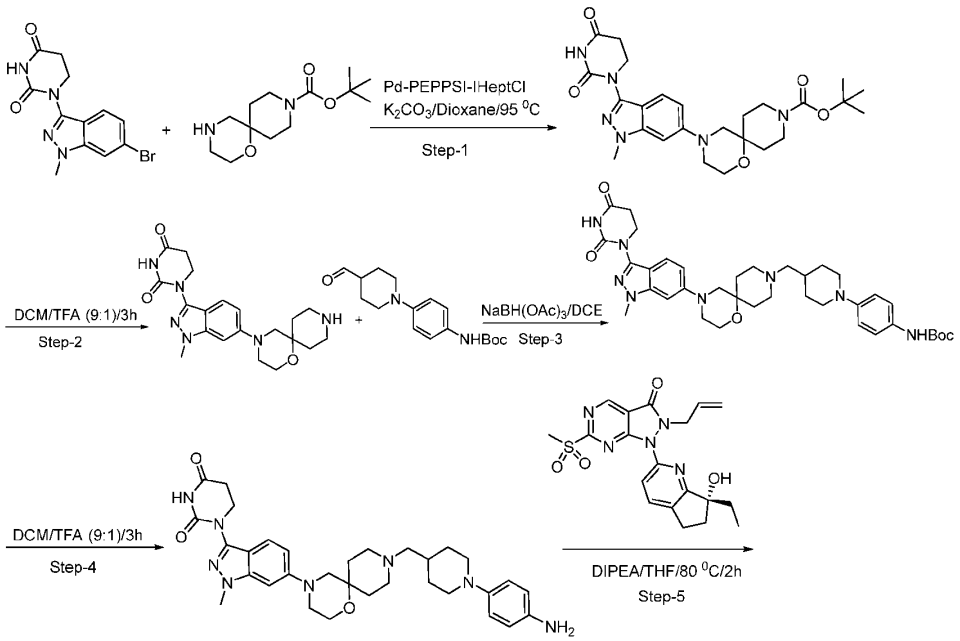


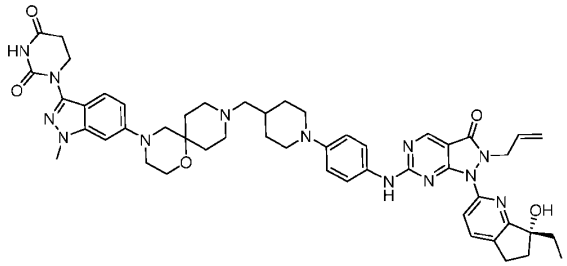
[0197] 3-(3-(9-((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-

yl)phenyl)piperidine-2,6-dione (16% for the final step) was synthesized by following a similar procedure as described for the synthesis of Example 7 using 3-(3-bromophenyl)piperidine-2,6-dione instead of 3-(4-bromophenyl)piperidine-2,6-dione used in Example 7. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84-10.77 (m, 1H), 10.22-10.03 (m, 1H), 8.86-8.79 (m, 1H), 8.24-8.14 (m, 1H), 7.98-7.90 (m, 1H), 7.73-7.68 (m, 1H), 7.65-7.48 (m, 2H), 7.20-7.13 (m, 1H), 6.98-6.87 (m, 2H), 6.87-6.78 (m, 2H), 6.67-6.59 (m, 1H), 5.74-5.59 (m, 1H), 5.14-4.96 (m, 2H), 4.92-4.80 (m, 1H), 4.80-4.68 (m, 1H), 4.62-4.49 (m, 1H), 3.80-3.69 (m, 3H), 3.69-3.56 (m, 2H), 3.45-3.15 (m, 2H), 3.09-3.03 (m, 2H), 3.03-2.90 (m, 3H), 2.84-2.71 (m, 1H), 2.71-2.55 (m, 3H), 2.36-2.13 (m, 6H), 2.10-1.95 (m, 2H), 1.95-1.54 (m, 9H), 1.29-1.14 (m, 2H), 0.92-0.81 (m, 3H). MS (APCI) m/z: 868.5 $[M+H]^+$.

Example 17

(*R*)-1-(6-(9-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**17**)





Step 1: *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate

[0198] To a solution of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (300 mg, 0.928 mmol), 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylic acid, 1,1-dimethylethyl ester (238 mg, 0.928 mmol), and Cesium carbonate (605 mg, 1.857 mmol) in Dioxane (4.6 mL) (pre-degassed) was added Pd-PEPPSI-iHeptCI (90 mg, 0.093 mmol). The mixture was then degassed with N_2 multiple times. It was heated at 95 °C for 3 h. LCMS shows the formation of product. The mixture was partitioned between DCM and water. The organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-10% MeOH in DCM) to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (170 mg, 0.341 mmol, 37%). MS (APCI) m/z: 443.2 $[M\text{-}ter\text{-}But]^+$.

Step 2: 1-(1-methyl-6-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0199] A solution of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1H-indazol-6-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (112 mg, 0.225 mmol) in DCM (2.04 mL) and TFA (204 µL) was stirred at rt for 90 min. LCMS shows the formation of product. All the solvents were evaporated to afford 1-(1-methyl-6-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (quantitative yield) as TFA salt. MS (APCI) m/z: 399.2 $[M+H]^+$.

Step 3: *tert*-butyl (4-(4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)piperidin-1-yl)phenyl)carbamate

[0200] To a solution of 1-(1-methyl-6-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione as TFA salt (90 mg, 0.225 mmol), in DCE (2.25 mL) at 0 °C was added *N,N*-Diisopropylethylamine (196 µL, 1.125 mmol). To this mixture was added a solution of *ter*t-butyl (4-(4-formylpiperidin-1-

yl)phenyl)carbamate (68.5 mg, 0.225 mmol) in DCE (0.5 mL) at 0 °C. The mixture was stirred at rt for 1 h. The reaction was cooled to 0 °C and was added Sodium triacetoxyborohydride (95 mg, 0.450 mmol). and the resulting mixture was stirred at rt for overnight. LCMS shows the formation of product. The mixture was partitioned between DCM and water. Washed the organic layer with dilute $NaHCO_3$ solution, followed by water. Separated the organic layer, dried over Na_2SO_4, concentrated and was purified by column chromatography (silica gel, 0-10% MeOH in DCM) to afford *tert*-butyl (4-(4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)piperidin-1-yl)phenyl)carbamate (85 mg, 0.124 mmol, 55%). MS (APCI) m/z: 687.4 $[M+H]^+$.

Step 4: 1-(6-(9-((1-(4-aminophenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0201] To a solution of *tert*-butyl (4-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)piperidin-1-yl)phenyl)carbamate (83 mg, 0.121 mmol) in DCM (2.2197 mL) and TFA (220 µL) was stirred at rt for 90 min. LCMS shows the formation of product. Evaporated all the solvents to afford 1-(6-(9-((1-(4-aminophenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (quantitative yield) as TFA salt. MS (APCI) m/z: 587.3 $[M+H]^+$.

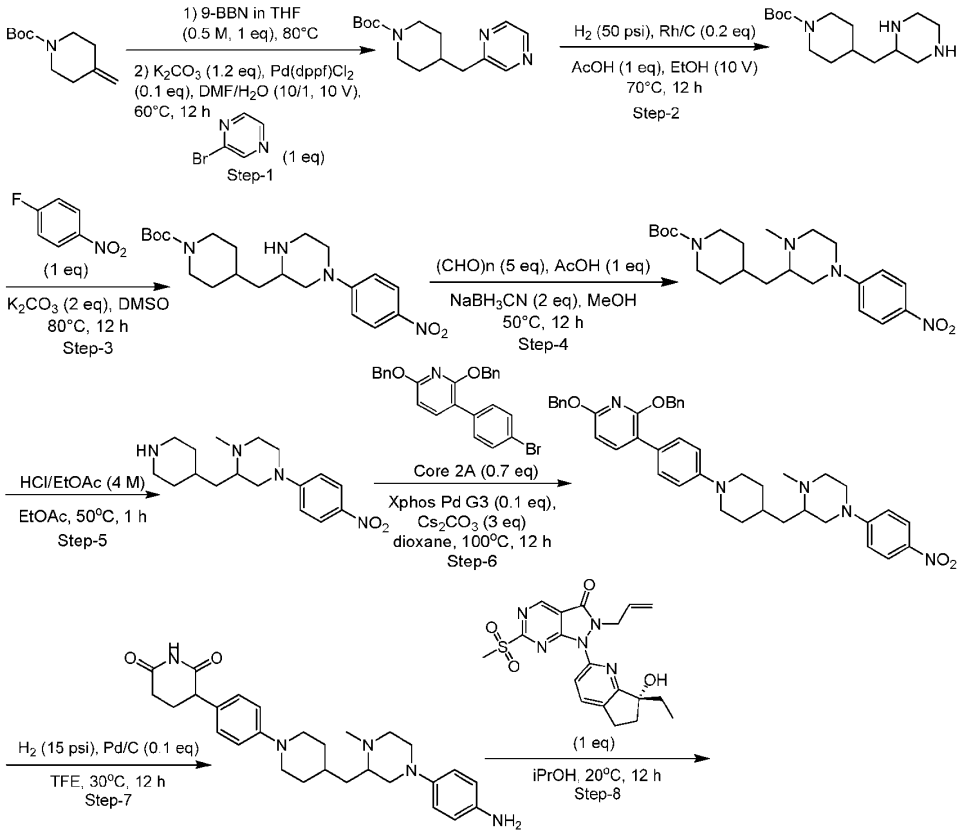
Step 5: Preparation of (*R*)-1-(6-(9-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

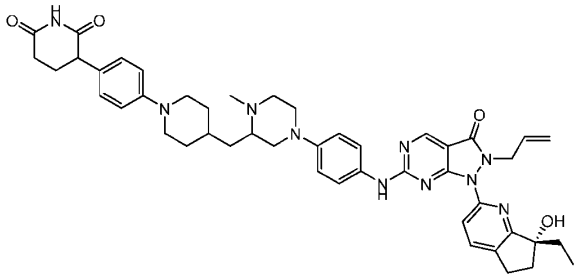
[0202] To a solution of 1-(6-(9-((1-(4-aminophenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (71.0 mg, 0.121 mmol) in THF (2.03 mL) at 0 °C was added *N*,*N*-Diisopropylethylamine (126 µL, 0.726 mmol). To this mixture was added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3H-pyrazolo[3,4-*d*]pyrimidin-3-one (35.2 mg, 0.085 mmol) and the mixture was heated at 80 °C for 3 h. LCMS shows the formation of product. The mixture was partitioned with DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-10% MeOH in DCM) to afford slightly impure product. This was again purified by reverse phase preparative

HPLC using 10-80% acetonitrile (contains 0.1% formic acid) in water (contains 0.1% formic acid) to afford (*R*)-1-(6-(9-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (37 mg, 0.040 mmol, 33%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.56-10.47 (m, 1H), 10.22-10.01 (m, 1H), 8.85-8.78 (m, 1H), 8.01-7.86 (m, 1H), 7.74-7.66 (m, 1H), 7.66-7.41 (m, 3H), 6.99-6.81 (m, 4H), 5.76-5.57 (m, 1H), 5.12-4.93 (m, 2H), 4.93-4.66 (m, 2H), 4.66-4.49 (m, 1H), 4.00-3.74 (m, 7H), 3.70-3.57 (m, 2H), 3.23-3.14 (m, 2H), 3.14-3.05 (m, 2H), 3.05-2.87 (m, 1H), 2.87-2.70 (m, 3H), 2.70-2.55 (m, 3H), 2.38-2.13 (m, 5H), 2.09-1.96 (m, 1H), 1.96-1.57 (m, 10H), 1.33-1.13 (m, 2H), 0.92-0.80 (m, 3H). MS (APCI) m/z: 922.5 $[M+H]^+$.

Example 18

3-(4-(4-((4-(4-((2-allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-methylpiperazin-2-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**18**)





Step 1: *tert*-butyl 4-(pyrazin-2-ylmethyl)piperidine-1-carboxylate

[0203] *Tert*-butyl 4-methylenepiperidine-1-carboxylate (2 g, 10.14 mmol) was added to a solution of 9-BBN in THF (0.5 M, 20.28 mL) at 25 °C and then the mixture was stirred at 60 °C for 1 h. After cooling to 20 °C, the solution was added to another a solution of 2-bromopyrazine (1.61 g, 10.14 mmol), K_2CO_3 (1.68 g, 12.17 mmol) and $Pd(dppf)Cl_2$ (741.82 mg, 1.01 mmol) in DMF (20 mL)/H_2O (2 mL) at 20 °C. After the addition, the mixture was stirred at 60 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was cooled to 0 °C and poured into NaOH solution (1 N, 20 mL) and stirred for 5 min. The aqueous phase was extracted with EA (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtered, the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (eluted with PE:EA = 100:1 to 0:1) to give *tert*-butyl 4-(pyrazin-2-ylmethyl)piperidine-1-carboxylate (2.0 g, 59%). MS (ESI^+): m/z = 278.2 $[M+H]^+$.

Step 2: *tert*-butyl 4-(piperazin-2-ylmethyl)piperidine-1-carboxylate

[0204] To a solution of *tert*-butyl 4-(pyrazin-2-ylmethyl)piperidine-1-carboxylate (2.0 g, 5.98 mmol, 83% purity) in EtOH (20 mL) were added AcOH (359.41 mg, 5.98 mmol) and Rh/C (1.23 g, 598.50 μmol, 5% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 70 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filtrate was concentrated to give *tert*-butyl 4-(piperazin-2-ylmethyl)piperidine-1-carboxylate (1.5 g, 80%). MS (ESI^-): m/z = 284.3 $[M+H]^+$.

Step 3: *tert*-butyl 4-[[4-(4-nitrophenyl)piperazin-2-yl]methyl]piperidine-1-carboxylate

[0205] To a solution of *tert*-butyl 4-(piperazin-2-ylmethyl)piperidine-1-carboxylate (1.49 g, 4.73 mmol) in DMSO (30 mL) was added K_2CO_3 (1.31 g, 9.46 mmol) and stirred at 80 °C for 0.5 h. Then 1-fluoro-4-nitro-benzene (667.64 mg, 4.73 mmol) was

added and stirred at 80 °C and stirred for 11.5 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was cooled to 25 °C and poured into water (50 mL). The aqueous phase was extracted with EA (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum to give a residue. The crude product was purified by column chromatography on silica gel (eluted with PE:EA = 100:1 to 0:1) to afford *tert*-butyl 4-[[4-(4-nitrophenyl)piperazin-2-yl]methyl]piperidine-1-carboxylate (1.2 g, 44%). MS (ESI^+): m/z = 405.1 $[M+H]^+$.

Step 4: *tert*-butyl 4-[[1-methyl-4-(4-nitrophenyl)piperazin-2-yl]methyl]piperidine-1-carboxylate

[0206] To a solution of *tert*-butyl-[[4-(4-nitrophenyl)piperazin-2-yl]methyl]piperidine-1-carboxylate (0.7 g, 1.21 mmol) in MeOH (7 mL) was added formaldehyde (181.86 mg, 6.06 mmol) and AcOH (72.74 mg, 1.21 mmol) at 20 °C. After stirred for 1 h, $NaBH_3CN$ (152.25 mg, 2.42 mmol) was added to the reaction and the resulting mixture was stirred at 50 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The suspension was filtered through a pad of celite and the filter cake was washed with MeOH (10 mL). The filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel (eluted with PE:EA = 100:1 to 0:1) to afford *tert*-butyl 4-[[1-methyl-4-(4-nitrophenyl)piperazin-2-yl]methyl]piperidine-1-carboxylate (0.5 g, 81%). MS (ESI+): m/z = 419.3 $[M+H]^+$.

Step 5: 1-methyl-4-(4-nitrophenyl)-2-(4-piperidylmethyl)piperazine

[0207] To a solution of *tert*-butyl 4-[[1-methyl-4-(4-nitrophenyl)piperazin-2-yl]methyl]piperidine-1-carboxylate (0.5 g, 979.62 μmol, 1 eq) in EtOAc (5 mL) was added HCl/EtOAc (4 M, 5 mL). The mixture was stirred at 50 °C for 1 h. LCMS showed the reaction was completed and the desired product was detected. LCMS showed the starting material was consumed completely. The reaction solution was concentrated and acidified with Saturated sodium bicarbonate aqueous solution to pH = 8. The mixture was concentrated to give a residue. The residue was triturated with THF (30 mL) and filtered, the filtrate was concentrated to give 1-methyl-4-(4-nitrophenyl)-2-(4-piperidylmethyl)piperazine (0.3 g, 71%). MS (ESI^+): m/z = 319.2 $[M+H]^+$.

Step 6: 2-[[1-[4-(2,6-dibenzyloxy-3-pyridyl)phenyl]-4-piperidyl]methyl]-1-methyl-4-(4-nitrophenyl)piperazine

[0208] To a solution of 1-methyl-4-(4-nitrophenyl)-2-(4-piperidylmethyl)piperazine (0.3 g, 697.21 μmol) and 2,6-dibenzyloxy-3-(4-

bromophenyl)pyridine (217.83 mg, 488.05 μmol) in dioxane (6 mL) was added Xphos Pd G3 (59.02 mg, 69.72 μmol) and Cs_2CO_3 (681.49 mg, 2.09 mmol). The mixture was stirred at100 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The suspension was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-TLC (EtOAc:MeOH = 5:1) to give 2-[[1-[4-(2,6-dibenzyloxy-3-pyridyl)phenyl]-4-piperidyl]methyl]-1-methyl-4-(4-nitrophenyl)piperazine (0.3 g, 55%). MS (ESI^+): m/z = 684.4 $[M+H]^+$.

Step 7: 3-(4-(4-((4-(4-aminophenyl)-1-methylpiperazin-2-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione

[0209] To a solution of 2-[[1-[4-(2,6-dibenzyloxy-3-pyridyl)phenyl]-4-piperidyl]methyl]-1-methyl-4-(4-nitrophenyl)piperazine (0.28 g, 365.58 μmol, 88% purity) in TFE (5 mL) was added Pd/C (38.91 mg, 36.56 μmol, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 30 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filter was concentrated to give 3-(4-(4-((4-(4-aminophenyl)-1-methylpiperazin-2-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (0.05 g, 24%). MS (ESI^+): *m/z* = 476.3 $[M+H]^+$.

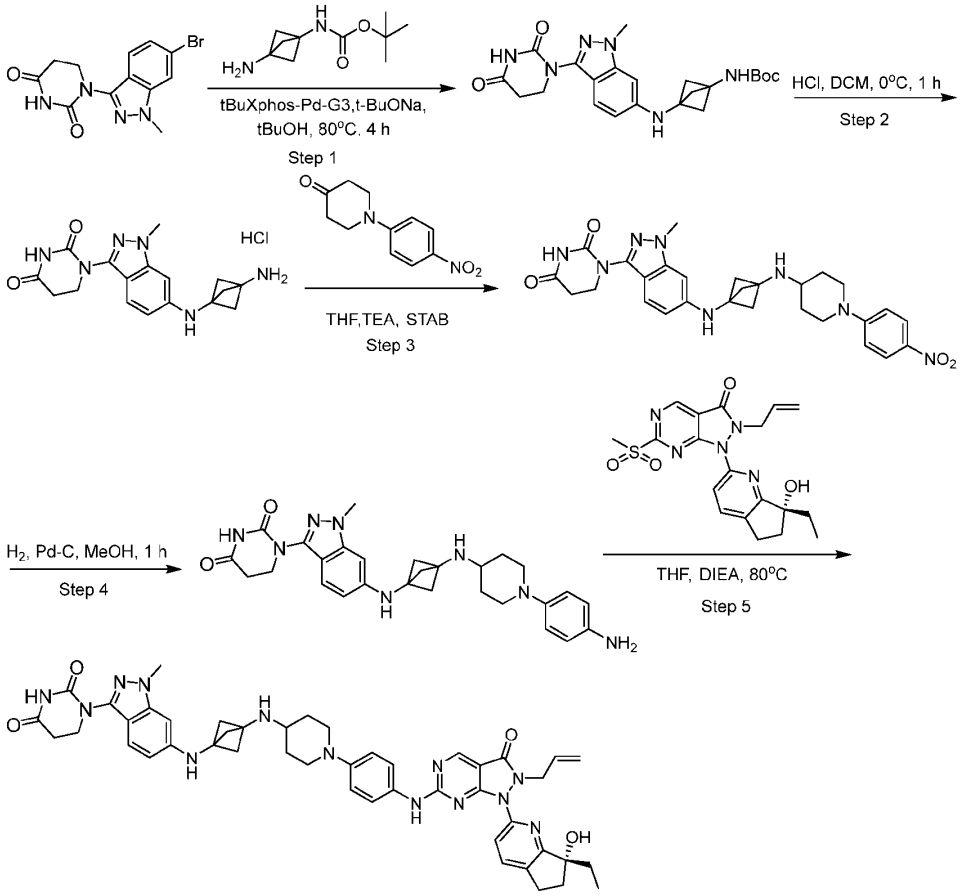
Step 8: 3-(4-(4-((4-(4-((2-allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-methylpiperazin-2-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione.

[0210] To a mixture of 3-(4-(4-((4-(4-aminophenyl)-1-methylpiperazin-2-yl)methyl)piperidin-1-yl) phenyl)piperidine-2,6-dione (0.05 g, 89.36 mmol) in *i*PrOH (0.5 mL) was added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3H-pyrazolo[3,4-*d*]pyrimidin-3-one (37.12 mg, 89.36 mmol) at 20 °C. Then the mixture was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure to give the crude product. The residue was purified by prep-HPLC to afford 3-(4-(4-((4-(4-((2-allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-1-methylpiperazin-2-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione(4.5 mg, 6%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 8.82 (s, 1H), 7.91 (br d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.58 (br d, *J* = 2.3 Hz, 2H), 7.03 (d, *J* =

8.7 Hz, 2H), 6.91 (dd, *J* = 8.8, 19.6 Hz, 4H), 5.66 (tdd, *J* = 5.9, 10.5, 16.9 Hz, 1H), 5.04 (s, 1H), 4.99 (dd, *J* = 1.1, 10.3 Hz, 1H), 4.85 (br d, *J* = 17.0 Hz, 1H), 4.80-4.68 (m, 1H), 4.56 (br dd, *J* = 5.2, 15.7 Hz, 1H), 3.76-3.57 (m, 3H), 3.43 (br t, *J* = 11.9 Hz, 2H), 2.98 (br s, 1H), 2.87-2.57 (m, 6H), 2.49-2.41 (m, 2H), 2.41-2.27 (m, 2H), 2.25 (s, 3H), 2.22 – 1.95 (m, 5H), 1.93-1.79 (m, 2H), 1.79-1.64 (m, 2H), 1.58 (br d, *J* = 9.2 Hz, 2H), 1.38-1.20 (m, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): *m/z* = 811.4 $[M+H]^+$.

Example 19

(*R*)-1-(6-((3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**20**)



Step 1: *tert*-butyl (3-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate

[0211] In a microwave tube (20 mL) was loaded 1-(6-bromo-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (442 mg, 1.368 mmol), tBuOH (5 mL), *tert*-butyl (3-aminobicyclo[1.1.1]pent-1-yl)carbamate (271 mg, 1.368 mmol), sodium *tert*-butylate (394 mg, 4.10 mmol). The mixture was bubbled nitrogen for 1 min before adding [(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate (tBuXphos-Pd-G3, 122 mg, 0.137 mmol). The tube was sealed and heated at 100 °C for 3 h. The reaction was diluted with EtOAc (50 mL) and brine (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel chromatography eluted with 0-100% EtOAc/hexanes to give *tert*-butyl (3-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (48 mg, 0.109 mmol, 7.97%). MS (APCI) *m/z* 441.20 $[M+1]^+$.

Step 2: 1-(6-((3-aminobicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride

[0212] To a solution of *tert*-butyl (3-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (40 mg, 0.091 mmol) in DCM (1 mL) was added 4N HCl in dioxane (0.1 mL, 0.8 mmol). The reaction was stirred at 0 °C for 1 h. The resulting product was collected and afforded 1-(6-((3-aminobicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione as HCl salt. MS (APCI) *m/z* 341.2 $[M+1]^+$.

Step 3: 1-(1-methyl-6-((3-((1-(4-nitrophenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0213] To a stirred solution of 1-(4-nitrophenyl)piperidin-4-one (30 mg, 0.136 mmol) in THF (3 mL) was added 1-(6-((3-aminobicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride (51.3 mg, 0.136 mmol). The mixture was stirred at rt for 1 h and then cooled to 0°C. Sodium triacetoxyborohydride (115 mg, 0.545 mmol) was added in portions and stirred at RT 1 h. The mixture was loaded on column with celite. The product was purified by silica gel chromatography eluted with 0-10% MeOH/DCM to give product 1-(1-methyl-6-((3-((1-(4-nitrophenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (40 mg, 54%). MS (APCI) *m/z* 545.3 $[M+1]^+$.

Step 4: 1-(6-((3-((1-(4-aminophenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

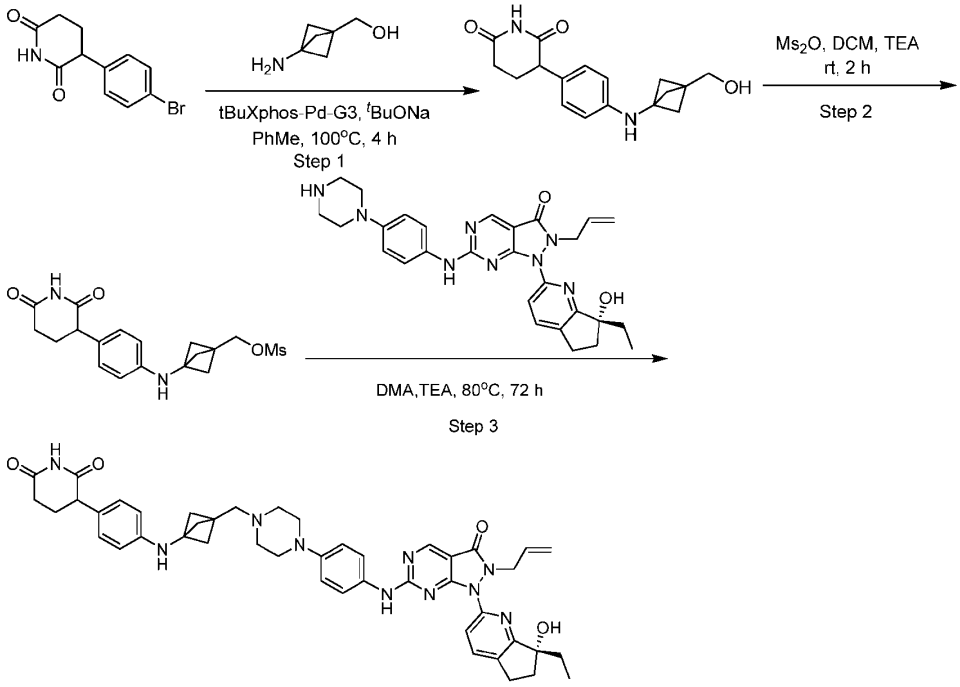
[0214] To a flask (100 mL) was loaded 1-(1-methyl-6-((3-((1-(4-nitrophenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (40 mg, 0.073 mmol) in MeOH (20 mL) and DCM (10.00 mL). The solution was babbled nitrogen for 1 min before adding Pd-C (10%). The suspension bubbled hydrogen for 1 min and then the hydrogen balloon was put on flask. The hydrogenation took 1 h. The catalyst was filtered off and the filtrate was concentrated and dried. The product 1-(6-((3-((1-(4-aminophenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (37 mg, 0.072 mmol, 98%) was afforded as yellow wax. MS (APCI) *m/z* 515.4 $[M+1]^+$.

Step 5: (*R*)-1-(6-((3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0215] To a solution of 1-(6-((3-((1-(4-aminophenyl)piperidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (37 mg, 0.072 mmol) in THF (2 mL) were added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (44.8 mg, 0.108 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL, 2.87 mmol). The mixture was heated at 80 °C for 2 days. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration. The product was purified by silica gel chromatography eluted with 0-10% DCM/MeOH (containing 10% 7N NH_3 in MeOH). The product was further purified by reverse C18 column eluted with 0-100% MeCN/H_2O (with 0.1% formic acid). The pure product fractions were combined and concentrated. The residue was added saturated $NaHCO_3$ and extracted with EtOAc (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered, concentrated. The product was dissolved in MeCN (1 mL) and water (1 mL) and frozen and lyophilized for 2 days. The product (*R*)-1-(6-((3-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-

yl)amino)bicyclo[1.1.1]pentan-1-yl)amino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.1 mg, 1.152 µmol, 1.602%) was obtained. MS (APCI) *m/z* 850.4 $[M+1]^+$.

Example 20
3-(4-((3-((4-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)bicyclo[1.1.1]pentan-1-yl)amino)phenyl)piperidine-2,6-dione **(21)**



Step 1: 3-(4-((3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)amino)phenyl)piperidine-2,6-dione

[0216] In a microwave tube (20 mL) was loaded 3-(4-bromophenyl)piperidine-2,6-dione (310 mg, 1.158 mmol), PhMe (10 mL), (3-aminobicyclo[1.1.1]pentan-1-yl)methanol (131 mg, 1.158 mmol), sodium *tert*-butylate (223 mg, 2.315 mmol). The mixture was bubbled nitrogen for 1 min before adding [(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate (tBuXphos-Pd-G3, 170 mg, 0.191 mmol). The tube was sealed and heated at 100°C for 3 h. The reaction was diluted with EtOAc (20 mL) and brine (20 mL). The organic layer was separated and aqueous was extracted with EtOAc (20 mL x 3). The combined organic

layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel chromatography eluted with 0-10% MeOH-DCM to give crude 3-(4-((3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)amino)phenyl)piperidine-2,6-dione (114 mg, 0.304 mmol, 26.2%) as yellow wax. MS (APCI) *m/z* 301.2 $[M+1]^+$.

Step 2: (3-((4-(2,6-dioxopiperidin-3-yl)phenyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate

[0217] The solution of 3-(4-((3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)amino)phenyl)piperidine-2,6-dione (24 mg, 0.080 mmol) in DCM (3 mL) was cold in ice bath and the methanesulfonic anhydride (13.92 mg, 0.080 mmol) was added follow by adding *N,N*-diisopropylethylamine (0.3 mL, 1.722 mmol). The reaction was stirred at 0°C for 1 h. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and DCM (20 mL). The organic layer was separated and aqueous was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel chromatography eluted with 0-10% MeOH-DCM to give (3-((4-(2,6-dioxopiperidin-3-yl)phenyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate (16 mg, 0.042 mmol, 53%). MS (APCI) *m/z* 379.1 $[M+1]^+$.

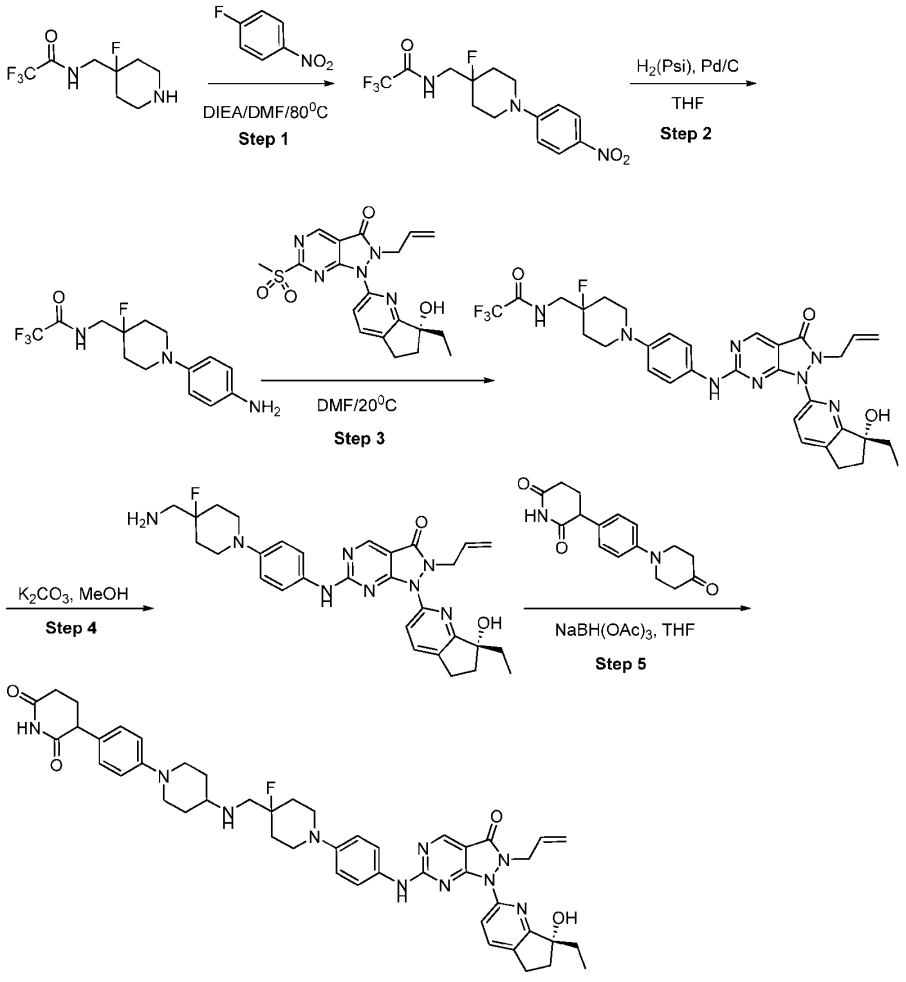
Step 3: 3-(4-((3-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)bicyclo[1.1.1]pentan-1-yl)amino)phenyl)piperidine-2,6-dione

[0218] To a solution of (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-((4-(piperazin-1-yl)phenyl)amino)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (21.67 mg, 0.042 mmol) in DMA (3 mL) was added (3-((4-(2,6-dioxopiperidin-3-yl)phenyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl methanesulfonate (16 mg, 0.042 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.15 mmol). The reaction was stirred at 80 °C for 18 h. the reaction was quenched with saturated $NaHCO_3$ (20 mL) and DCM (20 mL). The organic layer was separated and aqueous was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel chromatography eluted with 0-10% MeOH-DCM to give crude product. The product was further purified by reverse C18 column eluted with 0-100% MeCN/H_2O (with 0.1% formic acid). The pure product fractions were combined and concentrated. The residue was added saturated $NaHCO_3$ and extracted with EtOAc (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered, concentrated. The product was dissolved in MeCN

(1 mL) and water (1 mL) and frozen and lyophilized for 2 days. 3-(4-((3-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)bicyclo[1.1.1]pentan-1-yl)amino)phenyl)piperidine-2,6-dione (1.2 mg, 1.494 μmol, 3.53%) was obtained. MS (APCI) *m/z* 795.40 $[M+1]^+$.

Example 21

3-(4-(4-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**26**)



Step 1: 2,2,2-trifluoro-*N*-((4-fluoro-1-(4-nitrophenyl)piperidin-4-yl) methyl)acetamide

[0219] To a solution of 1-fluoro-4-nitrobenzene (667.82 mg, 4.73 mmol) in DMF (20 mL) at 25 °C were added 2,2,2-trifluoro-N-((4-fluoropiperidin-4-yl)methyl)acetamide (0.90 g, 3.94 mmol) and DIEA (2.55 g, 19.72 mmol). The reaction was stirred at 80 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2,2,2-trifluoro-N-((4-fluoro-1-(4-nitrophenyl)piperidin-4-yl) methyl)acetamide (0.70 g, 49%). LC/MS (ESI) *m/z* 350.0 $[M+H]^+$.

Step 2: *N*-((1-(4-aminophenyl)-4-fluoropiperidin-4-yl)methyl)-2,2,2-trifluoroacetamide

[0220] To a solution of 2,2,2-trifluoro-*N*-((4-fluoro-1-(4-nitrophenyl)piperidin-4-yl)methyl) acetamide (0.70 g, 1.94 mmol) in THF (20 mL) was added Pd/C (103.44 mg, 97.20 μmol, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 3 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filter cake was washed with THF (30 mL), and the collected filtrate was concentrated to afford *N*-((1-(4-aminophenyl)-4-fluoropiperidin-4-yl)methyl)-2,2,2-trifluoroacetamide (0.55 g, 81%). LC/MS (ESI) *m/z* 320.0 $[M+H]^+$.

Step 3: (*R*)-*N*-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)-2,2,2-trifluoroacetamide

[0221] To a solution of *N*-((1-(4-aminophenyl)-4-fluoropiperidin-4-yl)methyl)-2,2,2- trifluoroacetamide (0.20 g, 626.38 μmol) in DMF (4 mL) at 25 °C was added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (216.86 mg, 521.98 μmol). The reaction was stirred at 25 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (5 mL) and extracted with DCM (3 × 5 mL). The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford (*R*)-*N*-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-

dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)-2,2,2-trifluoroacetamide (0.17 g, 49%). LC/MS (ESI) *m/z* 655.1 $[M+H]^+$.

Step 4: (*R*)-2-Allyl-6-((4-(4-(aminomethyl)-4-fluoropiperidin-1-yl)phenyl)amino)-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one

[0222] To a solution of (*R*)-*N*-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)-2,2,2-trifluoroacetamide (170 mg, 259.68 μmol) in MeOH (2 mL) at 25 °C was added K_2CO_3 (179.45 mg, 1.30 mmol). The reaction was stirred at 25 °C for 72 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was diluted with water (5 mL) and extracted with DCM (3 × 5 mL). The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give (*R*)-2-allyl-6-((4-(4-(aminomethyl)-4-fluoropiperidin-1-yl)phenyl)amino)-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (40.00 mg, 27%). LC/MS (ESI) *m/z* 559.2 $[M+H]^+$.

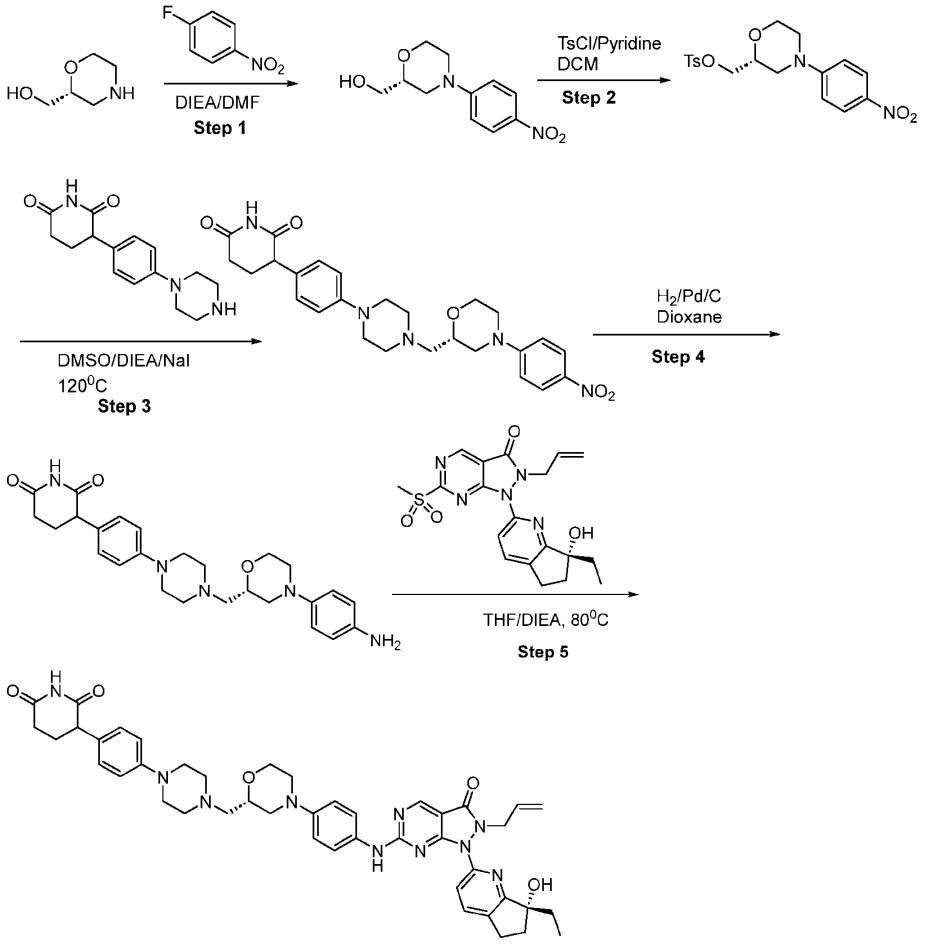
Step 5: 3-(4-(4-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione

[0222] To a solution of 2-allyl-6-[4-[4-(aminomethyl)-4-fluoro-1-piperidyl]anilino]-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[b]pyridin-2-yl]pyrazolo[3,4-d]pyrimidin-3-one (40.00 mg, 71.60 μmol) in DCM (1 mL) at 25 °C were added 3-(4-(4-oxopiperidin-1-yl)phenyl)piperidine -2,6-dione (30.75 mg, 107.40 μmol), AcOH (4.30 mg, 71.60 μmol) and $NaBH(OAc)_3$ (30.35 mg, 143.20 μmol). The reaction was stirred at 25 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by reverse phase HPLC to afford 3-(4-(4-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (13.80 mg, 23%). LC/MS (ESI) *m/z* 829.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 10.14 (br d, *J* = 1.7 Hz, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.58 (br s, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.96 (br d, *J* = 8.7 Hz, 2H), 6.88 (br d, *J* = 8.6 Hz, 2H),

5.74-5.58 (m, 1H), 5.10-4.96 (m, 2H), 4.91-4.68 (m, 2H), 4.65-4.50 (m, 1H), 3.71 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.60 (br d, *J* = 12.4 Hz, 2H), 3.48-3.41 (m, 2H), 3.03-2.88 (m, 3H), 2.84-2.66 (m, 5H), 2.64-2.58 (m, 1H), 2.57-2.52 (m, 2H), 2.48-2.41 (m, 1H), 2.25-2.15 (m, 1H), 2.15-2.06 (m, 1H), 2.06-1.95 (m, 2H), 1.94-1.83 (m, 5H), 1.82-1.76 (m, 1H), 1.76-1.58 (m, 2H), 1.34 (q, *J* = 10.1 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

Example 22

3-(4-(4-(((*S*)-4-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (**27**)



Step 1: (*S*)-1-(6-(2-((4-(4-aminophenyl)piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0223] To a solution of (*R*)-morpholin-2-ylmethanol (1.99 g, 17.01 mmol) and 1-fluoro-4-nitrobenzene (2 g, 14.17 mmol) in DMF (20 mL) at 20 °C was added DIEA (1.83 g, 14.17 mmol). The reaction was stirred at 80 °C for 12 h. LCMS shows the formation of product. The reaction was poured into water (50 mL) and a product was obtained. After filtration, the filter cake was collected and dried to afford (*R*)-(4-(4-nitrophenyl)morpholin-2-yl)methanol (2.5 g, 10.49 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.09 (d, *J* = 9.4 Hz, 2H), 7.04 (d, *J* = 9.4 Hz, 2H), 4.86 (t, *J* = 5.5 Hz, 1H), 3.97 (dd, *J* = 2.3, 11.6 Hz, 1H), 3.92 (br d, *J* = 12.6 Hz, 1H), 3.85 (br d, *J* = 12.9 Hz, 1H), 3.60 (dt, *J* = 2.9, 11.6 Hz, 1H), 3.55-3.43 (m, 3H), 2.96 (dt, *J* = 3.6, 12.2 Hz, 1H), 2.78-2.68 (m, 1H).

Step 2: (*R*)-(4-(4-nitrophenyl)morpholin-2-yl)methyl 4-methylbenzenesulfonate

[0224] To a solution of [(2*R*)-4-(4-nitrophenyl)morpholin-2-yl]methanol (2 g, 8.39 mmol) in DCM (30 mL) at 20 °C were added TsCl (3.20 g, 16.79 mmol) and pyridine (1.99 g, 25.18 mmol). The reaction was stirred at 20 °C for 12 h. LCMS showed the reaction was completed. The reaction was concentrated to give the crude product, which was purified by column chromatography (silica gel, 0-80 % EA in PE) to afford [(2*R*)-4-(4-nitrophenyl)morpholin-2-yl]methyl 4-methylbenzenesulfonate (2 g, 5.10 mmol, 61%). MS (ESI) m/z: 392.9 $[M+H]^+$.

Step 3: 3-(4-(4-(((*S*)-4-(4-nitrophenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione

[0225] To a solution of 3-(4-(piperazin-1-yl)phenyl)piperidine-2,6-dione (0.35 g, 1.55 mmol) and (*R*)-(4-(4-nitrophenyl)morpholin-2-yl)methyl 4-methylbenzenesulfonate (729.43 mg, 1.86 mmol) in DMSO (6 mL) were added DIEA (600.57 mg, 4.65 mmol) and NaI (23.22 mg, 154.90 μmol). The mixture was stirred at 120 °C for 4 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered, and the filter cake was washed with dichloromethane. The collected filtrate was concentrated. The crude product was purified by prep-TLC (EA: MeOH=10:1) to afford 3-(4-(4-(((*S*)-4-(4-nitrophenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (0.1 g, 22%). MS (ESI) m/z: 494.3 $[M+H]^+$.

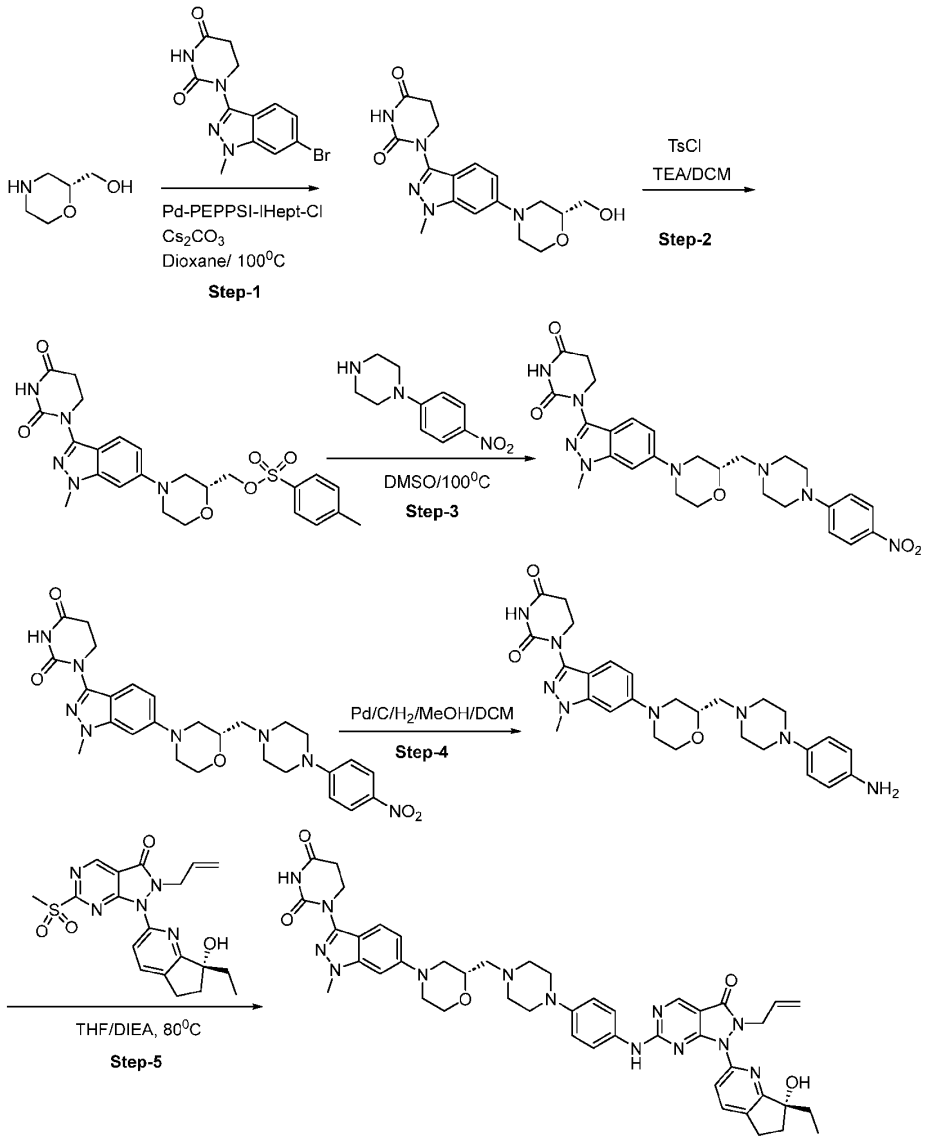
Step 4: 3-(4-(4-(((*S*)-4-(4-aminophenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione

[0226] To a solution of Pd/C (20.12 mg, 18.90 μmol, 10% purity) in dioxane (5 mL) was added 3-(4-(4-(((*S*)-4-(4-nitrophenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (0.1 g, 189.04 μmol) at 25 °C under Ar. The mixture was backfilled with H_2 multiple times and was stirred at 25 °C under H_2 (15 Psi) for 0.5 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filter cake was washed with THF. The collected filtrate was concentrated to afford 3-(4-(4-(((*S*)-4-(4-aminophenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (0.08 g, 67%), which was used to next step without further purification. MS (ESI) m/z: 464.3 $[M+H]^+$.

Step 5: 3-(4-(4-(((*S*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione

[0227] A solution of 3-(4-(4-(((*S*)-4-(4-aminophenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (80 mg, 172.57 μmol) and (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (71.70 mg, 172.57 μmol) in i-PrOH (1.6 mL) was stirred at 60 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure at 40 °C. The crude product was purified by reverse phase HPLC to afford 3-(4-(4-(((*S*)-4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)morpholin-2-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (13.8 mg, 10%). MS (ESI) m/z: 799.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 10.21-10.08 (m, 1H), 8.82 (s, 1H), 7.91 (br d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.60 (br s, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.92 (br dd, *J* = 8.8, 15.1 Hz, 4H), 5.66 (tdd, *J* = 5.9, 10.6, 16.8 Hz, 1H), 5.06 (s, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 4.85 (br d, *J* = 17.1 Hz, 1H), 4.80-4.69 (m, 1H), 4.56 (br dd, *J* = 5.4, 15.7 Hz, 1H), 3.95 (br d, *J* = 11.1 Hz, 1H), 3.82-3.61 (m, 3H), 3.56 (br d, *J* = 11.4 Hz, 1H), 3.46 (br d, *J* = 11.3 Hz, 1H), 3.13 (br t, *J* = 4.3 Hz, 4H), 3.00-2.88 (m, 1H), 2.81-2.70 (m, 1H), 2.68-2.57 (m, 6H), 2.49-2.35 (m, 4H), 2.21-2.07 (m, 2H), 2.06-1.95 (m, 2H), 1.94-1.82 (m, 1H), 1.77-1.63 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H).

Example 23
1-(6-((*S*)-2-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**44**)



Step 1: (*R*)-1-(6-(2-(hydroxymethyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0228] To a solution of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (100 mg, 0.309 mmol), 2-morpholinemethanol,

(2*R*)- (43.5 mg, 0.371 mmol) and cesium carbonate (302 mg, 0.928 mmol) in dioxane (1.7 mL) and NMP (344 µL) was added Pd-PEPPSI-iHeptCI (30.1 mg, 0.031 mmol). The mixture was degassed with N_2 multiple times. The mixture was heated at 90 °C for 8 h. LCMS shows the formation of product. The mixture partitioned with DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-10 % Methanol in dichloromethane) to afford (*R*)-1-(6-(2-(hydroxymethyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (78 mg, 0.217 mmol, 70%). MS (ESI) m/z: 360.0 $[M+H]^+$.

Step 2: (*R*)-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)morpholin-2-yl)methyl benzenesulfonate

[0229] To a solution of (*R*)-1-(6-(2-(hydroxymethyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (250 mg, 0.696 mmol) in DCM (3.5 mL) was added triethylamine (194 µl, 1.391 mmol) followed by 4-methylbenzenesulfonyl chloride (146 mg, 0.765 mmol) and 4-(dimethylamino)pyridine (17.00 mg, 0.139 mmol). The mixture was stirred at rt for overnight. LCMS shows the formation of product. The mixture was partitioned with DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-10 % Methanol in dichloromethane) to afford (*R*)-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)morpholin-2-yl)methyl 4-methylbenzenesulfonate (187 mg, 0.364 mmol, 52%). MS (ESI) m/z: 514.0 $[M+H]^+$.

Step 3: (*S*)-1-(1-methyl-6-(2-((4-(4-nitrophenyl) piperazin-1-yl)methyl)morpholino)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0230] To a solution of (*R*)-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)morpholin-2-yl)methyl 4-methylbenzenesulfonate (200 mg, 0.389 mmol) in DMSO (2.6 mL) was added *N,N*-diisopropylethylamine (204 µL, 1.168 mmol) followed by 1-(p-nitrophenyl)piperazine (105 mg, 0.506 mmol). The mixture was heated at 100 °C for 12 h. LCMS shows the formation of product. The mixture was partitioned with DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-7 % Methanol in dichloromethane) to afford (*S*)-1-(1-methyl-6-(2-((4-(4-nitrophenyl)piperazin-1-yl)methyl)morpholino)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (85 mg, 0.155 mmol, 39%). MS (ESI) m/z: 549.10 $[M+H]^+$.

Step 4: (*S*)-1-(6-(2-((4-(4-aminophenyl)piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0231] To a solution of (*S*)-1-(1-methyl-6-(2-((4-(4-nitrophenyl)piperazin-1-yl)methyl)morpholino)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (95 mg, 0.173 mmol) in MeOH (2.3 mL) and dichloromethane (1.2 mL) was added palladium (27.6 mg, 0.026 mmol, 10% by weight). The mixture was backfilled with H_2 multiple times and was stirred under H_2 overnight. LCMS shows the formation of product. The mixture was diluted with DCM and filtered using a celite pad. The filtrate was concentrated to afford (*S*)-1-(6-(2-((4-(4-aminophenyl)piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (85 mg, 0.164 mmol, 95%), which was used for next step. MS (ESI) m/z: 519.10 $[M+H]^+$.

Step 5: 1-(6-((*S*)-2-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*] pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl) piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0232] To a solution of (*S*)-1-(6-(2-((4-(4-aminophenyl)piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (90 mg, 0.173 mmol) in THF (1.7 mL) was added *N*,*N*-diisopropylethylamine (60.3 µL, 0.346 mmol) followed by (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (43.1 mg, 0.104 mmol). The mixture was heated at 80 °C for 2 h. LCMS shows the formation of product. The mixture was partitioned with DCM and water. The organic layer was separated, dried over Na_2SO_4, concentrated and was purified by column chromatography (silica gel, 0-10 % Methanol in dichloromethane) to afford the impure product, which was again purified by reverse phase HPLC to afford 1-(6-((*S*)-2-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*] pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl) piperazin-1-yl)methyl)morpholino)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (27 mg, 0.032 mmol, 18%). MS (ESI) m/z: 854.40 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.56-10.47 (m, 1H), 10.22-10.07 (m, 1H), 8.85-8.80 (m, 1H), 8.01-7.88 (m, 1H), 7.73-7.67 (m,1H), 7.67-7.53 (m, 2H), 7.53-7.44 (m, 1H), 6.99-6.88 (m, 3H), 6.88-6.82 (m, 1H), 5.74-5.60 (m, 1H), 5.11-4.96 (m, 2H), 4.91-4.81 (m, 1H), 4.81 -4.68 (m, 1H), 4.65-4.50 (m, 1H), 4.02-3.95 (m, 1H), 3.95-3.78 (m, 6H), 3.76-3.57 (m, 3H), 3.340-3.30 (m,

3H), 3.18-3.07 (m, 4H), 3.03-2.91 (m, 1H), 2.84-2.58 (m, 8H), 2.27-2.16 (m, 1H), 2.08-1.97 (m, 1H), 1.96-1.83 (m, 1H), 1.77-1.64 (m, 1H), 0.92-0.82 (m, 3H).

Example 24
Cell proliferation assay

[0233] Cell proliferation was measured using the CellTiter-Glo® Luminescent Cell Viability Assay. The assay involved the addition of a single reagent (CellTiter-Glo® Reagent) directly to cells cultured in serum-supplemented medium. A427 cells (ATCC, HTB-53), OVCAR3 (ATCC, HTB-161) and MDA-MB-231 (ATCC, CRM-HTB-26) cells were cultured according to ATCC recommendations and were seeded at 3,000 cells for A427, 5000 cells for OVCAR3 and 3000 for MDA-MB-231 cells per well.

[0234] Each compound evaluated was prepared as a DMSO stock solution (10 mM). Compounds were tested in duplicate on each plate, with a 10-point serial dilution curve (1:3 dilution). The highest compound concentration was 10 μM (final), with a 0.1% final DMSO concentration. Plates were then incubated at 37 °C, 5% CO_2 for 72 h for A427 or 6 day for OVCAR3 and MDA-MB-231, and then were equilibrated at rt for approximately 30 mins. An equi-volume amount of CellTiter-Glo® Reagent (100 μL) was added to each well. Plates were mixed for 2 mins on an orbital shaker to induce cell lysis and then incubated at rt for 10 mins to stabilize the luminescent signal. Luminescence was recorded using a Spectramax i3x (Molecular Devices) plate reader according to CellTiter-Glo protocol. IC_{50} determination was performed using a non-linear regression, variable slope (four parameter), inhibitor v. response equation (Prism 9.0). IC_{50} values are provided in Table 2. For comparison, Table 2 also includes IC_{50} value for reference compound ZN-c3.

Table 2. IC_{50} values.

Compound No.	A427 (nM)	OVCAR3 (nM)	MDA-MB-231 (nM)
1	A	A	A
2	A	B	A
3	A	ND	ND
5	A	A	A
6	A	B	A
7	A	B	A
8	A	B	B
9	A	B	A
10	B	C	B
11	A	A	A

Compound No.	A427 (nM)	OVCAR3 (nM)	MDA-MB-231 (nM)
12	B	B	B
13	A	A	A
14	A	A	A
16	A	B	B
17	A	A	A
18	A	B	A
20	B	ND	ND
21	A	B	A
26	A	A	A
27	A	A	A
44	A	B	A
ZN-c3 (Reference)	B	B	B

For A427, OVCAR3 and MDA-MB-231 CTG IC_{50}: A = a single $IC_{50} \leq 100$ nM; B = a single $IC_{50} > 100$ nM and < 500 nM; C = a single $IC_{50} \geq 500$ nM, ND: Not Determined

Example 25
Protein degradation assay in MOLT-4 cells

[0235] 1.5 million MOLT-4 cells (ATCC, CRL-1582) were incubated with vehicle (DMSO) or 10 μM, 1 μM, 0.1 μM, or 0.01 μM concentrations of the indicated compounds for 5 hours. After treatment, the cells were harvested in RIPA lysis buffer supplemented with 1% Phosphatase Inhibitor and Protease Inhibitor Cocktail and protein concentration was determined by BCA assay. An equal amount of protein (3.5 μg/lane) from each cell extract was loaded onto 12-230KDa Separation 25 Capillary Cartridges from ProteinSimple and probed with WEE1 (1:200 dilution, final concentration of 1 μg/mL) and β-Actin (1:100 dilution, final concentration of 5 μg/mL) antibodies on a ProteinSimple Jess system according to ProteinSimple/SimpleWestern protocols. The area under the curve (AUC) from the resulting eletropherograms for each protein peak at the concentrations tested was used to calculate percent degradation for WEE1 using the equation percent degradation = 100 – [100*(WEE1/β-Actin)/($WEE1_{DMSO}$/$β\text{-}Actin_{DMSO}$)]. For illustrative purposes, electopherograms were exported as virtual blots using Compass for SW v 6.0 (ProteinSimple). The WEE-1 antibody (sc-5285) was purchased from Santa Cruz Biotechnology and β-actin (MAB8929) was purchased from R&D Systems. Percent remaining of WEE1 after 5 hour treatment in MOLT-4 cells at the tested concentrations are provided in Table 3. A "hook effect" is observed at higher concentrations, however these results indicate that many of the exemplified compounds are potent degraders of WEE1.

Table 3. Percent of remaining WEE1.

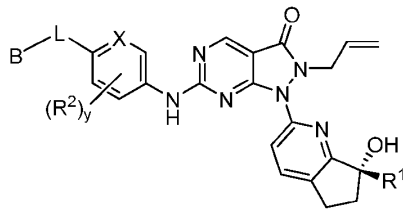
Percent remaining of WEE1 after 5 hours in MOLT-4 cells				
Compound No.	0.001 μM	0.01 μM	0.1 μM	1 μM
1	39	6	3	7
2	111	15	8	12
3	62	13	6	16
4	65	15	6	10
5	68	15	5	15
6	56	13	7	16
7	67	19	12	27
8	84	28	15	18
9	57	14	6	14
10	103	56	17	27
11	61	11	5	10
12	102	30	9	13
13	55	13	6	16
14	56	19	14	30
15	79	24	10	21
16	64	19	11	22
17	42	11	7	10
18	63	18	11	29
20	72	20	9	27
21	80	20	10	15
26	70	18	16	26
27	68	17	8	12
44	63	15	9	21

[0236] Compounds of Formula (I) provided herein exhibit highly desirable properties for a DNA damage response (DDR) kinase inhibitor/degrader, including cancer cell proliferation and WEE1 kinase degradation, as demonstrated in the data presented in Tables 2 and 3. In addition, compounds of Formula (I) exhibit superior solubility as well as *in vivo* safety and pharmacokinetic-pharmacodynamic properties as characterized using assay methods readily known by a person having ordinary skill in the art.

[0237] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the disclosure.

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

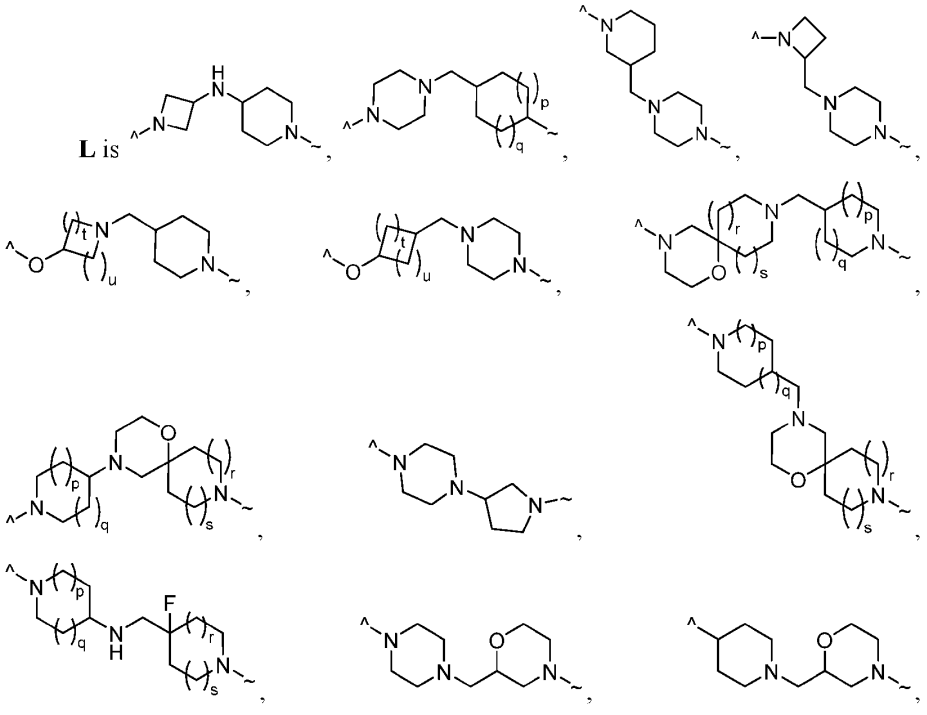
wherein:

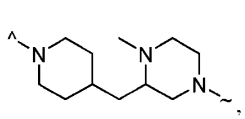
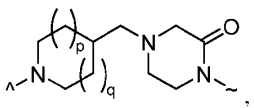
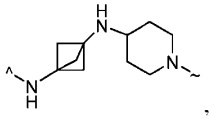
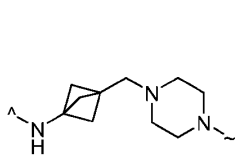
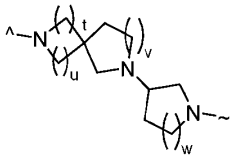
X is N or −CH;

R^1 is a substituted or an unsubstituted C$_1$-C$_6$ alkyl;

R^2 is halogen, −CN, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl or C$_1$-C$_6$ alkoxy;

y is 0, 1 or 2;

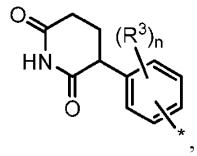
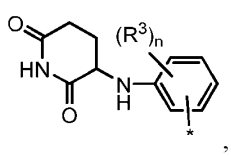
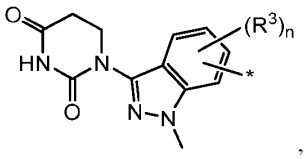
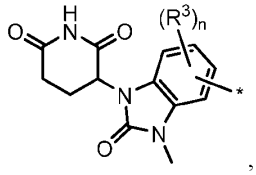
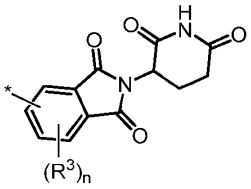
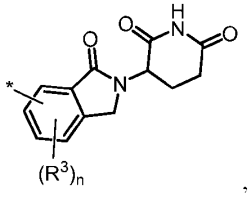
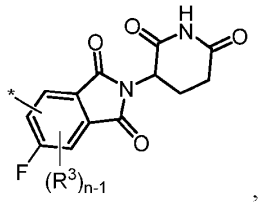
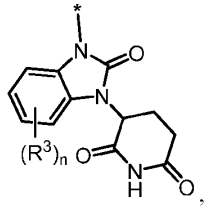
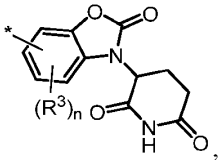
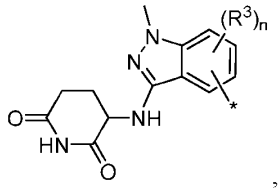
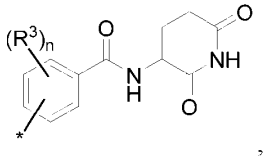
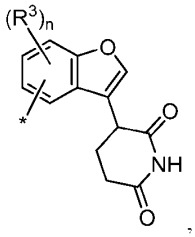
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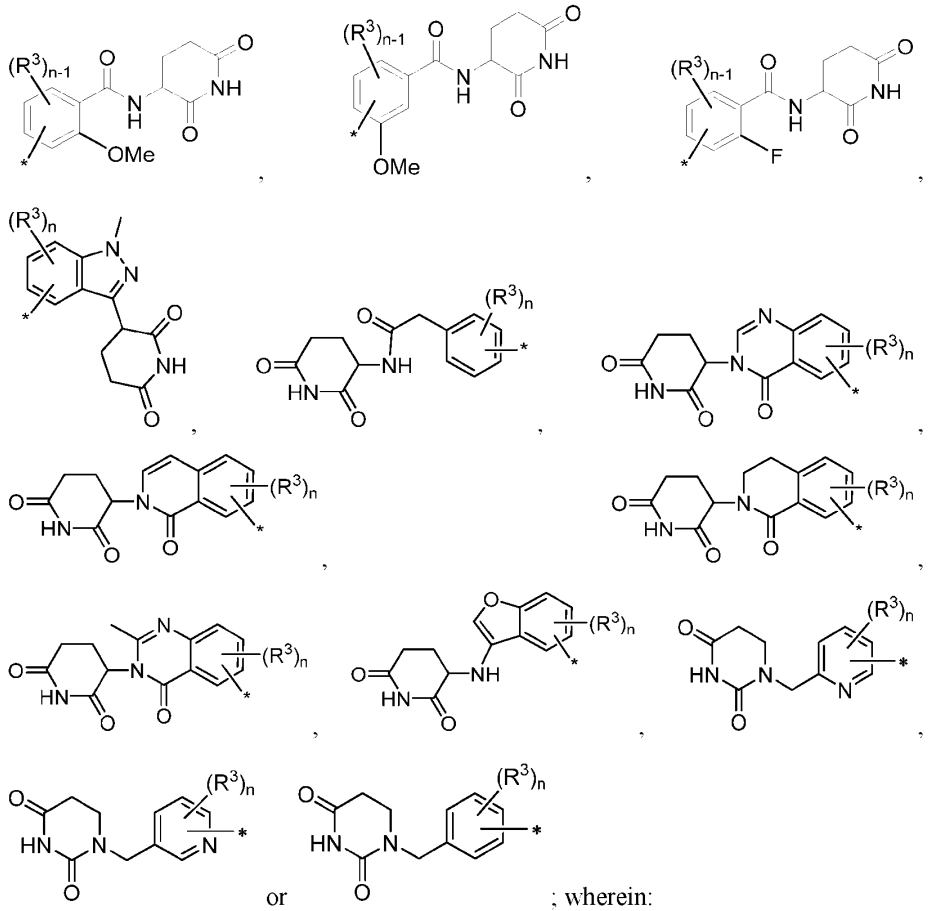
, , ,  or ; wherein:

^ and ~ each indicate the point of attachment to **B** or the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$;

p, **q**, **r**, and **s**, for each instance, and **v** and **w**, are each independently 0, 1 or 2;

t and **u**, for each instance, are each independently 1 or 2; and

B is , , , , , , , , , , , .



; wherein:

* indicates the point of attachment to **L**;

$\mathbf{R^3}$ is halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkoxy; and

n, for each instance, is 0, 1 or 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein **X** is −CH.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein ~ indicates the point of attachment to **B** and ^ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein **p** and **q**, for each instance, are each 0.

6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein **p**, for each instance, is 0 and **q**, for each instance, is 1; or **p**, for each instance, is 1 and **q**, for each instance, is 0.

7. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein **p** and **q**, for each instance, are each 1.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **r** and **s**, for each instance, are each 0.

9. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **r**, for each instance, is 0 and **s**, for each instance, is 1; or **r**, for each instance, is 1 and **s**, for each instance, is 0.

10. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **r** and **s**, for each instance, are each 1.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein **v** is 0.

12. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein **v** is 1.

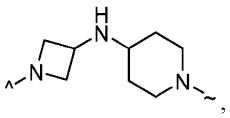
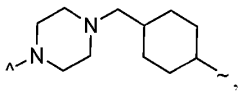
13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **w** is 0.

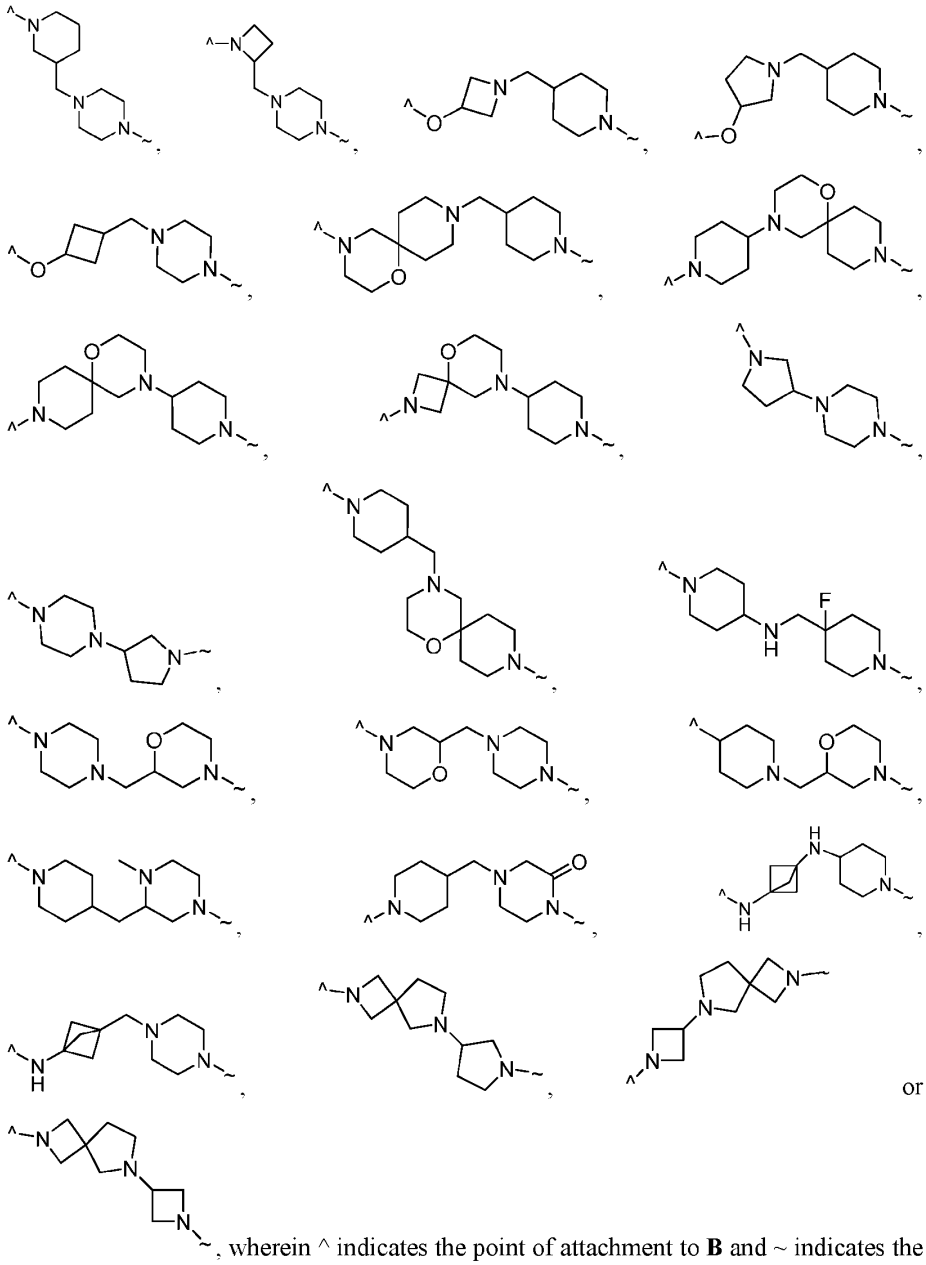
14. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **w** is 1.

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein **t** and **u**, for each instance, are each 1.

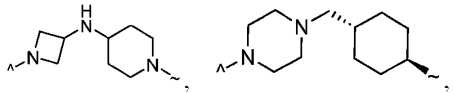
16. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein **t**, for each instance, is 1 and **u**, for each instance, is 2; or **t**, for each instance, is 2 and **u**, for each instance, is 1.

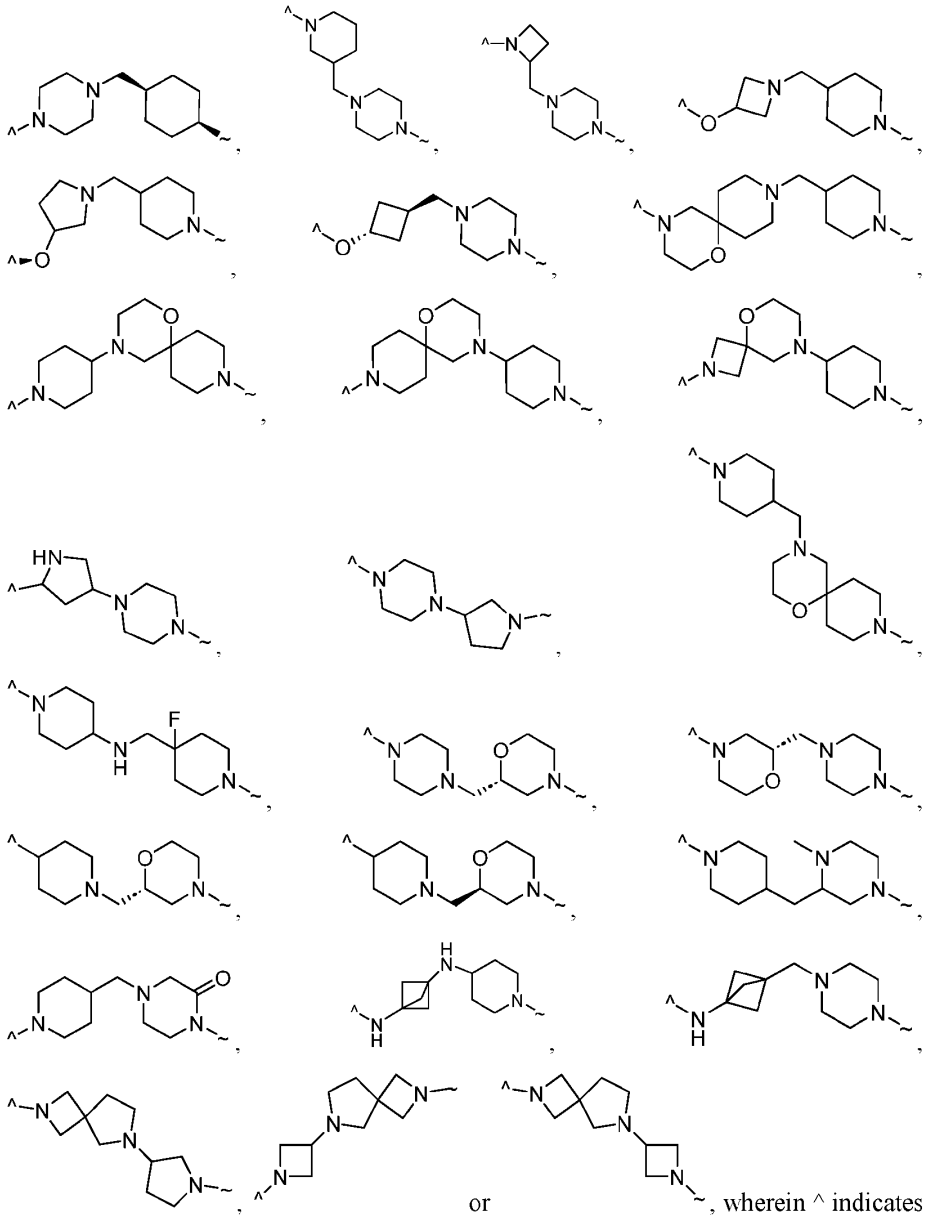
17. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein **t** and **u**, for each instance, are each 2.

18. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein **L** is , ,

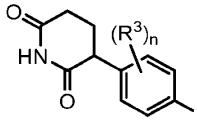
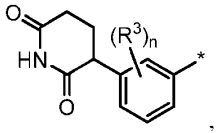
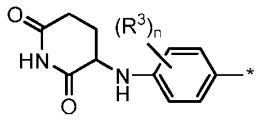
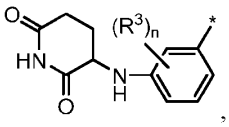
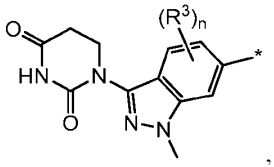
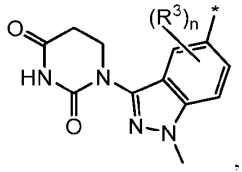
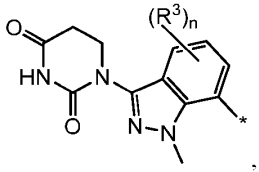
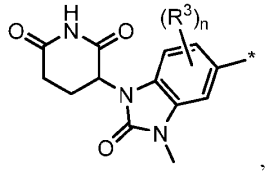
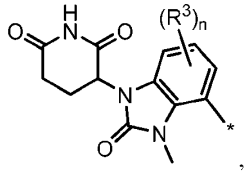
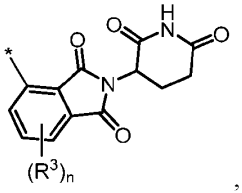
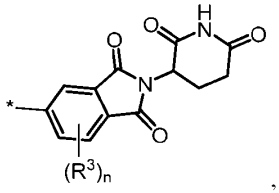
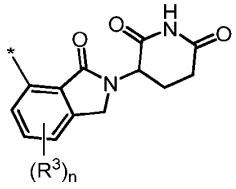
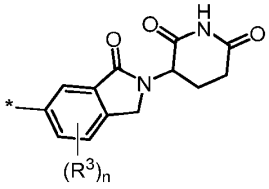
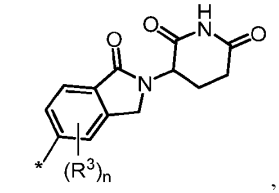
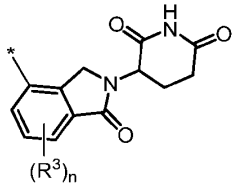
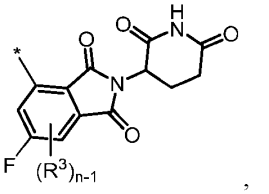
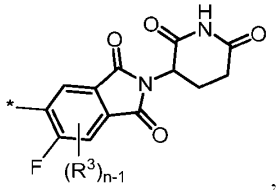
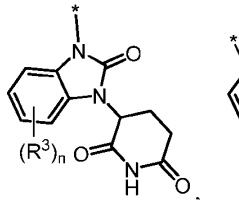
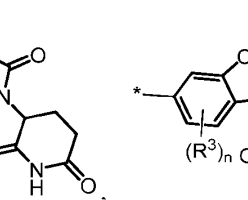
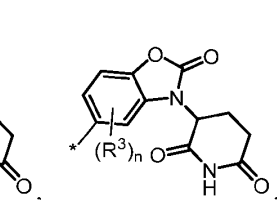
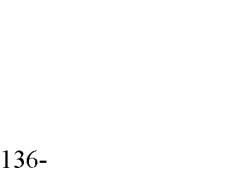


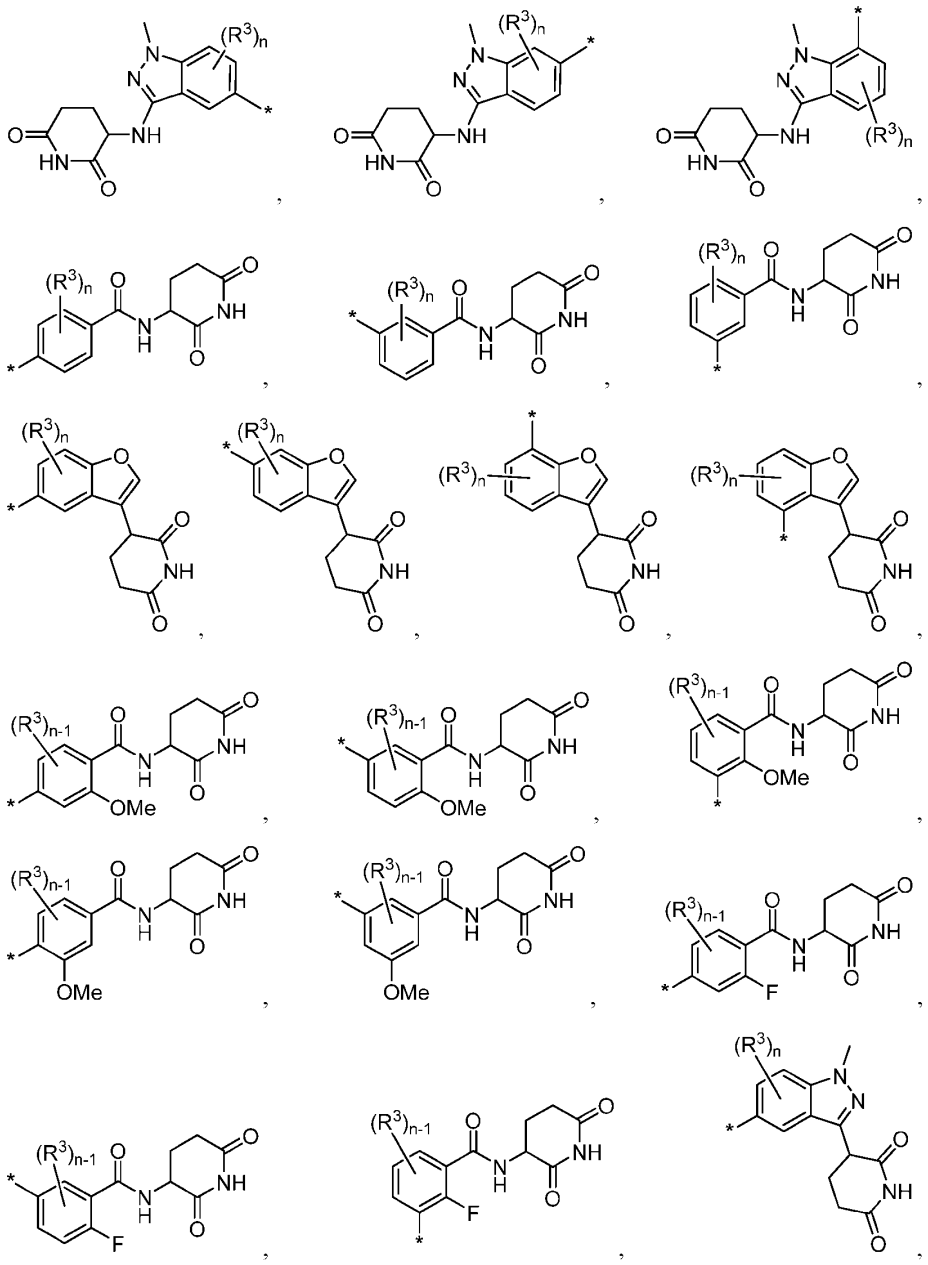
, wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$.

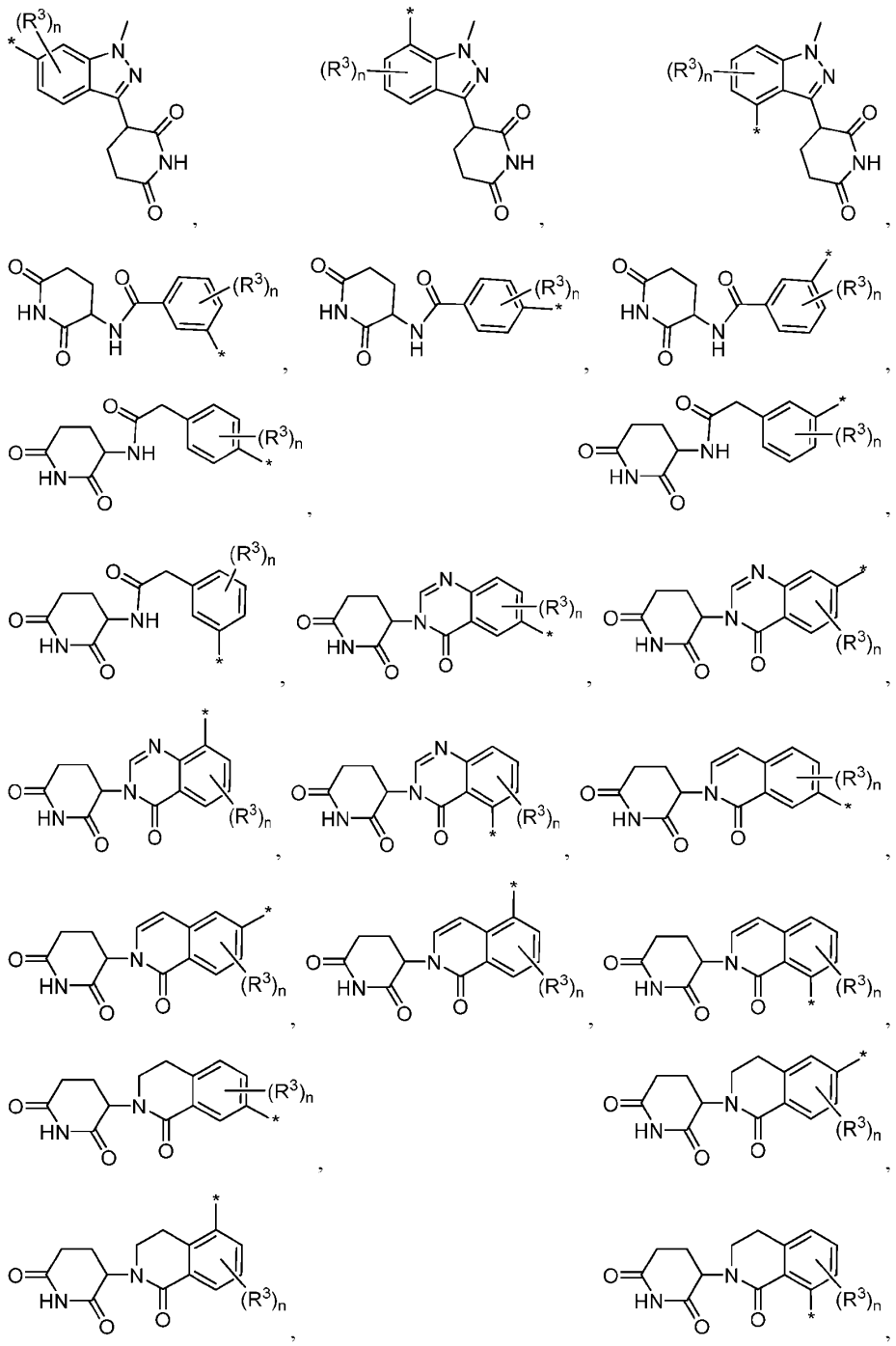
19. The compound of any one of claims 1 to 3 and 18, or a pharmaceutically acceptable salt thereof, wherein **L** is 

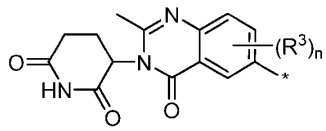
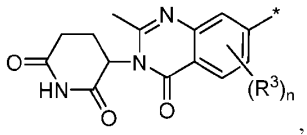
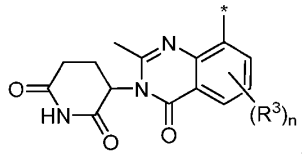
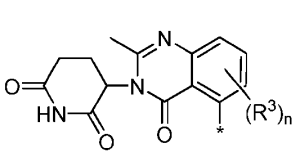
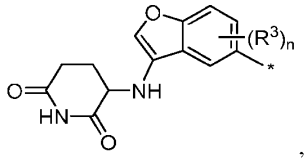
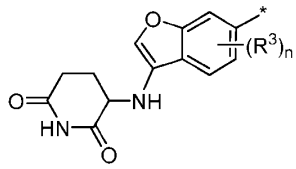
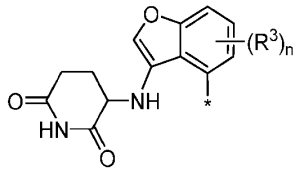
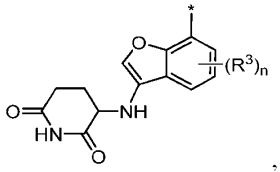
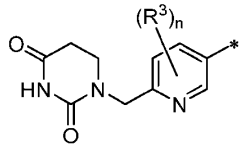
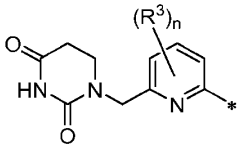
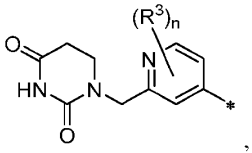
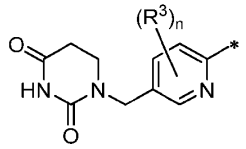
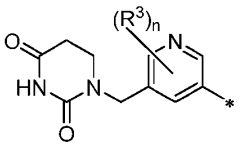
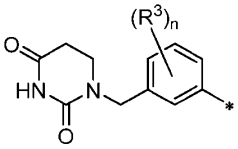
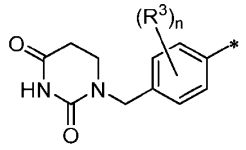


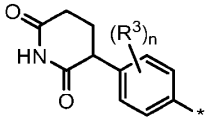
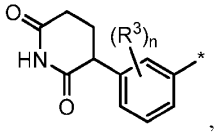
or , wherein ^ indicates the point of attachment to **B** and ~ indicates the phenyl or pyridinyl in Formula (I) that is optionally substituted with $\mathbf{R^2}$.

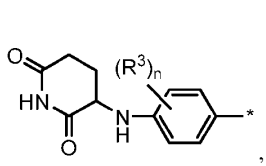
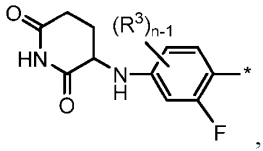
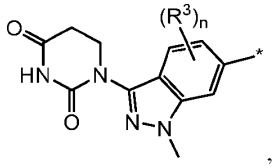
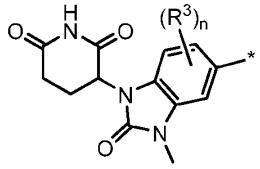
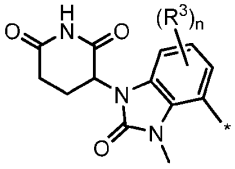
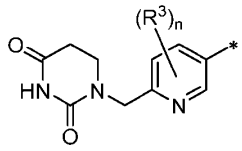
20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein **B** is , , , , , , , , , , , , , , , , , , , , , , , .






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or

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21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein **B** is

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22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^3}$ is F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl or C_1-C_4 alkoxy.

23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein **n**, for each instance, is 0 or 1.

24. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is an unsubstituted C_1-C_4 alkyl or a C_1-C_4 haloalkyl.

25. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is ethyl.

26. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^2}$ is F, −CN, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl or C_1-C_4 alkoxy.

27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein **y** is 0 or 1.

28. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein any one or more hydrogen atoms in the compound is substituted with deuterium.

29. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound has a structure selected from those of Compound Nos. 1 to 44 as listed in Table 1.

30. A pharmaceutical composition comprising an effective amount of the compound of any one of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or a combination thereof.

31. Use of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30 in the manufacture

of a medicament for ameliorating or treating a cancer, wherein the cancer is selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.

32. Use of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30 in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.

33. Use of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30 in the manufacture of a medicament for ameliorating or treating a malignant growth or tumor, wherein the malignant growth or tumor is due to a cancer selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an

osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.