

BENZAMIDE COMPOUNDS

RELATED APPLICATION INFORMATION

[0001] This application claims priority to U.S. Serial No. 62/615,857, filed January 10, 2018, which is hereby incorporated by reference in its entirety for all purposes.

Field

[0002] The present application relates to compounds that are Bcl-2 inhibitors and methods of using them to treat conditions characterized by excessive cellular proliferation, such as cancer and tumors, and viral infections such as infection with the human immunodeficiency virus (HIV).

Description

[0003] Bcl-2 plays a role in cell death regulation, including apoptosis, necrosis and autophagy. Accordingly, alterations in Bcl-2 expression and function contribute to pathogenesis and progression of human cancers and tumors, and may facilitate certain viral infections such as HIV.

SUMMARY

[0004] Some embodiments provide a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments disclosed herein relate to a pharmaceutical composition that can include an effective amount of one or more of compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0006] Some embodiments described herein relate to a method for treating a cancer or a tumor 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 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for treating a cancer or a tumor 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for treating a cancer or a tumor described herein.

[0007] Some embodiments described herein relate to a method for inhibiting replication of a malignant growth or a tumor described herein 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). 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) in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor 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) for inhibiting replication of a malignant growth or a tumor described herein.

[0008] Some embodiments described herein relate to a method for treating a cancer described herein that can include contacting a malignant growth or a tumor described herein with 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) in the manufacture of a medicament for treating a cancer described herein, wherein the use comprises contacting a malignant growth or a tumor described herein with the medicament. 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) for contacting a malignant growth or a tumor described herein, wherein the malignant growth or tumor is due to a cancer described herein.

[0009] Some embodiments described herein relate to a method for inhibiting the activity of Bcl-2 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject and can also include contacting a cell that expresses Bcl-2 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 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) in the manufacture of a medicament for inhibiting the activity of Bcl-2 in a subject or, in the manufacture of a medicament for inhibiting the activity of Bcl-2, wherein the use comprises contacting a cell that expresses Bcl-2. 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) for inhibiting the activity of Bcl-2 in a subject; or for inhibiting the activity of Bcl-2 by contacting a cell that expresses Bcl-2.

[0010] Some embodiments described herein relate to a method of ameliorating or treating a HIV infection 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a compound described herein (for example, a compound of Formula

(I), or a pharmaceutically acceptable salt thereof), and an effective amount of a HIV latency reversing agent, 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating or treating a HIV infection in a subject suffering from the HIV infection; or, in the manufacture of a medicament for ameliorating or treating a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for ameliorating or treating a HIV infection in a subject suffering from the HIV infection; or for ameliorating or treating a HIV infection by contacting a cell infected with HIV.

[0011] Some embodiments described herein relate to a method of reducing the population of HIV infected 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), and an effective amount of a HIV latency reversing agent, 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an

effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the population of HIV infected cells in a subject suffering from the HIV infection; or, for reducing the population of HIV infected cells, wherein the use comprises contacting a cell infected with HIV with the medicament. 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the population of HIV infected cells in a subject suffering from the HIV infection; or for reducing the population of HIV infected cells by contacting a cell infected with HIV.

[0012] Some embodiments described herein relate to a method of reducing the reoccurrence of a HIV infection in a subject 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or, for reducing the reoccurrence of a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the reoccurrence

of a HIV infection in a subject suffering from the HIV infection; or for reducing the reoccurrence of a HIV infection by contacting a cell infected with HIV.

[0013] Some embodiments described herein relate to a method of ameliorating or treating a HIV infection that can include administering an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to the use of an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating or treating a HIV infection; or, in the manufacture of a medicament for ameliorating or treating a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. Still other embodiments described herein relate to an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for ameliorating or treating a HIV infection in a subject suffering from the HIV infection; or for ameliorating or treating a HIV infection by contacting a cell infected with HIV.

[0014] Some embodiments described herein relate to a method of reducing the population of HIV infected cells that can include administering an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to the use of an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for reducing the population of HIV infected cells; or, in the manufacture of a medicament for reducing the population of HIV infected cells, wherein the use comprises contacting a cell infected with HIV with the medicament. Still other embodiments described herein relate to an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the population of HIV infected cells in a subject suffering from the HIV infection; or for reducing the population of HIV infected cells by contacting a cell infected with HIV.

[0015] Some embodiments described herein relate to a method of reducing the reoccurrence of a HIV infection in a subject 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to the use of an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or, for reducing the reoccurrence of a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. Still other embodiments described herein relate to an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or for reducing the reoccurrence of a HIV infection by contacting a cell infected with HIV.

[0016] These and other embodiments are described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0017] Figure 1 shows example HIV latency reversing agents.
- [0018] Figure 2 shows example Bcl protein inhibitors.
- [0019] Figure 3 shows examples of compounds of the Formula (I).
- [0020] Figures 4A, 4B and 4C show examples of compounds of the Formula (I).
- [0021] Figure 5 shows a plot illustrating HIV assay data for examples of compounds of the Formula (I).

DETAILED DESCRIPTION

[0022] Bcl-2 is a critical regulator of programmed cell death (apoptosis). Bcl-2 belongs to the B cell lymphoma 2 (BCL-2) a family of proteins, which includes both pro-apoptotic proteins (such as Bak, Bax, Bim, Bid, tBid, Bad, Bik, PUMA, Bnip-1, Hrk, Bmf and Noxa) and anti-apoptotic proteins (such as Bcl-2, Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1). For example, under normal conditions, Bcl-2 inhibits apoptosis in part by preventing activation of Bak and Bax. Activation of the intrinsic apoptosis pathway (e.g., by cellular stress) inhibits Bcl-2, thus activating Bak and Bax. These proteins facilitate mitochondrial outer membrane permeabilization, releasing cytochrome c and Smac. This initiates the caspase signaling pathway, ultimately resulting in cell death. Dysregulation of Bcl-2 leads to sequestration of cell-death-promoting proteins, leading to evasion of apoptosis. This process contributes to malignancy, and facilitates cell survival under other disadvantageous conditions, such as during viral infection. For example, transcriptionally active HIV can incidentally generate a caspase protein fragment. This fragment binds to and activates the pro-apoptotic Bak. However, this fragment also binds to, and is sequestered by, Bcl-2 reducing its effectiveness at inducing cell death. Inhibition of Bcl-2 disrupts sequestration of pro-apoptotic proteins, restoring apoptotic signaling, and promoting damaged cells to undergo programmed cell death. Therefore, Bcl-2 inhibition has the potential to ameliorate or treat cancers and tumors, as well as ameliorate or treat certain viral infections in combination with other agents.

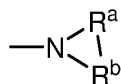
Definitions

[0023] 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.

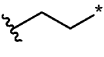
[0024] Whenever a group is described as being “optionally substituted” that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent(s) may be selected from one or more the indicated substituents. If no substituents are indicated, it is meant that the indicated “optionally substituted” or “substituted” 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, haloalkoxy, an amino, a mono-substituted amine group, a di-substituted amine group, a mono-substituted amine(alkyl) and a di-substituted amine(alkyl).

[0025] 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 “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated, the broadest range described in these definitions is to be assumed.

[0026] 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:



[0027] 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.

[0028] As used herein, the term “alkylene” refers to a bivalent fully saturated straight chain aliphatic hydrocarbon group. Examples of alkylene groups include, but are not limited to, methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene and octylene. An alkylene group may be represented by , followed by the number of carbon atoms, followed by a “*”. For example,  to represent ethylene. The alkylene 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 “alkylene” where no numerical range is designated). The alkylene group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkylene group could also be a lower alkyl having 1 to 4 carbon atoms. An alkylene group may be substituted or unsubstituted. For example, a lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group and/or by substituting both hydrogens on the same carbon with a C₃₋₆

monocyclic cycloalkyl group (*e.g.*, ).

[0029] 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.

[0030] 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-butyne, 2-butyne and the like. An alkynyl group may be unsubstituted or substituted.

[0031] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic (such as bicyclic) 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.

[0032] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic (such as bicyclic) 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.

[0033] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or multicyclic (such as bicyclic) 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 C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0034] As used herein, “heteroaryl” refers to a monocyclic or multicyclic (such as bicyclic) 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 14 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.

[0035] As used herein, “heterocyclyl” or “heteroalicyclyl” 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 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” or “bridged heteroalicyclyl” refers to compounds wherein the heterocyclyl or heteroalicyclyl 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. Heterocyclyl and heteroalicyclyl 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 heteroalicyclic may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such “heterocyclyl” or “heteroalicyclyl” 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 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.

[0036] As used herein, “aralkyl” and “aryl(alkyl)” refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aralkyl may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenylalkyl, 3-phenylalkyl and naphthylalkyl.

[0037] As used herein, “heteroaralkyl” and “heteroaryl(alkyl)” refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaralkyl may be substituted or unsubstituted. Examples include but are not limited to 2-thienylalkyl, 3-thienylalkyl, furylalkyl, thienylalkyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl and imidazolylalkyl and their benzo-fused analogs.

[0038] A “heteroalicycyl(alkyl)” and “heterocyclyl(alkyl)” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicycyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0039] As used herein, the term “hydroxy” refers to a –OH group.

[0040] 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 (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0041] 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.

[0042] A “cyano” group refers to a “-CN” group.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] An “N-amido” group refers to a “ $\text{RC(=O)N(R}_A\text{)-}$ ” 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.

[0051] An “S-sulfonamido” group refers to a “ $\text{-SO}_2\text{N(R}_A\text{R}_B\text{)-}$ ” 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.

[0052] An “N-sulfonamido” group refers to a “ $\text{RSO}_2\text{N(R}_A\text{)-}$ ” 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.

[0053] 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.

[0054] 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.

[0055] A “nitro” group refers to an “ -NO_2 ” group.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] The terms “amino” and “unsubstituted amino” as used herein refer to a -NH_2 group.

[0062] 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. A mono-substituted amine group can include, for example, a mono-alkylamine group, a mono- $\text{C}_1\text{-C}_6$ alkylamine group, a mono-arylamine group, a mono- $\text{C}_6\text{-C}_{10}$ arylamine group and the like. Examples of mono-substituted amine groups include, but are not limited to, -NH(methyl) , -NH(phenyl) and the like.

[0063] A “di-substituted amine” group refers to a “ $\text{-NR}_A\text{R}_B$ ” 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. A di-substituted amine group can include, for example, a di-alkylamine group, a di- $\text{C}_1\text{-C}_6$ alkylamine group, a di-arylamine group, a di- $\text{C}_6\text{-C}_{10}$ arylamine group and the like. Examples of di-substituted amine groups include, but are not limited to, -N(methyl)_2 , $\text{-N(phenyl)(methyl)}$, -N(ethyl)(methyl) and the like.

[0064] As used herein, “mono-substituted amine(alkyl)” group refers to a mono-substituted amine as provided herein connected, as a substituent, via a lower alkylene group. A mono-substituted amine(alkyl) may be substituted or unsubstituted. A mono-substituted amine(alkyl) group can include, for example, a mono-alkylamine(alkyl) group, a mono- $\text{C}_1\text{-C}_6$ alkylamine($\text{C}_1\text{-C}_6$ alkyl) group, a mono-arylamine(alkyl) group, a

mono-C₆-C₁₀ arylamine(C₁-C₆ alkyl) group and the like. Examples of mono-substituted amine(alkyl) groups include, but are not limited to, -CH₂NH(methyl), -CH₂NH(phenyl), -CH₂CH₂NH(methyl), -CH₂CH₂NH(phenyl) and the like.

[0065] As used herein, “di-substituted amine(alkyl)” group refers to a di-substituted amine as provided herein connected, as a substituent, via a lower alkylene group. A di-substituted amine(alkyl) may be substituted or unsubstituted. A di-substituted amine(alkyl) group can include, for example, a dialkylamine(alkyl) group, a di-C₁-C₆ alkylamine(C₁-C₆ alkyl) group, a di-arylamine(alkyl) group, a di-C₆-C₁₀ arylamine(C₁-C₆ alkyl) group and the like. Examples of di-substituted amine(alkyl) groups include, but are not limited to, -CH₂N(methyl)₂, -CH₂N(phenyl)(methyl), -NCH₂(ethyl)(methyl), -CH₂CH₂N(methyl)₂, -CH₂CH₂N(phenyl)(methyl), -NCH₂CH₂(ethyl)(methyl) and the like.

[0066] 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, “C₁-C₃ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0067] 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.”

[0068] 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-toluensulfonic, 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, C₁-C₇ 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, NH₂), the nitrogen-based group can be associated with a positive charge (for example, NH₂ can become NH₃⁺) and the positive charge can be balanced by a negatively charged counterion (such as Cl⁻).

[0069] Latently infected HIV cells harbor transcriptionally silent virus that may still replicate to produce active HIV. The term “HIV latency reversing agent” refers to an agent (including small molecules and proteins) that stimulates HIV transcription, converting latently infected HIV cells into cells expressing replicating HIV. HIV latency reversing agents include, but are not limited to protein kinase C agonists (such as prostratin, bryostatin-1 and ingenol), PD-1 inhibitors (such as nivolumab, pembrolizumab, BGB-A317, pidilizumab, AMP-224, AMP-514, PDR001, REGN2810 and MEDI0680), PD-L1 inhibitors (such as atezolizumab, durvalumab, avelumab and BMS-936559), HDAC inhibitors (such as vorinostat, panobinostat, romidepsin and valproic acid), phorbol esters (such as phorbol 12-myristate-13-acetate and (S)-tert-butyl-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate) and bromodomain inhibitors (such as JQ1, I-BET762, OTX015, I-BET151, CPI203, PFI-1, MS436, CPI-0610, RVX2135, FT-1101, BAY1238097, INCB054329, TEN-010, GSK2820151, ZEN003694, BAY-299, BMS-986158, ABBV-075 and GS-5829).

[0070] The term “Bcl protein inhibitor” refers to an agent (including small molecules and proteins) that inhibit the binding of an anti-apoptotic Bcl protein (such as Bcl-2, Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1) to a pro-apoptotic Bcl protein (such as Bak, Bax, Bim, Bid, tBid, Bad, Bik, PUMA, Bnip-1, Hrk, Bmf and Noxa). Bcl protein inhibitors include, but are not limited to venetoclax, navitoclax, obatoclax, S55746, APG-2575, ABT-737,

AMG176, AZD5991 and APG-1252. Additional Bcl protein inhibitors include, but are not limited to, compounds disclosed in PCT Application Publication Nos. WO2017/132474, WO 2014/113413 and WO 2013/110890, U.S. Patent Application Publication No. 2015/0051189 and Chinese Patent Application No. CN 106565607, which are each incorporated herein by reference for the limited purpose of disclosing additional Bcl protein inhibitors. As will be understood by those of skill in the art, there are numerous methods of evaluating protein binding interactions, including, but not limited to co-immunoprecipitation, fluorescence resonance energy transfer (FRET), surface plasmon resonance (SPR) and fluorescence polarization/anisotropy.

[0071] 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.

[0072] 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).

[0073] 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.

[0074] 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.

[0075] 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.

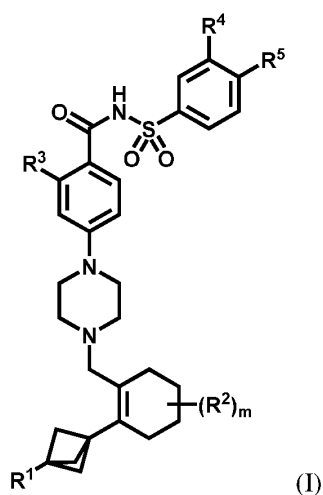
[0076] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' '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.

[0077] 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.

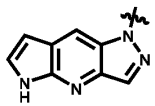
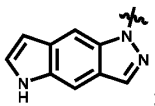
Compounds

[0078] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



wherein: R^1 can be selected from hydrogen, halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6

cycloalkyl, a substituted or unsubstituted C₁-C₆ alkoxy, an unsubstituted mono-C₁-C₆ alkylamine and an unsubstituted di-C₁-C₆ alkylamine; each R² can be independently selected from halogen, a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl; R³ can be selected from

hydrogen, halogen, X-R^{3A},  and ; R^{3A} can be a substituted or unsubstituted 5 to 10 membered heteroaryl; R⁴ can be selected from NO₂, S(O)R⁶, SO₂R⁶, halogen, cyano and an unsubstituted C₁-C₆ haloalkyl; R⁵ can be selected from -X¹-(Alk¹)_n-R⁷ and -X²(CHR⁸)-(Alk²)_p-X³-R⁹; Alk¹ and Alk² can be independently selected from an unsubstituted C₁-C₄ alkylene and a C₁-C₄ alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C₁-C₃ alkyl and an unsubstituted C₁-C₃ haloalkyl; R⁶ can be selected from a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl; R⁷ can be selected from a substituted or unsubstituted C₁-C₆ alkoxy, a substituted or unsubstituted C₃-C₁₀ cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, an amino group, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido; R⁸ can be selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl), a substituted or unsubstituted di-C₁-C₆ alkylamine(C₁-C₆ alkyl) and a substituted or unsubstituted mono-C₁-C₆ alkylamine(C₁-C₆ alkyl); R⁹ can be selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted monocyclic or bicyclic C₆-C₁₀ aryl; m can be 0, 1, 2 and 3; n and p can be independently selected from 0 and 1; X, X¹, X² and X³ can be independently selected from -O-, -S- and -NH-; and wherein when m is 2 or 3, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted C₃-C₆ cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl.

[0079] In some embodiments, R¹ can be halogen, for example, fluoro, chloro, bromo or iodo. In some embodiments, R¹ can be fluoro. In some embodiments, R¹ can be chloro. In some embodiments, R¹ can be hydrogen.

[0080] In some embodiments, R^1 can be a substituted or unsubstituted C_1 - C_6 alkyl. For example, in some embodiments, R^1 can be a substituted C_1 - C_6 alkyl. In other embodiments, R^1 can be an unsubstituted C_1 - C_6 alkyl. Examples of suitable C_1 - C_6 alkyl groups include, but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained). In some embodiments, R^1 can be an unsubstituted methyl or an unsubstituted ethyl.

[0081] In some embodiments, R^1 can be a substituted or unsubstituted C_1 - C_6 haloalkyl, for example, a substituted or unsubstituted mono-halo C_1 - C_6 alkyl, a substituted or unsubstituted di-halo C_1 - C_6 alkyl, a substituted or unsubstituted tri-halo C_1 - C_6 alkyl, a substituted or unsubstituted tetra-halo C_1 - C_6 alkyl or a substituted or unsubstituted penta-halo C_1 - C_6 alkyl. In some embodiments, R^1 can be an unsubstituted $-CHF_2$, $-CF_3$, $-CH_2CF_3$ or $-CF_2CH_3$.

[0082] In some embodiments, R^1 can be a substituted or unsubstituted monocyclic or bicyclic C_3 - C_6 cycloalkyl. For example, in some embodiments, R^1 can be a substituted monocyclic C_3 - C_6 cycloalkyl. In other embodiments, R^1 can be an unsubstituted monocyclic C_3 - C_6 cycloalkyl. Examples of suitable monocyclic or bicyclic C_3 - C_6 cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, [1.1.1]bicyclopentyl and cyclohexyl.

[0083] In some embodiments, R^1 can be a substituted or unsubstituted C_1 - C_6 alkoxy. For example, in some embodiments, R^1 can be a substituted C_1 - C_6 alkoxy. In other embodiments, R^1 can be an unsubstituted C_1 - C_6 alkoxy. Examples of suitable C_1 - C_6 alkoxy groups include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained) and hexoxy (branched and straight-chained). In some embodiments, R^1 can be an unsubstituted methoxy or an unsubstituted ethoxy.

[0084] In some embodiments, R^1 can be an unsubstituted mono- C_1 - C_6 alkylamine, for example, methylamine, ethylamine, n-propylamine, isopropylamine, n-butylamine, isobutylamine, tert-butylamine, pentylamine (branched and straight-chained) and hexylamine (branched and straight-chained). In some embodiments, R^1 can be methylamine or ethylamine.

[0085] In some embodiments, R^1 can be an unsubstituted di- C_1 - C_6 alkylamine. In some embodiments, each C_1 - C_6 alkyl in the di- C_1 - C_6 alkylamine is the same. In other embodiments, each C_1 - C_6 alkyl in the di- C_1 - C_6 alkylamine is different. Examples of suitable di- C_1 - C_6 alkylamine groups include, but are not limited to di-methylamine, di-ethylamine, (methyl)(ethyl)amine, (methyl)(isopropyl)amine and (ethyl)(isopropyl)amine.

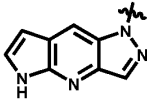
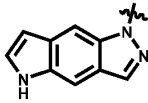
[0086] In some embodiments, m can be 0. When m is 0, those skilled in the art understand that the ring to which R^2 is attached is unsubstituted. In some embodiments, m can be 1. In some embodiments, m can be 2. In some embodiments, m can be 3.

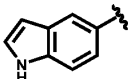
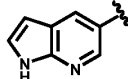
[0087] In some embodiments, one R^2 can be an unsubstituted C_1 - C_6 alkyl (for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained)) and any other R^2 , if present, can be independently selected from halogen (for example, fluoro or chloro), a substituted or unsubstituted C_1 - C_6 alkyl (such as those described herein), a substituted or unsubstituted C_1 - C_6 haloalkyl (such as those described herein) and a substituted or unsubstituted monocyclic or bicyclic C_3 - C_6 cycloalkyl (such as those described herein). In some embodiments, each R^2 can be independently selected from an unsubstituted C_1 - C_6 alkyl, such as those described herein.

[0088] In some embodiments, m can be 2; and each R^2 can be geminal. In some embodiments, m can be 2; and each R^2 can be vicinal. In some embodiments, m can be 2; and each R^2 can be an unsubstituted methyl. In some embodiments, m can be 2; and each R^2 can be a geminal unsubstituted methyl.

[0089] In some embodiments, two R^2 groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted monocyclic C_3 - C_6 cycloalkyl. For example, in some embodiments, two R^2 groups can be taken together with the atom(s) to which they are attached to form a substituted monocyclic C_3 - C_6 cycloalkyl, such as those described herein. In other embodiments, two R^2 groups can be taken together with the atom(s) to which they are attached to form an unsubstituted monocyclic C_3 - C_6 cycloalkyl, such as those described herein. In some embodiments, two R^2 groups can be taken together with the atom to which they are attached to form an unsubstituted cyclopropyl.

[0090] In some embodiments, two R^2 groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted monocyclic 3 to 6 membered heterocyclyl. For example, in some embodiments, two R^2 groups can be taken together with the atom(s) to which they are attached to form a substituted monocyclic 3 to 6 membered heterocyclyl. In other embodiments, two R^2 groups can be taken together with the atom(s) to which they are attached to form an unsubstituted monocyclic 3 to 6 membered monocyclic heterocyclyl. In some embodiments, the substituted monocyclic 3 to 6 membered heterocyclyl can be substituted on one or more nitrogen atoms. Examples of suitable substituted or unsubstituted monocyclic 3 to 6 membered heterocyclyl groups include, but are not limited to aziridine, oxirane, azetidine, oxetane, pyrrolidine, tetrahydrofuran, imidazoline, pyrazolidine, piperidine, tetrahydropyran, piperazine, morpholine, thiomorpholine and dioxane.

[0091] In some embodiments, R^3 can be . In some embodiments, R^3 can be .

[0092] In some embodiments, R^3 can be $X-R^{3A}$. In some embodiments, X can be $-O-$. In some embodiments, X can be $-S-$. In some embodiments, X can be $-NH-$. In some embodiments, R^{3A} can be . In some embodiments, R^{3A} can be .

[0093] In some embodiments, R^{3A} can be a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments, R^{3A} can be a substituted 5 to 10 membered monocyclic heteroaryl. In other embodiments, R^{3A} can be a substituted 5 to 10 membered bicyclic heteroaryl. In some embodiments, R^{3A} can be an unsubstituted 5 to 10 membered monocyclic heteroaryl. In other embodiments, R^{3A} can be an unsubstituted 5 to 10 membered bicyclic heteroaryl. Examples of suitable substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl groups include, but are not limited to pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazole, pyridine, pyridazine, pyrimidine, pyrazine, pyrrolo-pyrroles, pyrrolo-furans, pyrrolo-thiophenes, indole, isoindole,

indolizine, indazole, benzimidazole, azaindoles, azaindazoles, purine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, quinoline, isoquinoline, quinoxaline, phthalazine, quinoxaline, cinnoline, 1,8-naphthyridine, pyrido-pyrimidines and pteridine.

[0094] In some embodiments, R^3 can be hydrogen. In some embodiments, R^3 can be halogen. In some embodiments, R^3 can be fluoro or chloro.

[0095] In some embodiments, R^4 can be NO_2 . In some embodiments, R^4 can be cyano. In some embodiments, R^4 can be halogen.

[0096] In some embodiments, R^4 can be an unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl, such as those described herein. In some embodiments, R^4 can be -CF_3 .

[0097] In some embodiments, R^4 can be $\text{S(O)}R^6$. In some embodiments, R^4 can be SO_2R^6 . In some embodiments, R^4 can be SO_2CF_3 .

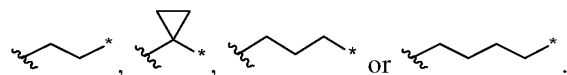
[0098] In some embodiments, R^6 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl. For example, in some embodiments, R^6 can be a substituted $\text{C}_1\text{-C}_6$ alkyl, such as those described herein. In other embodiments, R^6 can be an unsubstituted $\text{C}_1\text{-C}_6$ alkyl, such as those described herein.

[0099] In some embodiments, R^6 can be a substituted or unsubstituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl. For example, in some embodiments, R^6 can be a substituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl. In other embodiments, R^6 can be an unsubstituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl. Examples of suitable monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, [1.1.1]bicyclopentyl and cyclohexyl.

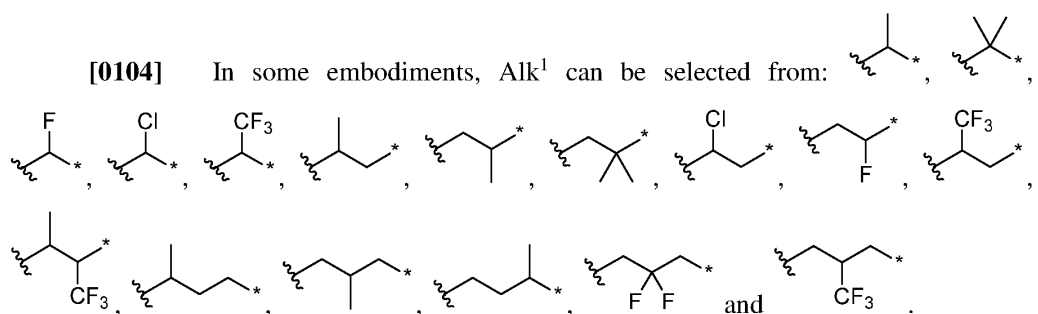
[0100] In some embodiments, R^6 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl, such as those described herein. In some embodiments, R^6 can be -CF_3 .

[0101] In some embodiments, R^5 can be $\text{-X}^1\text{-(Alk}^1)_n\text{-R}^7$. In some embodiments, X^1 can be -O- . In some embodiments, X^1 can be -S- . In some embodiments, X^1 can be -NH- .

[0102] In some embodiments, Alk^1 can be unsubstituted $\text{-(CH}_2\text{)}_{1-4}\text{-}^*$ for which “*” represents the point of attachment to R^7 . In some embodiments, Alk^1 can be .



[0103] In some embodiments, Alk¹ can be a substituted $\overset{\text{R}^7}{\text{C}}_1\text{-C}_4$ alkylene* for which “*” represents the point of attachment to R⁷. For example, in some embodiments, Alk¹ can be a substituted methylene, a substituted ethylene, a substituted propylene or a substituted butylene. In some embodiments, Alk¹ can be mono-substituted, di-substituted or tri-substituted. In some embodiments, Alk¹ can be mono-substituted with a halogen (such as fluoro or chloro) or unsubstituted C₁-C₃ alkyl, such as those described herein. In other embodiments, Alk¹ can be mono-substituted unsubstituted C₁-C₃ haloalkyl, such as those described herein. In some embodiments, Alk¹ can be mono-substituted with fluoro or unsubstituted methyl. In some embodiments, Alk¹ can be di-substituted with one fluoro and one unsubstituted C₁-C₃ alkyl, such as those described herein. In other embodiments, Alk¹ can be di-substituted with one unsubstituted C₁-C₃ haloalkyl, such as those described herein, and one unsubstituted C₁-C₃ alkyl, such as those described herein. In some embodiments, Alk¹ can be di-substituted with one fluoro and one unsubstituted methyl. In some embodiments, Alk¹ can be di-substituted with two independently selected unsubstituted C₁-C₃ alkyl groups, such as those described herein. In some embodiments, Alk¹ can be di-substituted with unsubstituted methyl.



[0105] In some embodiments, n can be 0. When n is 0, those skilled in the art understand that X^1 is directly connected to R^7 . In some embodiments, n can be 1.

[0106] In some embodiments, R^7 can be a substituted or unsubstituted mono-substituted amine group. For example, R^7 can be an amino group mono-substituted with a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_2 - C_6 alkenyl, a substituted or unsubstituted C_2 - C_6 alkynyl, a substituted or unsubstituted monocyclic or bicyclic C_3 - C_6 cycloalkyl, a substituted or unsubstituted monocyclic or bicyclic C_6 - C_{10} aryl, a

substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl, a substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl, a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl(unsubstituted C₁-C₆ alkyl), a substituted or unsubstituted monocyclic or bicyclic C₆-C₁₀ aryl(unsubstituted C₁-C₆ alkyl), a substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl(unsubstituted C₁-C₆ alkyl) or a substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl(unsubstituted C₁-C₆ alkyl). Examples of suitable mono-substituted amine groups include, but are not limited to -NH(methyl), -NH(isopropyl), -NH(cyclopropyl), -NH(phenyl), -NH(benzyl) and -NH(pyridine-3-yl).

[0107] In some embodiments, R⁷ can be a substituted or unsubstituted di-substituted amine group. For example, R⁷ can be an amino group substituted with two substituents independently selected from a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₂-C₆ alkenyl, a substituted or unsubstituted C₂-C₆ alkynyl, a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl, a substituted or unsubstituted monocyclic or bicyclic C₆-C₁₀ aryl, a substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl, a substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl, a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl(unsubstituted C₁-C₆ alkyl), a substituted or unsubstituted monocyclic or bicyclic C₆-C₁₀ aryl(unsubstituted C₁-C₆ alkyl), a substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl(unsubstituted C₁-C₆ alkyl) or a substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl(unsubstituted C₁-C₆ alkyl). In some embodiments the two substituents can be the same. In other embodiments the two substituents can be different. Examples of suitable di-substituted amine groups include, but are not limited to, -N(methyl)₂, -N(ethyl)₂, -N(isopropyl)₂, -N(benzyl)₂, -N(ethyl)(methyl), -N(isopropyl)(methyl), -N(ethyl)(isopropyl), -N(phenyl)(methyl) and -N(benzyl)(methyl).

[0108] In some embodiments, R⁷ can be selected from a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido.

[0109] In some embodiments, R⁷ can be a substituted or unsubstituted C₃-C₁₀ cycloalkyl. In some embodiments, R⁷ can be a substituted or unsubstituted monocyclic C₃-

C₁₀ cycloalkyl. In other embodiments, R⁷ can be a substituted or unsubstituted bicyclic C₃-C₁₀ cycloalkyl, for example, a bridged, fused or spiro C₃-C₁₀ cycloalkyl. Suitable substituted or unsubstituted monocyclic or bicyclic C₃-C₁₀ cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3.3]heptyl, spiro[2.3]hexyl, spiro[3.4]octyl, spiro[3.5]nonyl, spiro[3.6]decyl, spiro[2.4]heptyl, spiro[4.4]nonyl, spiro[4.5]decyl, spiro[2.5]octyl, spiro[3.5]nonyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, decahydronaphthalenyl, octahydro-1H-indenyl, octahydropentalenyl, bicyclo[4.2.0]octyl, bicyclo[2.1.0]pentyl and bicyclo[3.2.0]heptyl.

[0110] In some embodiments, R⁷ can be a substituted or unsubstituted C₆-C₁₀ spirocycloalkyl. In some embodiments, R⁷ can be a substituted C₆-C₁₀ spirocycloalkyl. In other embodiments, R⁷ can be an unsubstituted C₆-C₁₀ spirocycloalkyl. In some embodiments, R⁷ can be a substituted or unsubstituted -cyclopropyl-cyclobutyl spiroalkyl, -cyclopropyl-cyclopentyl spiroalkyl, -cyclopropyl-cyclohexyl spiroalkyl, -cyclopropyl-cycloheptyl spiroalkyl, -cyclopropyl-cyclooctyl spiroalkyl, -cyclobutyl-cyclopropyl spiroalkyl, -cyclobutyl-cyclobutyl spiroalkyl, -cyclobutyl-cyclopentyl spiroalkyl, -cyclobutyl-cyclohexyl spiroalkyl, -cyclobutyl-cycloheptyl spiroalkyl, -cyclopentyl-cyclopropyl spiroalkyl, -cyclopentyl-cyclobutyl spiroalkyl, -cyclopentyl-cyclopentyl spiroalkyl, cyclopentyl-cyclohexyl spiroalkyl, -cyclohexyl-cyclopropyl spiroalkyl, -cyclohexyl-cyclobutyl spiroalkyl, -cyclohexyl-cyclopentyl spiroalkyl, -cycloheptyl-cyclopropyl spiroalkyl, -cycloheptyl-cyclobutyl spiroalkyl or -cyclooctyl-cyclopropyl spiroalkyl.

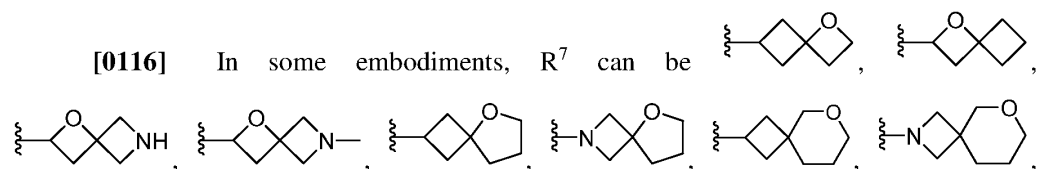
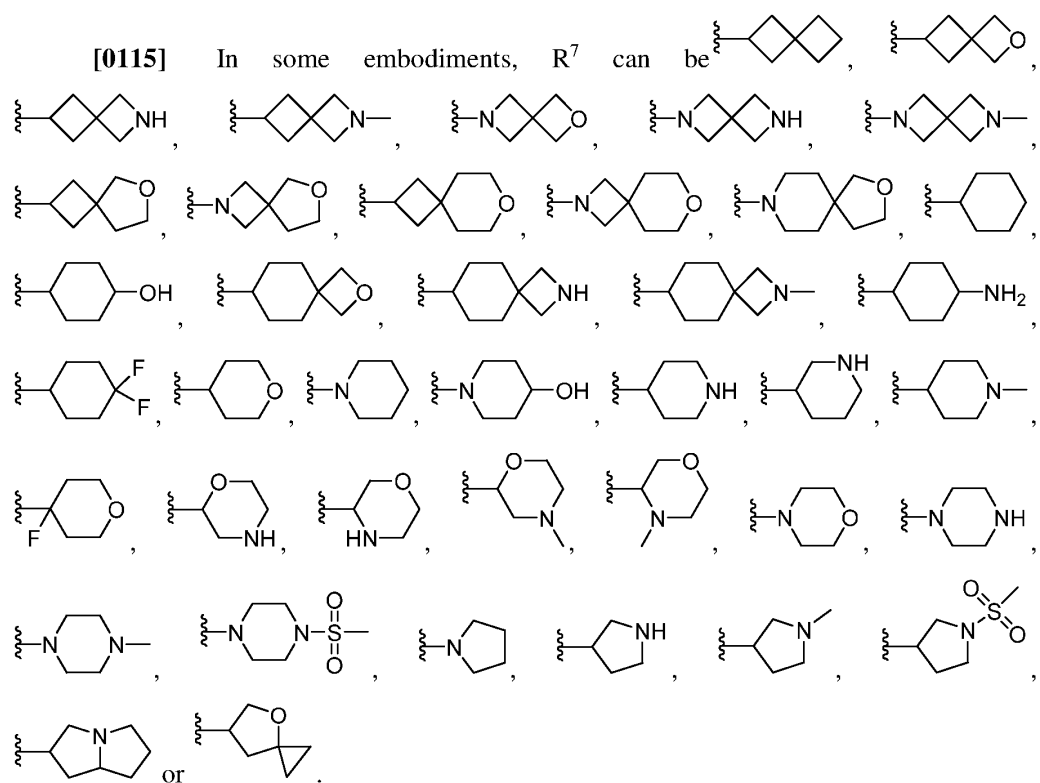
[0111] In some embodiments, R⁷ can be a substituted or unsubstituted 3 to 10 membered heterocyclyl. In some embodiments, R⁷ can be a substituted 3 to 10 membered heterocyclyl. In other embodiments, R⁷ can be an unsubstituted 3 to 10 membered heterocyclyl. In some embodiments, R⁷ can be a substituted or unsubstituted monocyclic 3 to 10 membered heterocyclyl. In other embodiments, R⁷ can be a substituted or unsubstituted bicyclic 5 to 10 membered heterocyclyl, for example, a fused, bridged or spiro 5 to 10 membered heterocyclyl. Suitable substituted or unsubstituted 3 to 10 membered heterocyclyl groups include, but are not limited to, aziridine, oxirane, azetidine, oxetane, pyrrolidine,

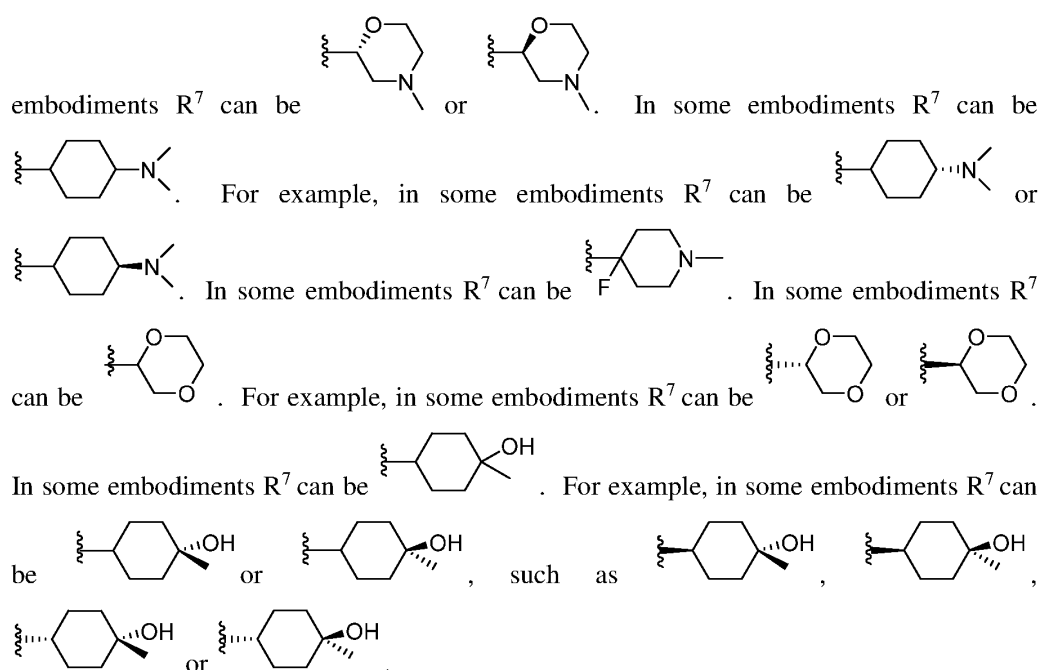
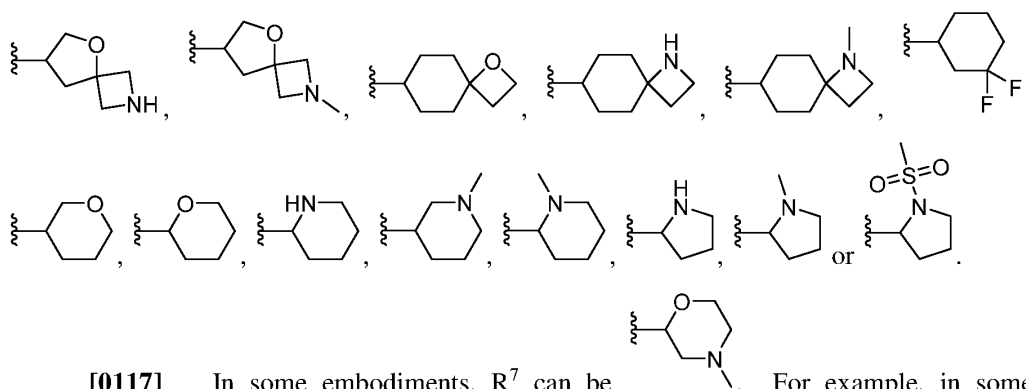
tetrahydrofuran, imidazoline, pyrazolidine, piperidine, tetrahydropyran, piperazine, morpholine, thiomorpholine, dioxane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2-azaspiro[3.4]octane, 6-oxaspiro[3.4]octane, 6-oxa-2-azaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane and 2-oxa-8-azaspiro[4.5]decane. In some embodiments, the substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl can be connected to the rest of the molecule through a nitrogen atom. In other embodiments, the substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl can be connected to the rest of the molecule through a carbon atom. In some embodiments, the substituted monocyclic or bicyclic 3 to 10 membered heterocyclyl can be substituted on one or more nitrogen atoms.

[0112] In some embodiments, R^7 can be a substituted or unsubstituted 6 to 10 membered spiro heterocyclyl. In some embodiments, R^7 can be a substituted 6 to 10 membered spiro heterocyclyl. In other embodiments, R^7 can be an unsubstituted 6 to 10 membered spiro heterocyclyl. In some embodiments, R^7 can be a substituted or unsubstituted azaspirohexane, azaspiroheptane, azaspirooctane, oxaspirohexane, oxaspiroheptane, oxaspirooctane, diazaspirohexane, diazaspiroheptane, diazaspirooctane, dioxaspirohexane, dioxaspiroheptane, dioxaspirooctane, oxa-azaspirohexane, oxa-azaspiroheptane or oxa-azaspirooctane. Suitable substituted or unsubstituted 3 to 10 membered heterocyclyl groups include, but are not limited to, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2-azaspiro[3.4]octane, 6-oxaspiro[3.4]octane, 6-oxa-2-azaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane and 2-oxa-8-azaspiro[4.5]decane. In some embodiments, the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl can be connected to the rest of the molecule through a nitrogen atom. In other embodiments, the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl can be connected to the rest of the molecule through a carbon atom. In some embodiments, the substituted 6 to 10 membered spiroheterocyclyl can be substituted on one or more nitrogen atoms.

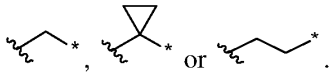
[0113] In some embodiments, R^7 can be hydroxy or amino.

[0114] In some embodiments, R^7 can be unsubstituted. In other embodiments, R^7 can be substituted. In some embodiments, R^7 can be substituted with 1 or 2 substituents independently selected from an unsubstituted C_1 - C_6 alkyl (such as those described herein), an unsubstituted C_1 - C_6 alkoxy (such as those described herein), fluoro, chloro, hydroxy and - SO_2 -(unsubstituted C_1 - C_6 alkyl). For example, the C_1 - C_6 alkoxy, C_3 - C_{10} cycloalkyl, 3 to 10 membered heterocyclyl, mono-substituted amine group, di-substituted amine group, N-carbamyl, C-amido and N-amido groups of R^7 can be substituted with 1 or 2 substituents independently selected from any of the aforementioned substituents.

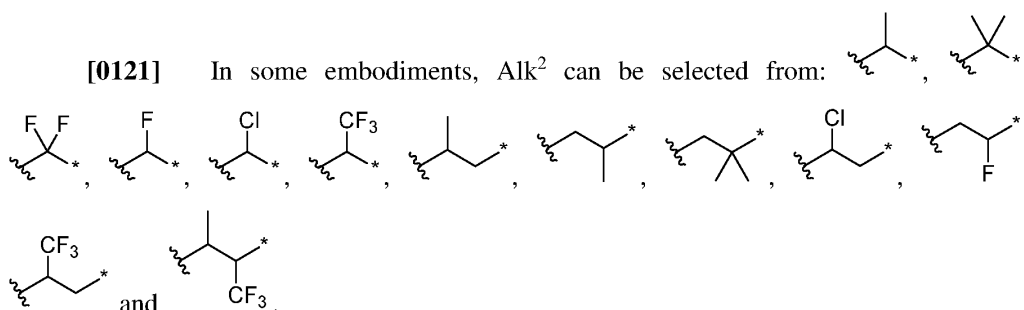




[0118] In some embodiments, R^5 can be $-X^2-(CHR^8)-(Alk^2)_p-X^3-R^9$. In some embodiments, X^2 can be $-O-$. In some embodiments, X^2 can be $-S-$. In some embodiments, X^2 can be $-NH-$. In some embodiments, X^3 can be $-O-$. In some embodiments, X^3 can be $-S-$. In some embodiments, X^3 can be $-NH-$. In some embodiments, X^2 can be $-NH-$ and X^3 can be $-S-$. In some embodiments, X^2 can be $-O-$ and X^3 can be $-S-$. In some embodiments, X^2 can be $-NH-$ and X^3 can be $-O-$. In some embodiments, X^2 can be $-O-$ and X^3 can be $-O-$.

[0119] In some embodiments, Alk^2 can be unsubstituted $-(\text{CH}_2)_{1-4}-^*$ for which “*” represents the point of attachment to X^3 . In some embodiments, Alk^2 can be an unsubstituted methylene, an unsubstituted ethylene, an unsubstituted propylene or an unsubstituted butylene. In some embodiments, Alk^2 can be .

[0120] In some embodiments, Alk^2 can be a substituted $\text{C}_1\text{-C}_4$ alkylene* for which “*” represents the point of attachment to X^3 . In some embodiments, Alk^2 can be a substituted methylene, a substituted ethylene, a substituted propylene or a substituted butylene. In some embodiments, Alk^2 can be mono-substituted, di-substituted or tri-substituted. In some embodiments, Alk^2 can be mono-substituted with fluoro or unsubstituted $\text{C}_1\text{-C}_3$ alkyl, such as those described herein. In some embodiments, Alk^2 can be mono-substituted with fluoro or unsubstituted methyl. In some embodiments, Alk^2 can be di-substituted with one fluoro and one unsubstituted $\text{C}_1\text{-C}_3$ alkyl, such as those described herein. In some embodiments, Alk^2 can be di-substituted with one fluoro and one unsubstituted methyl. In some embodiments, Alk^2 can be di-substituted with two independently selected unsubstituted $\text{C}_1\text{-C}_3$ alkyl, such as those described herein. In some embodiments, Alk^2 can be di-substituted with unsubstituted methyl.



[0122] In some embodiments, p can be 0. When p is 0, those skilled in the art understand that the (CHR^8) group is directly connected to X^3 . In some embodiments, p can be 1.

[0123] In some embodiments, the $\text{C}_1\text{-C}_6$ alkyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl($\text{C}_1\text{-C}_6$ alkyl) of R^8 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl such as those described herein. In some embodiments, the 3 to 10 membered

heterocyclyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) of R⁸ can be monocyclic. In some embodiments, the 3 to 10 membered heterocyclyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) can be bicyclic. In other embodiments, the 3 to 10 membered heterocyclyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) can be connected to the C₁-C₆ alkyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) through a carbon atom. In some embodiments, the 3 to 10 membered heterocyclyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) can be unsubstituted. In other embodiments, the 3 to 10 membered heterocyclyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) can be substituted. In some embodiments, the 3 to 10 membered heterocyclyl of the substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl) can be substituted on one or more nitrogen atoms. Examples of suitable substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl groups of R⁸ include, but are not limited to aziridine, oxirane, azetidine, oxetane, pyrrolidine, tetrahydrofuran, imidazoline, pyrazolidine, piperidine, tetrahydropyran, piperazine, morpholine, thiomorpholine, dioxane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2-azaspiro[3.4]octane, 6-oxaspiro[3.4]octane, 6-oxa-2-azaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane and 2-oxa-8-azaspiro[4.5]decane. In some embodiments, the C₁-C₆ alkyl of R⁸ can be an unsubstituted methyl or an unsubstituted ethyl and the substituted or unsubstituted 3 to 10 membered heterocyclyl of R⁸ can be a piperidine, tetrahydropyran, piperazine, morpholine, thiomorpholine, dioxane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2-azaspiro[3.4]octane, 6-oxaspiro[3.4]octane, 6-oxa-2-azaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane or 2-oxa-8-azaspiro[4.5]decane.

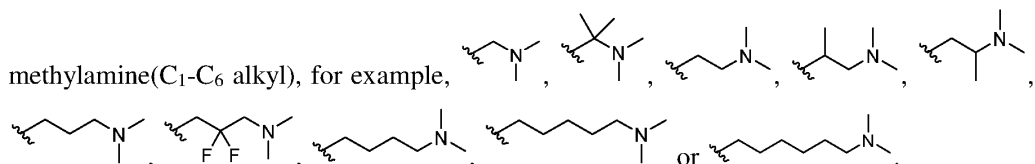
[0124] In some embodiments, R⁸ can be a substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl). In some embodiments, the C₁-C₆ alkyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) of R⁸ can be a substituted or unsubstituted C₁-C₆ alkyl, such as those described herein. In some embodiments, the C₁-C₆ alkyl of the substituted or unsubstituted 6 to 10 membered spiro

heterocyclyl(C₁-C₆ alkyl) can be unsubstituted. In some embodiments, the 6 to 10 membered spiro heterocyclyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be connected to the C₁-C₆ alkyl of R⁸ through a nitrogen atom. In other embodiments, the 6 to 10 membered spiro heterocyclyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be connected to the C₁-C₆ alkyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) through a carbon atom. In some embodiments, the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be unsubstituted. In other embodiments, 6 to 10 membered spiro heterocyclyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be substituted. In some embodiments, the 6 to 10 membered spiro heterocyclyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be substituted on one or more nitrogen atoms. In some embodiments, the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be an azaspirohexane, azaspiroheptane, azaspirooctane, oxaspirohexane, oxaspiroheptane, oxaspirooctane, diazaspirohexane, diazaspiroheptane, diazaspirooctane, dioxaspirohexane, dioxaspiroheptane, dioxaspirooctane, oxa-azaspirohexane, oxa-azaspiroheptane or oxa-azaspirooctane. Examples of suitable substituted or unsubstituted 6 to 10 membered spiro heterocyclyl of R⁸ include, but are not limited to, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2-azaspiro[3.4]octane, 6-oxaspiro[3.4]octane, 6-oxa-2-azaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane and 2-oxa-8-azaspiro[4.5]decane. In some embodiments, the C₁-C₆ alkyl of the substituted or unsubstituted 6 to 10 membered spiro heterocyclyl(C₁-C₆ alkyl) can be an unsubstituted methyl or an unsubstituted ethyl and the 6 to 10 membered spiro heterocyclyl of R⁸ can be an azaspirohexane, azaspiroheptane, azaspirooctane, oxaspirohexane, oxaspiroheptane, oxaspirooctane, diazaspirohexane, diazaspiroheptane, diazaspirooctane, dioxaspirohexane, dioxaspiroheptane, dioxaspirooctane, oxa-azaspirohexane, oxa-azaspiroheptane or oxa-azaspirooctane, for example, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2-azaspiro[3.4]octane, 6-

oxaspiro[3.4]octane, 6-oxa-2-azaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane or 2-oxa-8-azaspiro[4.5]decane.

[0125] In some embodiments, R^8 can be a substituted or unsubstituted di- C_1 - C_6 alkylamine(C_1 - C_6 alkyl), for example, a di- C_1 - C_6 alkylamine(ethyl), di- C_1 - C_6 alkylamine(propyl), di- C_1 - C_6 alkylamine(butyl), di- C_1 - C_6 alkylamine(pentyl) or di- C_1 - C_6 alkylamine(hexyl). In some embodiments, each C_1 - C_6 alkyl group in the di- C_1 - C_6 alkylamine can be the same. In other embodiments, each C_1 - C_6 alkyl group in the di- C_1 - C_6 alkylamine can be different. Suitable substituted or unsubstituted di- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) include, but are not limited to, $-N(\text{methyl})_2$, $-N(\text{ethyl})_2$, $-N(\text{n-propyl})_2$, $-N(\text{isopropyl})_2$, $-N(\text{t-butyl})_2$, $-N(\text{ethyl})(\text{methyl})$, $-N(\text{isopropyl})(\text{methyl})$, $-N(\text{t-butyl})(\text{methyl})$ and $-N(\text{isopropyl})(\text{ethyl})$; each connected to a substituted or unsubstituted C_1 - C_6 alkyl group.

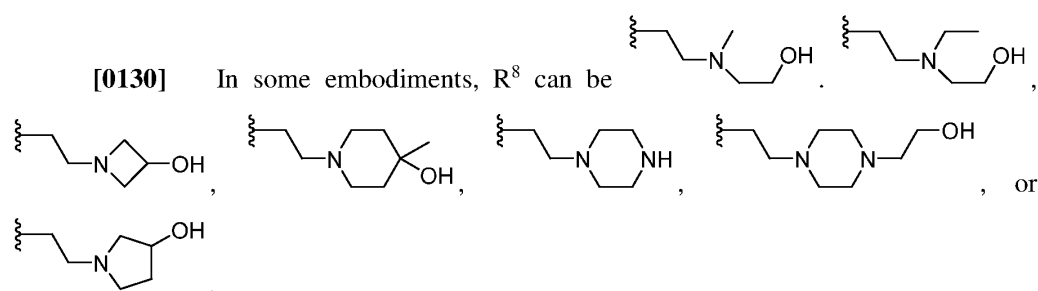
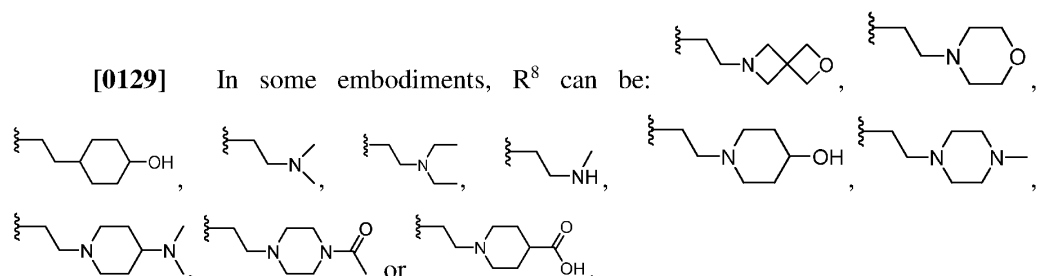
[0126] In some embodiments, R^8 can be a substituted or unsubstituted di-methylamine(C_1 - C_6 alkyl), for example,



[0127] In some embodiments, R^8 can be a substituted or unsubstituted mono- C_1 - C_6 alkylamine(C_1 - C_6 alkyl), for example, a substituted or unsubstituted mono- C_1 - C_6 alkylamine(ethyl), mono- C_1 - C_6 alkylamine(propyl), mono- C_1 - C_6 alkylamine(butyl), mono- C_1 - C_6 alkylamine(pentyl) or mono- C_1 - C_6 alkylamine(hexyl). In some embodiments, the C_1 - C_6 alkyl of the unsubstituted mono- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) group can be an unsubstituted C_1 - C_6 alkyl, such as those described herein.

[0128] In some embodiments, R^8 can be unsubstituted. In other embodiments, R^8 can be substituted. In some embodiments, R^8 can be substituted with 1 or 2 substituents independently selected from an unsubstituted C_1 - C_6 alkyl (such as those described herein), an unsubstituted C_1 - C_6 alkoxy (such as those described herein), an unsubstituted di- C_1 - C_6 alkylamine (such as those described herein), an unsubstituted acyl(C_1 - C_6 alkyl) (for example, acetyl or benzoyl), an unsubstituted C-carboxy (for example, $-\text{CO}_2\text{H}$, $-\text{CO}_2$ - C_1 - C_6 alkyl, $-\text{CO}_2$ - C_3 - C_6 cycloalkyl or $-\text{CO}_2$ - C_6 - C_{10} aryl), fluoro, chloro and hydroxy. For example, the 3 to 10 membered heterocyclyl(C_1 - C_6 alkyl), di- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) and mono- C_1 -

C₆ alkylamine(C₁-C₆ alkyl) groups of R⁸ can be substituted with 1 or 2 substituents independently selected from any of the aforementioned substituents.



[0131] In some embodiments, R⁹ can be a substituted or unsubstituted monocyclic or bicyclic C₆-C₁₀ aryl. In some embodiments, R⁹ can be a substituted monocyclic or bicyclic C₆-C₁₀ aryl. In other embodiments, R⁹ can be an unsubstituted monocyclic or bicyclic C₆-C₁₀ aryl. In some embodiments, R⁹ can be a substituted phenyl or a substituted naphthyl. In some embodiments, R⁹ can be an unsubstituted phenyl or an unsubstituted naphthyl.

[0132] In some embodiments, R⁹ can be a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments, R⁹ can be a substituted 5 to 10 membered heteroaryl. In other embodiments, R⁹ can be an unsubstituted 5 to 10 membered heteroaryl. In some embodiments, R⁹ can be a monocyclic substituted or unsubstituted 5 to 10 membered heteroaryl. In other embodiments, R⁹ can be a bicyclic substituted or unsubstituted 5 to 10 membered heteroaryl. Suitable substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl include, but are not limited to, pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazole, pyridine, pyridazine, pyrimidine, pyrazine, pyrrolo-pyrroles, pyrrolo-furans, pyrrolo-thiophenes, indole, isoindole, indolizine, indazole, benzimidazole, azaindoles, purine, benzofuran, isobenzofuran, benzothiophene,

isobenzothiophene, quinoline, isoquinoline, quinoxaline, phthalazine, quinazoline, cinnoline, 1,8-naphthyridine, pyrido-pyrimidines and pteridine.

[0133] In some embodiments, R^3 is hydrogen or halogen. For example, an embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0134] R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6 cycloalkyl, a substituted or unsubstituted C_1 - C_6 alkoxy, an unsubstituted mono- C_1 - C_6 alkylamine and an unsubstituted di- C_1 - C_6 alkylamine;

[0135] each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl; or

[0136] when m is 2 or 3, each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C_3 - C_6 cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;

[0137] R^3 is hydrogen or halogen;

[0138] R^4 is selected from the group consisting of NO_2 , $S(O)R^6$, SO_2R^6 , halogen, cyano and an unsubstituted C_1 - C_6 haloalkyl;

[0139] R^5 is selected from the group consisting of $-X^1-(Alk^1)_n-R^7$ and $-X^2(CHR^8)-(Alk^2)_p-X^3-R^9$;

[0140] Alk^1 and Alk^2 are independently selected from an unsubstituted C_1 - C_4 alkylene and a C_1 - C_4 alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C_1 - C_3 alkyl and an unsubstituted C_1 - C_3 haloalkyl;

[0141] R^6 is selected from the group consisting of a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl;

[0142] R^7 is selected from a substituted or unsubstituted C_1 - C_6 alkoxy, a substituted or unsubstituted C_3 - C_{10} cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, amino, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido;

[0143] R^8 is selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl(C_1 - C_6 alkyl), a substituted or unsubstituted di- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) and a substituted or unsubstituted mono- C_1 - C_6 alkylamine(C_1 - C_6 alkyl);

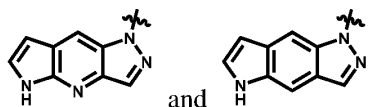
[0144] R^9 is selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted C_6 - C_{10} aryl;

[0145] m is 0, 1, 2 or 3;

[0146] n and p are independently selected from 0 and 1; and

[0147] X^1 , X^2 and X^3 are independently selected from the group consisting of $-O-$, $-S-$ and $-NH-$.

[0148] In some embodiments, R^3 is selected from the group consisting of $X-R^{3A}$,



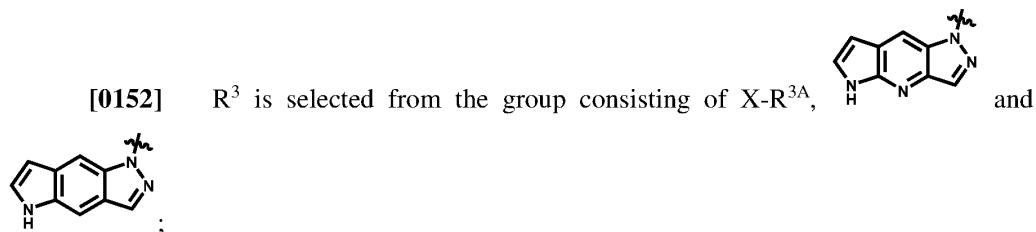
. For example, an embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0149] R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6 cycloalkyl, a substituted or unsubstituted C_1 - C_6 alkoxy, an unsubstituted mono- C_1 - C_6 alkylamine and an unsubstituted di- C_1 - C_6 alkylamine;

[0150] each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl; or

[0151] when m is 2 or 3, each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached form a substituted or

unsubstituted C₃-C₆ cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;



[0153] R^{3A} is a substituted or unsubstituted 5 to 10 membered heteroaryl;

[0154] R⁴ is selected from the group consisting of NO₂, S(O)R⁶, SO₂R⁶, halogen, cyano and an unsubstituted C₁-C₆ haloalkyl;

[0155] R⁵ is selected from the group consisting of -X¹-(Alk¹)_n-R⁷ and -X²(CHR⁸)-(Alk²)_p-X³-R⁹;

[0156] Alk¹ and Alk² are independently selected from an unsubstituted C₁-C₄ alkylene and a C₁-C₄ alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C₁-C₃ alkyl and an unsubstituted C₁-C₃ haloalkyl;

[0157] R⁶ is selected from the group consisting of a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl;

[0158] R⁷ is selected from a substituted or unsubstituted C₁-C₆ alkoxy, a substituted or unsubstituted C₃-C₁₀ cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, amino, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido;

[0159] R⁸ is selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl), a substituted or unsubstituted di-C₁-C₆ alkylamine(C₁-C₆ alkyl) and a substituted or unsubstituted mono-C₁-C₆ alkylamine(C₁-C₆ alkyl);

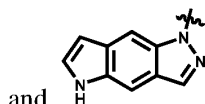
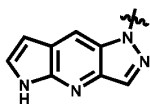
[0160] R⁹ is selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted C₆-C₁₀ aryl;

[0161] m is 0, 1, 2 or 3;

[0162] n and p are independently selected from 0 and 1;

[0163] X, X¹, X² and X³ are independently selected from the group consisting of –O–, –S– and –NH–.

[0164] In some embodiments, R³ is selected from the group consisting of X-R^{3A},

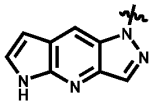


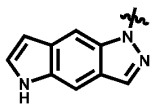
and X^1 and X^2 are –NH–. For example, an embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0165] R¹ is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C₁–C₆ alkyl, a substituted or unsubstituted C₁–C₆ haloalkyl, a substituted or unsubstituted C₃–C₆ cycloalkyl, a substituted or unsubstituted C₁–C₆ alkoxy, an unsubstituted mono-C₁–C₆ alkylamine and an unsubstituted di-C₁–C₆ alkylamine;

[0166] each R² is independently selected from the group consisting of halogen, a substituted or unsubstituted C₁–C₆ alkyl, a substituted or unsubstituted C₁–C₆ haloalkyl and a substituted or unsubstituted C₃–C₆ cycloalkyl; or

[0167] when m is 2 or 3, each R² is independently selected from the group consisting of halogen, a substituted or unsubstituted C₁–C₆ alkyl, a substituted or unsubstituted C₁–C₆ haloalkyl and a substituted or unsubstituted C₃–C₆ cycloalkyl, or two R² groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C₃–C₆ cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;

[0168] R³ is selected from the group consisting of X-R^{3A},  and



[0169] R^{3A} is a substituted or unsubstituted 5 to 10 membered heteroaryl;

[0170] R⁴ is selected from the group consisting of NO₂, S(O)R⁶, SO₂R⁶, halogen, cyano and an unsubstituted C₁–C₆ haloalkyl;

[0171] R⁵ is selected from the group consisting of –X¹–(Alk¹)_n–R⁷ and –X²–(CHR⁸)_p–X³–R⁹;

[0172] Alk^1 and Alk^2 are independently selected from an unsubstituted $\text{C}_1\text{-C}_4$ alkylene and a $\text{C}_1\text{-C}_4$ alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted $\text{C}_1\text{-C}_3$ alkyl and an unsubstituted $\text{C}_1\text{-C}_3$ haloalkyl;

[0173] R^6 is selected from the group consisting of a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, a substituted or unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl and a substituted or unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl;

[0174] R^7 is selected from a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkoxy, a substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, amino, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido;

[0175] R^8 is selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl($\text{C}_1\text{-C}_6$ alkyl), a substituted or unsubstituted di- $\text{C}_1\text{-C}_6$ alkylamine($\text{C}_1\text{-C}_6$ alkyl) and a substituted or unsubstituted mono- $\text{C}_1\text{-C}_6$ alkylamine($\text{C}_1\text{-C}_6$ alkyl);

[0176] R^9 is selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted $\text{C}_6\text{-C}_{10}$ aryl;

[0177] m is 0, 1, 2 or 3;

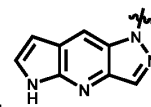
[0178] n and p are independently selected from 0 and 1;

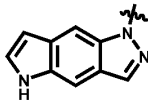
[0179] X^1 and X^2 are $-\text{NH}-$; and

[0180] X and X^3 are independently selected from the group consisting of $-\text{O}-$, $-\text{S}-$ and $-\text{NH}-$.

[0181] In some embodiments, R^1 is as described above with the proviso that it is

not $-\text{CH}_2\text{F}$, $-\text{CHF}_2$ or $-\text{CF}_3$; R^3 is selected from the group consisting of X-R^{3A} ,

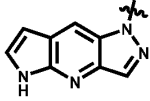
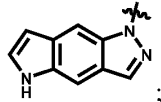


and ; and X^1 and X^2 are $-\text{NH}-$. For example, an embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0182] R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6 cycloalkyl, a substituted or unsubstituted C_1 - C_6 alkoxy, an unsubstituted mono- C_1 - C_6 alkylamine and an unsubstituted di- C_1 - C_6 alkylamine, with the proviso that R^1 is not $-CH_2F$, $-CHF_2$ or $-CF_3$;

[0183] each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl; or

[0184] when m is 2 or 3, each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C_3 - C_6 cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;

[0185] R^3 is selected from the group consisting of $X-R^{3A}$,  and  ;

[0186] R^{3A} is a substituted or unsubstituted 5 to 10 membered heteroaryl;

[0187] R^4 is selected from the group consisting of NO_2 , $S(O)R^6$, SO_2R^6 , halogen, cyano and an unsubstituted C_1 - C_6 haloalkyl;

[0188] R^5 is selected from the group consisting of $-X^1-(Alk^1)_n-R^7$ and $-X^2(CHR^8)-(Alk^2)_p-X^3-R^9$;

[0189] Alk^1 and Alk^2 are independently selected from an unsubstituted C_1 - C_4 alkylene and a C_1 - C_4 alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C_1 - C_3 alkyl and an unsubstituted C_1 - C_3 haloalkyl;

[0190] R^6 is selected from the group consisting of a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl;

[0191] R^7 is selected from a substituted or unsubstituted C_1 - C_6 alkoxy, a substituted or unsubstituted C_3 - C_{10} cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, amino, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido;

[0192] R^8 is selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl(C_1 - C_6 alkyl), a substituted or unsubstituted di- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) and a substituted or unsubstituted mono- C_1 - C_6 alkylamine(C_1 - C_6 alkyl);

[0193] R^9 is selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted C_6 - C_{10} aryl;

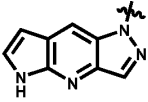
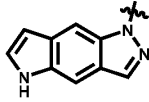
[0194] m is 0, 1, 2 or 3;

[0195] n and p are independently selected from 0 and 1;

[0196] X^1 and X^2 are $-NH-$; and

[0197] X and X^3 are independently selected from the group consisting of $-O-$, $-S-$ and $-NH-$.

[0198] In some embodiments, R^1 is $-CH_2F$, $-CHF_2$ or $-CF_3$; R^3 is selected from the

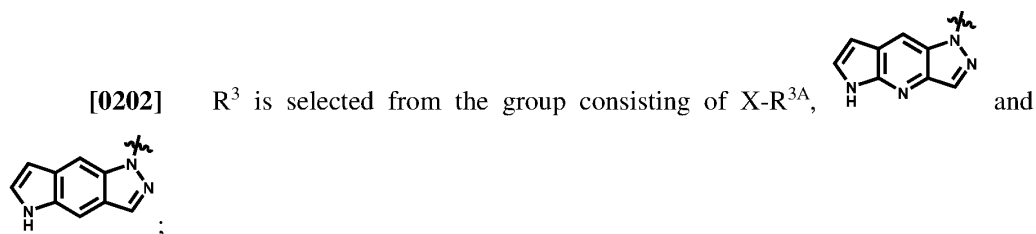
group consisting of $X-R^{3A}$,  and ; and X^1 and X^2 are $-NH-$. For example, an embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0199] R^1 is $-CH_2F$, $-CHF_2$ or $-CF_3$;

[0200] each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl; or

[0201] when m is 2 or 3, each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached form a substituted or

unsubstituted C₃-C₆ cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;



[0203] R^{3A} is a substituted or unsubstituted 5 to 10 membered heteroaryl;

[0204] R⁴ is selected from the group consisting of NO₂, S(O)R⁶, SO₂R⁶, halogen, cyano and an unsubstituted C₁-C₆ haloalkyl;

[0205] R⁵ is selected from the group consisting of -X¹-(Alk¹)_n-R⁷ and -X²(CHR⁸)-(Alk²)_p-X³-R⁹;

[0206] Alk¹ and Alk² are independently selected from an unsubstituted C₁-C₄ alkylene and a C₁-C₄ alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C₁-C₃ alkyl and an unsubstituted C₁-C₃ haloalkyl;

[0207] R⁶ is selected from the group consisting of a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl;

[0208] R⁷ is selected from a substituted or unsubstituted C₁-C₆ alkoxy, a substituted or unsubstituted C₃-C₁₀ cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, amino, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido;

[0209] R⁸ is selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl(C₁-C₆ alkyl), a substituted or unsubstituted di-C₁-C₆ alkylamine(C₁-C₆ alkyl) and a substituted or unsubstituted mono-C₁-C₆ alkylamine(C₁-C₆ alkyl);

[0210] R⁹ is selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted C₆-C₁₀ aryl;

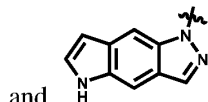
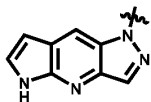
[0211] m is 0, 1, 2 or 3;

[0212] n and p are independently selected from 0 and 1;

[0213] X^1 and X^2 are $-NH-$; and

[0214] X and X^3 are independently selected from the group consisting of $-O-$, $-S-$ and $-NH-$.

[0215] In some embodiments, R^3 is selected from the group consisting of $X-R^{3A}$,

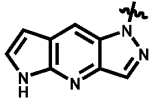


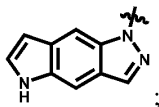
and X^1 and X^2 are $-O-$. For example, an embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0216] R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl, a substituted or unsubstituted C_3-C_6 cycloalkyl, a substituted or unsubstituted C_1-C_6 alkoxy, an unsubstituted mono- C_1-C_6 alkylamine and an unsubstituted di- C_1-C_6 alkylamine;

[0217] each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl and a substituted or unsubstituted C_3-C_6 cycloalkyl; or

[0218] when m is 2 or 3, each R^2 is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl and a substituted or unsubstituted C_3-C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C_3-C_6 cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocycle;

[0219] R^3 is selected from the group consisting of $X-R^{3A}$,  and



[0220] R^{3A} is a substituted or unsubstituted 5 to 10 membered heteroaryl;

[0221] R^4 is selected from the group consisting of NO_2 , $S(O)R^6$, SO_2R^6 , halogen, cyano and an unsubstituted C_1-C_6 haloalkyl;

[0222] R^5 is selected from the group consisting of $-X^1-(Alk^1)_n-R^7$ and $-X^2(CHR^8)-(Alk^2)_p-X^3-R^9$;

[0223] Alk^1 and Alk^2 are independently selected from an unsubstituted C_1-C_4 alkylene and a C_1-C_4 alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C_1-C_3 alkyl and an unsubstituted C_1-C_3 haloalkyl;

[0224] R^6 is selected from the group consisting of a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl and a substituted or unsubstituted C_3-C_6 cycloalkyl;

[0225] R^7 is selected from a substituted or unsubstituted C_1-C_6 alkoxy, a substituted or unsubstituted C_3-C_{10} cycloalkyl, a substituted or unsubstituted 3 to 10 membered heterocyclyl, hydroxy, amino, a substituted or unsubstituted mono-substituted amine group, a substituted or unsubstituted di-substituted amine group, a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido;

[0226] R^8 is selected from a substituted or unsubstituted 3 to 10 membered heterocyclyl(C_1-C_6 alkyl), a substituted or unsubstituted di- C_1-C_6 alkylamine(C_1-C_6 alkyl) and a substituted or unsubstituted mono- C_1-C_6 alkylamine(C_1-C_6 alkyl);

[0227] R^9 is selected from a substituted or unsubstituted 5 to 10 membered heteroaryl and a substituted or unsubstituted C_6-C_{10} aryl;

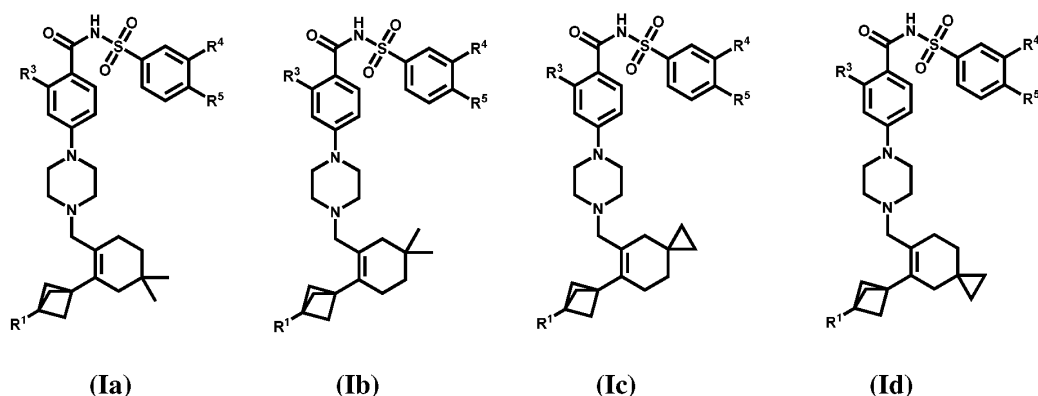
[0228] m is 0, 1, 2 or 3;

[0229] n and p are independently selected from 0 and 1;

[0230] X^1 and X^2 are $-O-$; and

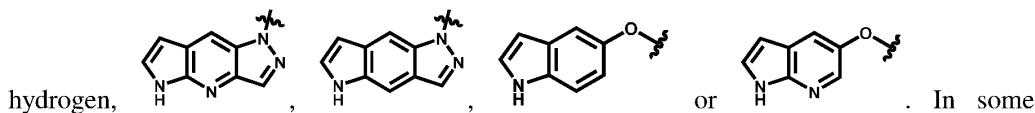
[0231] X and X^3 are independently selected from the group consisting of $-O-$, $-S-$ and $-NH-$.

[0232] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be selected from a compound of Formula (Ia), Formula (Ib), Formula (Ic) and Formula (Id):



or pharmaceutically acceptable salts of any of the foregoing.

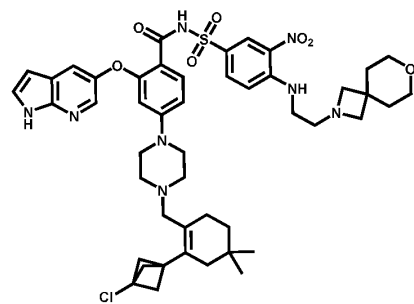
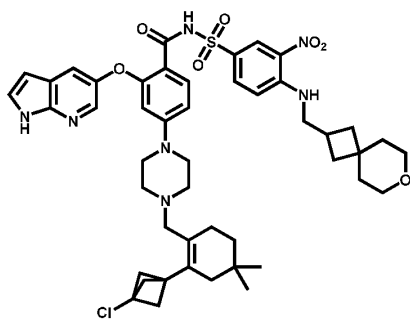
[0233] In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R³ can be

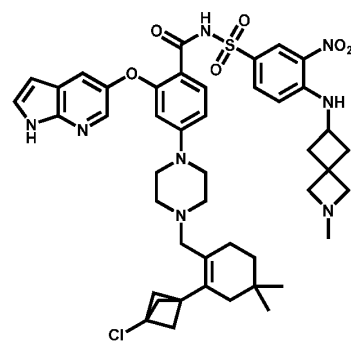
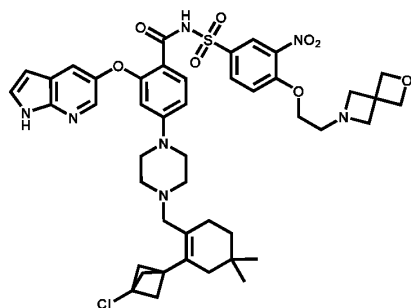
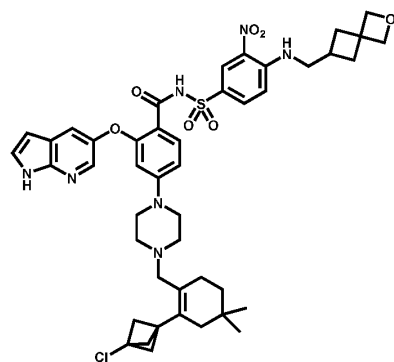


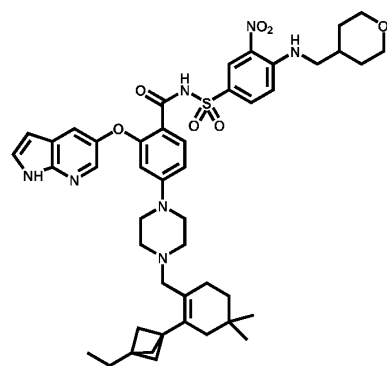
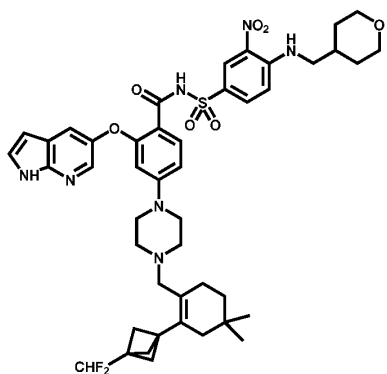
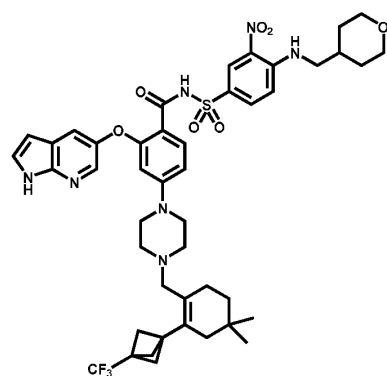
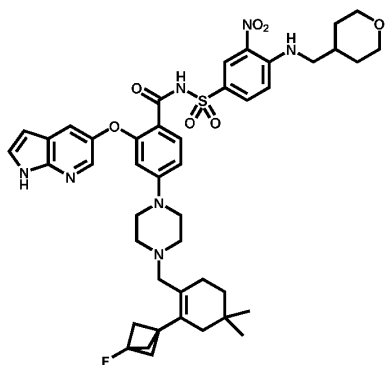
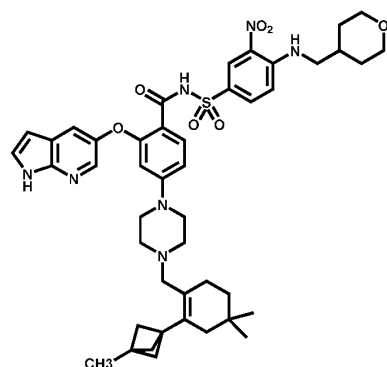
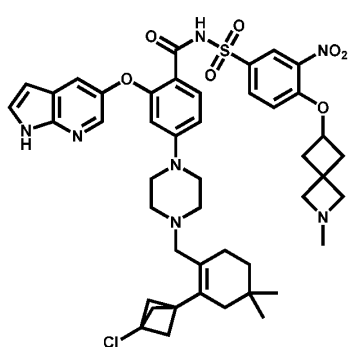
embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R⁴ can be nitro or -SO₂CF₃. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R¹ can be fluoro, chloro, -CH₃, -CH₂CH₃, -CHF₂, -CF₃, -CH₂CF₃, -CF₂CH₃, -OCH₃, -OCH₂CH₃, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂ or -N(CH₂CH₃)₂. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R⁵ can be -O-R⁷ or -NH-R⁷. In some embodiments Formulae (Ia), (Ib), (Ic) and/or (Id), R⁵ can be -O-Alk¹-R⁷ or -NH-Alk¹-R⁷. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), Alk¹ can be an unsubstituted methylene, an unsubstituted ethylene, or an ethylene mono-substituted with -CH₃. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R⁷ can be an unsubstituted cyclohexanyl or a cyclohexanyl substituted with one or two substituents independently selected from hydroxy, amino, fluoro and unsubstituted C₁-C₃ alkyl (such as those described herein). In some embodiments of this paragraph, R⁷ can be a substituted or unsubstituted monocyclic 5 or 6 membered heterocyclyl, for example, pyrrolidine, piperidine, morpholine, piperazine or tetrahydropyran; wherein each of the aforementioned substituted groups can be substituted with 1 or 2 substituents independently selected from hydroxy, amino, fluoro, an unsubstituted C₁-C₃ alkyl (such as those described herein), an unsubstituted C₁-C₃ alkoxy (such as those described herein), or -SO₂CH₃. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R⁷ can be connected to Alk¹ by a nitrogen atom. In some

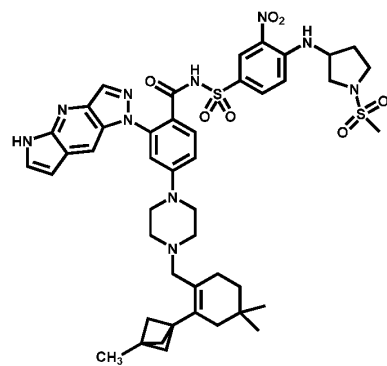
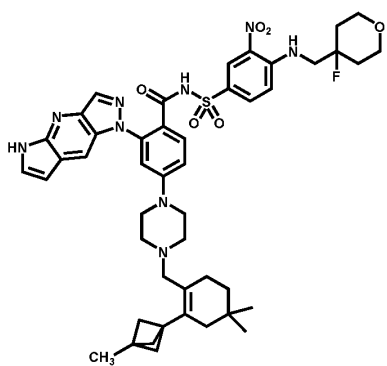
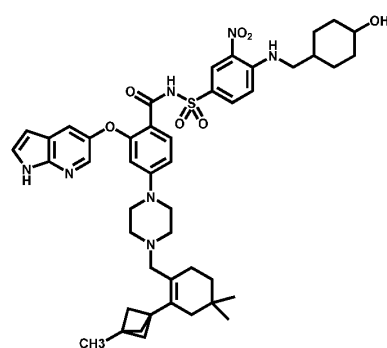
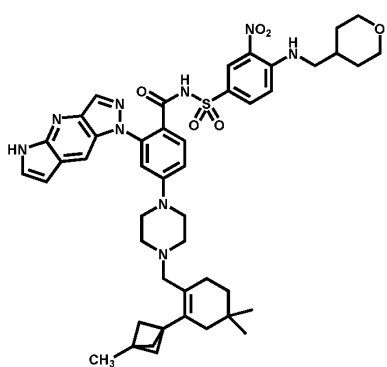
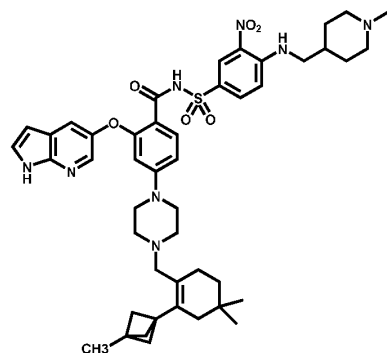
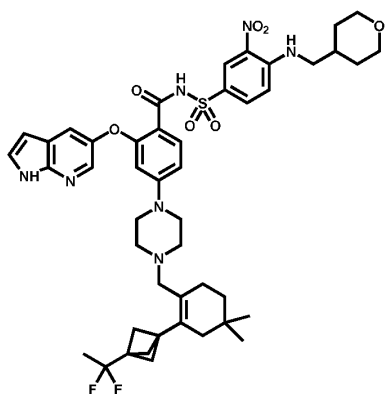
embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R^7 can be connected to Alk^1 by a carbon atom. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R^7 can be substituted on one or more nitrogen atoms. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R^5 can be $-NH-(CHR^8)-Alk^2-S-R^9$, $-O-(CHR^8)-Alk^2-S-R^9$, $-NH-(CHR^8)-Alk^2-O-R^9$ or $-O-(CHR^8)-Alk^2-O-R^9$. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), Alk^2 can be an unsubstituted methylene, an unsubstituted ethylene, a methylene mono-substituted with $-CH_3$ or a methylene di-substituted with $-CH_3$. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R^8 can be an unsubstituted di- C_1-C_3 alkylamine(methyl) or an unsubstituted di- C_1-C_3 alkylamine(ethyl). In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R^8 can be a substituted or unsubstituted 5 to 7 membered heterocyclyl(C_1-C_6 alkyl); wherein the C_1-C_6 alkyl can be an unsubstituted methyl, an unsubstituted ethyl or an unsubstituted n-propyl; the 5 to 7 membered heterocyclyl can (a) be monocyclic or spiro, (b) include 1 oxygen atom, 1 nitrogen atom, or 1 oxygen atom and one nitrogen atom, (c) be unsubstituted or substituted with 1 or 2 substituents independently selected from an unsubstituted C_1-C_3 alkyl (such as those described herein), $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, an unsubstituted acetyl, $-CO_2H$, fluoro or hydroxy. In some embodiments of Formulae (Ia), (Ib), (Ic) and/or (Id), R^9 can be unsubstituted phenyl.

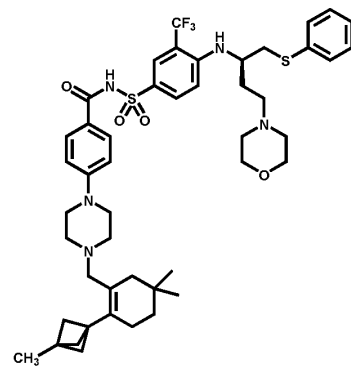
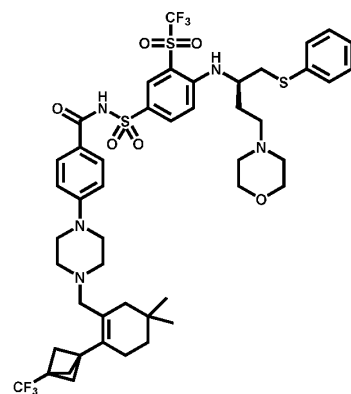
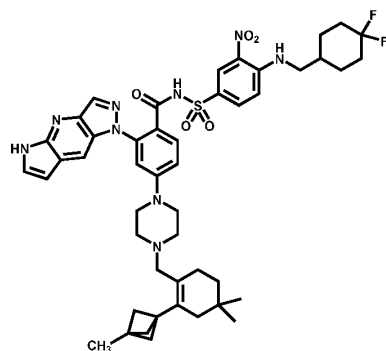
[0234] Examples of a compound of Formula (I) include:

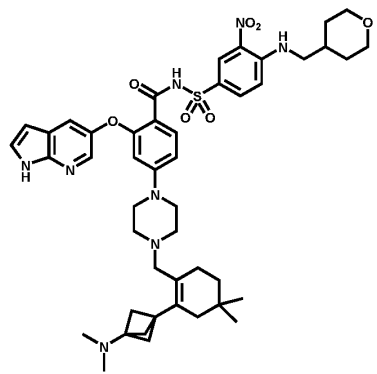
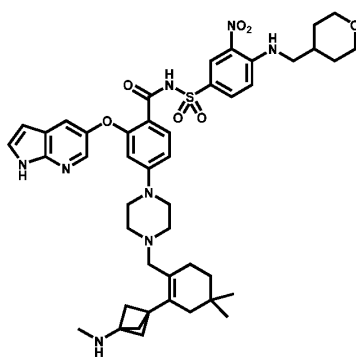
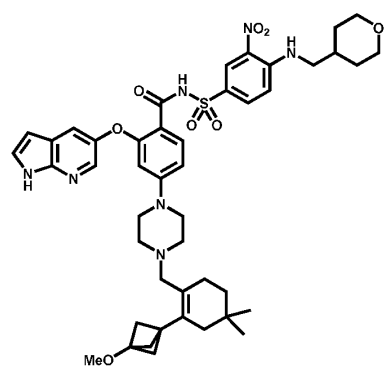
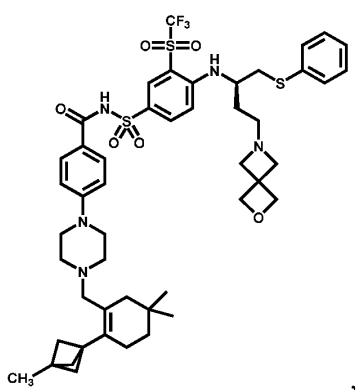
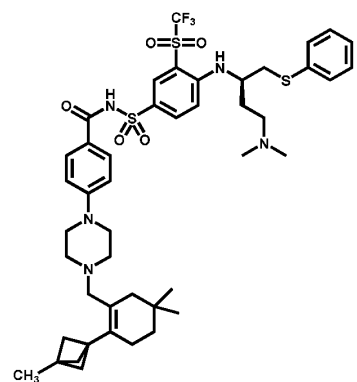
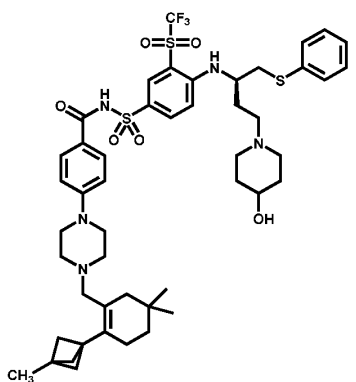


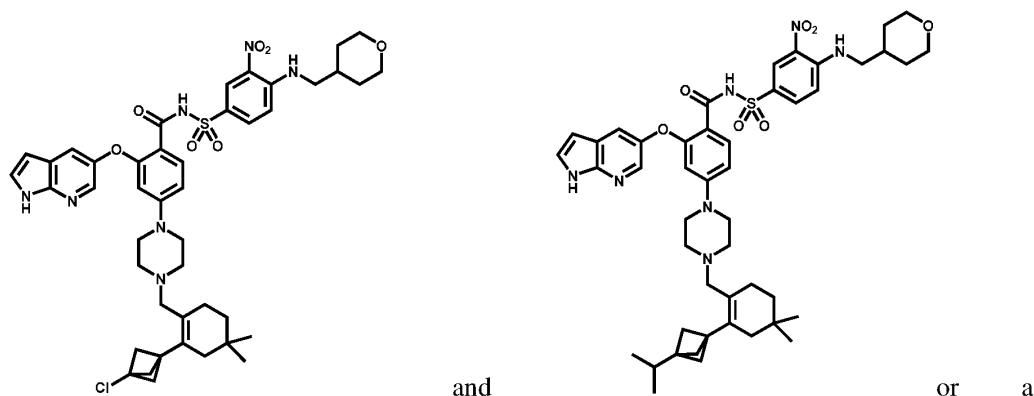






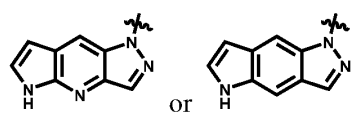






pharmaceutically acceptable salt of any of the foregoing.

[0235] FIG. 3 provides the chemical names and structures for examples of the compounds of Formula (I) listed above in which R^3 is hydrogen or halogen, along with other examples of such compounds. In an embodiment, the compound of Formula (I) is a compound selected from FIG. 3, or a pharmaceutically acceptable salt of any of the compounds listed in FIG. 3. FIGS. 4A, 4B and 4C provide the chemical names and structures for examples of the compounds of Formula (I) listed above in which R^3 is $X-R^{3A}$,



, along with other examples of such compounds, including those in which R^1 is any of the aforementioned options for R^1 except that R^1 is not $-CH_2F$, $-CHF_2$ or $-CF_3$, and X^1 and X^2 are $-NH-$ (FIG. 4A); those in which R^1 is any of the aforementioned options for R^1 , and X^1 and X^2 are $-O-$ (FIG. 4B); and those in which R^1 is $-CH_2F$, $-CHF_2$ or $-CF_3$, and X^1 and X^2 are $-NH-$ (FIG. 4C). In an embodiment, the compound of Formula (I) is a compound selected from FIGS. 3, 4A, 4B, and/or 4C, or a pharmaceutically acceptable salt of any of the compounds listed in FIGS. 3, 4A, 4B and/or 4C. In an embodiment, the compound of Formula (I) is a compound selected from FIG. 3, or a pharmaceutically acceptable salt of any of the compounds listed in FIG. 3. In an embodiment, the compound of Formula (I) is a compound selected from FIG. 4A, or a pharmaceutically acceptable salt of any of the compounds listed in FIG. 4A. In an embodiment, the compound of Formula (I) is a compound selected from FIG. 4B, or a pharmaceutically acceptable salt of any of the compounds listed in FIG. 4B. In an

embodiment, the compound of Formula (I) is a compound selected from FIG. 4C, or a pharmaceutically acceptable salt of any of the compounds listed in FIG. 4C.

[0236] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have increased metabolic and/or plasma stability. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be more resistant to hydrolysis and/or more resistant to enzymatic transformations. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have improved properties. A non-limiting list of example properties include, but are not limited to, increased biological half-life, increased bioavailability, increase potency, a sustained *in vivo* response, increased dosing intervals, decreased dosing amounts, decreased cytotoxicity, reduction in required amounts for treating disease conditions, a reduction of morbidity or mortality in clinical outcomes, decrease in or prevention of opportunistic infections, increased subject compliance and increased compatibility with other medications. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have more potent anticancer activity (for example, a lower EC₅₀ in a cell replication assay) as compared to the current standard of care (such as venetoclax). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have more potent antiviral activity (for example, a lower EC₅₀ in a HIV replicon assay) as compared to the current standard of care (such as dolutegravir).

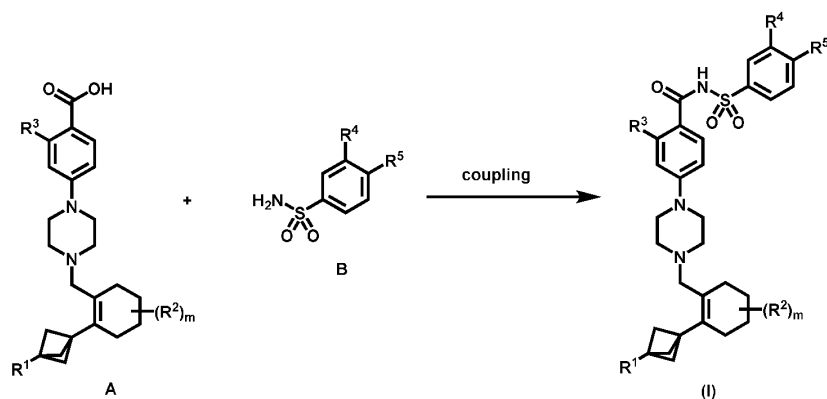
Synthesis

[0237] 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. For example, in an embodiment, compounds of the Formula (I) are prepared in accordance with General Scheme 1 as shown herein.

[0238] In general, the coupling reaction reactions between compounds of the general Formulae A and B to form compounds of the Formula (I) as illustrated in General Scheme 1 can be carried out in a manner similar to the reactions as described herein in the Examples, by appropriate adjustment of the reagents and conditions described in the Examples. Any preliminary reaction steps required to form starting compounds of the general

Formula A and B, or other precursors, can be carried out by those skilled in the art. In General Scheme 1, R^1 , R^2 , R^3 , R^4 , R^5 and m can be as described herein.

General Scheme 1



Pharmaceutical Compositions

[0239] 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.

[0240] 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.

[0241] 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.

[0242] 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.

[0243] 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.

[0244] 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.

[0245] 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.

[0246] 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.

[0247] 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.

[0248] 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.

[0249] 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

[0250] Some embodiments described herein relate to a method for treating a cancer or a tumor 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 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for treating a cancer or a tumor 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for treating a cancer or a tumor described herein.

[0251] Some embodiments described herein relate to a method for inhibiting replication of a malignant growth or a tumor described herein 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). 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) in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor described herein. In some embodiments, the use can include contacting the growth or the tumor with the medicament. 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) for inhibiting replication of a malignant growth or a tumor described herein.

[0252] Some embodiments described herein relate to a method for treating a cancer described herein that can include contacting a malignant growth or a tumor described herein with 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) in the manufacture

of a medicament for treating a cancer described herein. In some embodiments, the use can include contacting the malignant growth or a tumor described herein with the medicament. 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) for contacting a malignant growth or a tumor described herein, wherein the malignant growth or tumor is due to a cancer described herein.

[0253] Examples of suitable malignant growths, cancers and tumors include, but are not limited to: bladder cancers, brain cancers, breast cancers, bone marrow cancers, cervical cancers, colorectal cancers, esophageal cancers, hepatocellular cancers, lymphoblastic leukemias, follicular lymphomas, lymphoid malignancies of T-cell or B-cell origin, melanomas, myelogenous leukemias, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, head and neck cancers (including oral cancers), ovarian cancers, non-small cell lung cancer, chronic lymphocytic leukemias, myelomas (including multiple myelomas), prostate cancer, small cell lung cancer, spleen cancers, polycythemia vera, thyroid cancers, endometrial cancer, stomach cancers, gallbladder cancer, bile duct cancers, testicular cancers, neuroblastomas, osteosarcomas, Ewings's tumor and Wilm's tumor.

[0254] As described herein, a malignant growth, cancer or tumor, can become resistant to one or more anti-proliferative 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 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 malignant growth, cancer or tumor, that has become resistant to one or more anti-proliferative agents (such as one or more Bcl-2 inhibitors). Examples of anti-proliferative agents that a subject may have developed resistance to include, but are not limited to, Bcl-2 inhibitors (such as venetoclax, navitoclax, obatoclax, S55746, APG-1252, APG-2575 and ABT-737). In some embodiments, the malignant growth, cancer or tumor, that has become resistant to one or more anti-proliferative agents can be a malignant growth, cancer or tumor, described herein.

[0255] Some embodiments described herein relate to a method for inhibiting the activity of Bcl-2 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject and can also include contacting a cell that expresses Bcl-2 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 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) in the manufacture of a medicament for inhibiting the activity of Bcl-2 in a subject or, in the manufacture of a medicament for inhibiting the activity of Bcl-2, wherein the use comprises contacting a cell that expresses Bcl-2. 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) for inhibiting the activity of Bcl-2 in a subject; or for inhibiting the activity of Bcl-2 by contacting a cell that expresses Bcl-2.

[0256] Some embodiments described herein relate to a method of ameliorating or treating a HIV infection 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), and an effective amount of a HIV latency reversing agent, 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective

amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating or treating a HIV infection in a subject suffering from the HIV infection; or, in the manufacture of a medicament for ameliorating or treating a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for ameliorating or treating a HIV infection in a subject suffering from the HIV infection; or for ameliorating or treating a HIV infection by contacting a cell infected with HIV. In some embodiments, the cells can be in a subject. In some embodiments, the cells can be CD4+T cells. In some embodiments, the CD4+T cells can be in a subject.

[0257] Some embodiments described herein relate to a method of reducing the population of HIV infected 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), and an effective amount of a HIV latency reversing agent, 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the population of HIV infected cells in a subject suffering from the HIV infection; or, for reducing the population of HIV infected cells, wherein the use comprises contacting a cell infected with HIV with the medicament.

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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the population of HIV infected cells in a subject suffering from the HIV infection; or for reducing the population of HIV infected cells by contacting a cell infected with HIV. In some embodiments, the cells can be in a subject. In some embodiments, the cells can be CD4+T cells. In some embodiments, the CD4+T cells can be in a subject.

[0258] Some embodiments described herein relate to a method of reducing the reoccurrence of a HIV infection in a subject 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or, for reducing the reoccurrence of a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. 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) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or for reducing the reoccurrence of a HIV infection by contacting a cell infected with HIV. In some

embodiments, the cells can be in a subject. In some embodiments, the cells can be CD4+T cells. In some embodiments, the CD4+T cells can be in a subject.

[0259] Some embodiments described herein relate to a method of ameliorating or treating a HIV infection that can include administering an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to the use of an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating or treating a HIV infection; or, in the manufacture of a medicament for ameliorating or treating a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. Still other embodiments described herein relate to an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for ameliorating or treating a HIV infection in a subject suffering from the HIV infection; or for ameliorating or treating a HIV infection by contacting a cell infected with HIV. In some embodiments, the cells can be in a subject. In some embodiments, the cells can be CD4+T cells. In some embodiments, the CD4+T cells can be in a subject.

[0260] Some embodiments described herein relate to a method of reducing the population of HIV infected cells that can include administering an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to the use of an effective amount of a Bcl protein

inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the population of HIV infected cells; or, in the manufacture of a medicament for reducing the population of HIV infected cells, wherein the use comprises contacting a cell infected with HIV with the medicament. Still other embodiments described herein relate to an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for reducing the population of HIV infected cells in a subject suffering from the HIV infection; or for reducing the population of HIV infected cells by contacting a cell infected with HIV. In some embodiments, the cells can be in a subject. In some embodiments, the cells can be CD4+T cells. In some embodiments, the CD4+T cells can be in a subject.

[0261] Some embodiments described herein relate to a method of reducing the reoccurrence of a HIV infection in a subject 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 a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof to a subject suffering from the HIV infection; and can also include contacting a cell infected with HIV with an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to the use of an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or, for reducing the reoccurrence of a HIV infection, wherein the use comprises contacting a cell infected with HIV with the medicament. Still other embodiments described herein relate to an effective amount of a Bcl protein inhibitor, or a pharmaceutically acceptable salt thereof, and an effective amount of a HIV latency reversing agent, or a pharmaceutically

acceptable salt thereof, for reducing the reoccurrence of a HIV infection in a subject suffering from the HIV infection; or for reducing the reoccurrence of a HIV infection by contacting a cell infected with HIV. In some embodiments, the cells can be in a subject. In some embodiments, the cells can be CD4+T cells. In some embodiments, the CD4+T cells can be in a subject.

[0262] In some embodiments, the HIV latency reversing agent can be a protein kinase C agonist, a PD-1 inhibitor, a PD-L1 inhibitor, an HDAC inhibitor, a phorbol ester or a bromodomain inhibitor. In some embodiments, the HIV latency reversing agent can be a protein kinase C agonist, which includes, but is not limited to prostratin, bryostatin-1 and ingenol. In some embodiments, the HIV latency reversing agent can be a PD-1 inhibitor, which includes, but is not limited to nivolumab, pembrolizumab, BGB-A317, pidilizumab, AMP-224, AMP-514, PDR001, REGN2810 and MEDI0680. In some embodiments, the HIV latency reversing agent can be a PD-L1 inhibitor, which includes, but is not limited to atezolizumab, durvalumab, avelumab and BMS-936559. In some embodiments, the HIV latency reversing agent can be a HDAC inhibitor, which includes, but is not limited to vorinostat, panobinostat, romidepsin and valproic acid. In some embodiments, the HIV latency reversing agent can be a phorbol ester, which includes, but is not limited to phorbol 12-myristate-13-acetate and (S)-tert-butyl-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate. In some embodiments, the HIV latency reversing agent can be a bromodomain inhibitor, which includes, but is not limited to JQ1, I-BET762, OTX015, I-BET151, CPI203, PFI-1, MS436, CPI-0610, RVX2135, FT-1101, BAY1238097, INCB054329, TEN-010, GSK2820151, ZEN003694, BAY-299, BMS-986158, ABBV-075 and GS-5829. In some embodiments, a combination of two or more HIV latency reversing agents may be used.

[0263] In some embodiments, the Bcl protein inhibitor of Formula (I) can be a selective Bcl-2 inhibitor, a selective Bcl-X_L inhibitor, a selective Bcl-W inhibitor, a selective Mcl-1 inhibitor or a selective Bcl-2A1 inhibitor. In some embodiments, the Bcl protein inhibitor of Formula (I) can inhibit more than one Bcl protein. In some embodiments, the Bcl protein inhibitor can be an inhibitor of the activity of Bcl-2 and one of Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1. In some embodiments, the Bcl protein inhibitor can be an inhibitor of the

activity of Bcl-X_L and one of Bcl-W, Mcl-1 and Bcl-2A1. In some embodiments, the Bcl protein inhibitor of Formula (I) can inhibit both Bcl-2 and Bcl-X_L. In some embodiments, the Bcl protein inhibitor can be venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252, APG-2575, AMG176 or AZD5991, or a combination of any of the foregoing.

[0264] In some embodiments, the methods of ameliorating or treating a HIV infection can also include the use of one or more agents selected from a non-nucleoside reverse transcriptase inhibitor (NNRTI), a nucleoside reverse transcriptase inhibitor (NRTI), a protease inhibitor (PI), a fusion/entry inhibitor, an integrase strand transfer inhibitor (INSTI), a HIV vaccine, a HIV other antiretroviral therapy compound and combinations thereof, or a pharmaceutically acceptable salt of any of the aforementioned. In some embodiments, the subject suffering from the HIV infection is not using an agent selected from a non-nucleoside reverse transcriptase inhibitor (NNRTI), a nucleoside reverse transcriptase inhibitor (NRTI), a protease inhibitor (PI), a fusion/entry inhibitor, an integrase strand transfer inhibitor (INSTI), a HIV vaccine, a HIV other antiretroviral therapy compound and combinations thereof, or a pharmaceutically acceptable salt of any of the aforementioned.

[0265] Examples of suitable NNRTIs include, but are not limited to, delavirdine (Rescriptor®), efavirenz (Sustiva®), etravirine (Intelence®), nevirapine (Viramune®), rilpivirine (Edurant®), doravirine, and pharmaceutically acceptable salts of any of the foregoing, and/or a combination thereof. Examples of suitable NRTIs include, but are not limited to, abacavir (Ziagen®), adefovir (Hepsera®), amdoxovir, apricitabine, clevudine, didanosine (Videx®), elvucitabine, emtricitabine (Emtriva®), entecavir (Baraclude®), lamivudine (Epivir®), racivir, stavudine (Zerit®), tenofovir disoproxil (including Viread®), tenofovir alafenamide, zalcitabine (Hivid®), zidovudine (Retrovir®), and pharmaceutically acceptable salts of any of the foregoing, and/or a combination thereof. Examples of vaccines include, but are not limited to Hepslav®, ABX-203, INO-1800, and pharmaceutically acceptable salts of any of the foregoing, and/or combinations thereof. Examples of suitable protease inhibitors include, but are not limited to, atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®) and saquinavir (Invirase®). Examples of suitable fusion/entry inhibitors include, but are not limited to,

enfuvirtide (Fuzeon®), maraviroc (Selzentry®), vicriviroc, apliviroc, ibalizumab, fostemsavir and PRO-140. Examples of suitable INSTIs include, but are not limited to, raltegravir (Isentress®), dolutegravir (Tivicay®) and elvitegravir (Vitekta®).

[0266] Two types of HIV have been characterized, HIV-1 and HIV-2. HIV-1 is more virulent and more infective strain, and has a global prevalence. HIV-2 is considered to be less virulent and is geographically confined. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be effective to treat HIV-1. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be effective to treat HIV-2. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be effective to treat both genotypes of HIV (HIV-1 and HIV-2).

[0267] Various indicators for determining the effectiveness of a method for treating a HIV infection are known to those skilled in the art. Examples of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in plasma viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), an increase CD4+ T lymphocyte counts, a reduction in the population of HIV infected cells, a reduction of morbidity or mortality in clinical outcomes and/or a reduction in the rate of opportunistic infections. Similarly, successful therapy with an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, can reduce the incidence of opportunistic infections in HIV infected subjects.

[0268] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to reduce the population of CD4+ T lymphocyte cells harboring HIV to undetectable levels.

[0269] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to increase CD4+ T lymphocyte counts from less than about 200 cells/mL to greater than about 1,200 cells/mL. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to increase CD4+ T lymphocyte counts from less than about 200 cells/mL to greater than about 500 cells/mL.

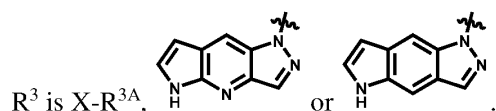
[0270] After a period of time, infectious agents can develop resistance to one or more therapeutic agents. The term “resistance” as used herein refers to a viral strain displaying a delayed, lessened and/or null response to a therapeutic agent(s). In some instances, the virus sometimes mutates or produces variations that are resistant or partially resistant to certain drugs. For example, after treatment with an antiviral agent, the viral load of a subject infected with a resistant virus may be reduced to a lesser degree compared to the amount in viral load reduction exhibited by a subject infected with a non-resistant strain. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be provided to a subject infected with a HIV strain that is resistant to one or more different anti-HIV agents (for example, an agent used in a conventional standard of care). Examples of anti-HIV agents include, but are not limited to, non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), fusion/entry inhibitors, integrase strand transfer inhibitors (INSTIs), HIV vaccines, and combinations thereof, or pharmaceutically acceptable salts of any of the aforementioned.

[0271] Several known Bcl-2 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, nausea and upper respiratory tract infection. 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 Bcl-2 inhibitors. 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 Bcl-2 inhibitors (such as venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252 and APG-2575). 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 Bcl-2 inhibitors (for example, venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252 and APG-2575). 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 Bcl-2 inhibitors (for example, venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252 and APG-2575). 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 Bcl-2 inhibitors (for example, venetoclax, navitoclax, obatoclax, ABT-737, S55746, APG-1252 and APG-2575).

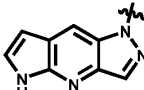
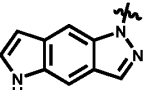
[0272] The one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used to treat, ameliorate and/or inhibit the replication of a cancer, malignant growth, or tumor wherein inhibiting the activity of Bcl-2 is beneficial is provided in any of the embodiments described above under the heading titled “Compounds.” For example, in various embodiments, the methods and uses described above in the Uses and Methods of Treatment section of this disclosure are carried out in the described manner (generally involving cancer, malignant growth, and/or tumor) using a compound of Formula (I) in which R³ is hydrogen or halogen, or a pharmaceutically acceptable salt thereof.

[0273] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally involving cancer, malignant growth, and/or tumor) using a compound of Formula (I) in which

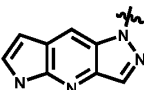
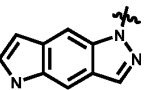


[0274] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section of this disclosure are carried out in the described manner

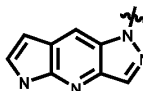
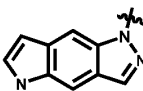
(generally involving cancer, malignant growth, and/or tumor) using a compound of Formula

(I) in which R^3 is $X-R^{3A}$,  or , and in which X^1 and X^2 are $-NH-$.

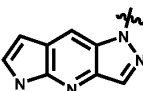
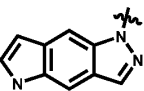
[0275] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally involving cancer, malignant growth, and/or tumor) using a compound of Formula (I) in which R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl, a substituted or unsubstituted C_3-C_6 cycloalkyl, a substituted or unsubstituted C_1-C_6 alkoxy, an unsubstituted mono- C_1-C_6 alkylamine and an unsubstituted di- C_1-C_6 alkylamine, with the proviso that R^1 is not $-CH_2F$, $-$

CHF_2 or $-CF_3$; R^3 is $X-R^{3A}$,  or ; and X^1 and X^2 are $-NH-$.

[0276] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally involving cancer, malignant growth, and/or tumor) using a compound of Formula (I) in which R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl, a substituted or unsubstituted C_3-C_6 cycloalkyl, a substituted or unsubstituted C_1-C_6 alkoxy, an unsubstituted mono- C_1-C_6

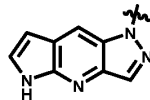
alkylamine and an unsubstituted di- C_1-C_6 alkylamine; R^3 is $X-R^{3A}$,  or ; and X^1 and X^2 are $-O-$.

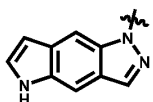
[0277] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally involving cancer, malignant growth, and/or tumor) using a compound of Formula (I) in which

R^1 is $-CH_2F$, $-CHF_2$ or $-CF_3$; R^3 is $X-R^{3A}$,  or ; and X^1 and X^2 are $-NH-$.

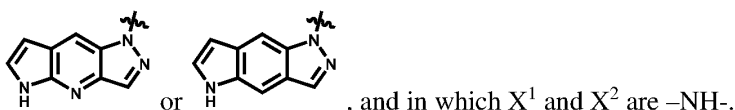
[0278] The one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used to treat and/or ameliorate a HIV infection and/or reducing the reoccurrence of a HIV infection and/or reducing the population of HIV infected cells, wherein inhibiting the activity of Bcl-2 is beneficial is provided in any of the embodiments described above under the heading titled “Compounds.” For example, in various embodiments, the methods and uses described above in the Uses and Methods of Treatment section of this disclosure are carried out in the described manner (generally involving HIV) using a compound of Formula (I) in which R^3 is hydrogen or halogen, or a pharmaceutically acceptable salt thereof.

[0279] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally

involving HIV) using a compound of Formula (I) in which R^3 is $X-R^{3A}$,  or

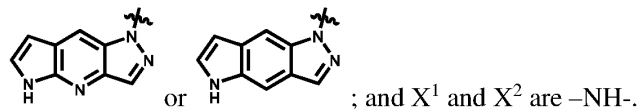


[0280] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section of this disclosure are carried out in the described manner (generally involving HIV) using a compound of Formula (I) in which R^3 is $X-R^{3A}$,



[0281] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally involving HIV) using a compound of Formula (I) in which R^1 is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 haloalkyl, a substituted or unsubstituted C_3-C_6 cycloalkyl, a substituted or unsubstituted C_1-C_6 alkoxy, an unsubstituted mono- C_1-C_6 alkylamine and an unsubstituted

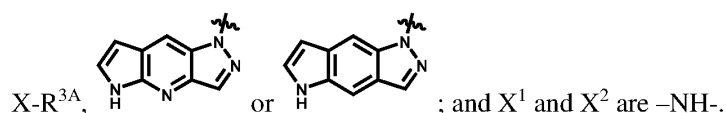
di-C₁-C₆ alkylamine, with the proviso that R¹ is not -CH₂F, -CHF₂ or -CF₃; R³ is X-R^{3A},



[0282] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally

involving HIV) using a compound of Formula (I) in which R³ is X-R^{3A}, and , and in which X¹ and X² are -O-.

[0283] In other embodiments, the methods and uses described above in the Uses and Methods of Treatment section are carried out in the described manner (generally involving HIV) using a compound of Formula (I) in which R¹ is -CH₂F, -CHF₂ or -CF₃; R³ is



[0284] 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 and/or an infant, for example, a child or infant with a fever. In other embodiments, the subject can be an adult.

[0285] 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.

[0286] 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.

[0287] For example, an effective amount of a compound 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 a Bcl-2 inhibitor is the amount which results in the reduction in Bcl-2 activity and/or an increase in apoptosis. The reduction in Bcl-2 activity is known to those skilled in the art and can be determined by the analysis of Bcl-2 binding and relative levels of cells undergoing apoptosis.

[0288] 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.

[0289] 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.

[0290] 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.

[0291] 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)

[0292] 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.

[0293] 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 administered 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.

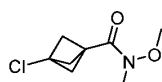
[0294] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards 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

[0295] 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.

Intermediate 1

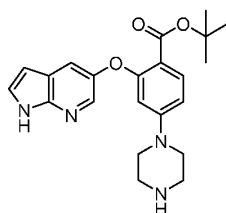
3-Chloro-*N*-methoxy-*N*-methylbicyclo[1.1.1]pentane-1-carboxamide



[0296] To a stirred solution of 3-chlorobicyclo[1.1.1]pentane-1-carboxylate (10.0 g, 62.3 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (12.15 g, 124.5 mmol) in anhydrous THF (200 mL) at -78 °C was added *i*-PrMgCl (2 M in THF, 124.5 mL, 249 mmol). The temperature was then raised to -50 °C and stirred for 2 h. The reaction was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with water, brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to provide **Intermediate 1** (7.30 g, 62%) as an oil. ¹H NMR (300 MHz, CDCl₃) δ 3.67 (s, 3H), 3.18 (s, 3H), 2.47 (s, 6H).

Intermediate 2

tert-Butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(piperazin-1-yl)benzoate

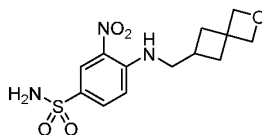


[0297] A solution of *tert*-butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-fluorobenzoate (3.5 g, 10.67 mmol) in DMSO (35 mL) was treated with piperazine (2.33 mL, 32.0 mmol) at rt and stirred at 100 °C for 4 h. The reaction was cooled to rt and water (50 mL) was added. The mixture was extracted with EtOAc (3 x 50 mL) and the organic layers

were concentrated and triturated with *n*-pentane to provide **Intermediate 2** (3.0 g, 71%) as a white solid. LC/MS (ESI) m/z 395.5 $[M+H]^+$.

Intermediate 3

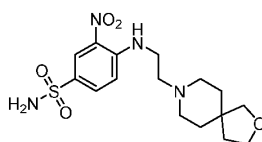
4-(2-oxaspiro[3.3]heptan-6-ylmethylamino)-3-nitrobenzenesulfonamide



[0298] A solution of 4-chloro-3-nitrobenzenesulfonamide (200 mg, 0.85 mmol) in CH₃CN (8 mL) was treated with (2-oxaspiro[3.3]heptan-6-yl)methanamine (129 mg, 1.01 mmol) and DIPEA (0.5 mL 2.95 mmol). The mixture was heated to 90 °C and stirred for 16 h. The reaction was cooled to rt, diluted with EtOAc, and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/hexanes) to afford **Intermediate 3** (120 mg, 43%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47-8.43 (m, 2H), 7.83-7.80 (m, 1H), 7.30 (br s, 2H), 7.22 (d, J =9.6 Hz, 1H), 4.56 (s, 2H), 4.49 (s, 2H), 3.42-3.38 (m, 2H), 2.45-2.39 (m, 1H), 2.33-2.27 (m, 2H), 1.99-1.94 (m, 2H).

Intermediate 4

4-(2-(2-oxa-8-azaspiro[4.5]decan-8-yl)ethylamino)-3-nitrobenzenesulfonamide



[0299] Step 1: A solution of 2-oxa-8-azaspiro[4.5] decane hydrochloride (500 mg, 2.81 mmol) in CH₃CN (20 mL) was treated with *tert*-butyl-2-bromoethylcarbamate (700 mg, 3.12 mmol) and K₂CO₃ (1.55 g, 11.24 mmol) and heated to 80 °C for 16 h. The reaction was concentrated, diluted with water (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, EtOAc/pet. ether) to afford *tert*-butyl-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)ethylcarbamate (**Intermediate 4-1**) (500 mg, 62%) as an oil. ¹H

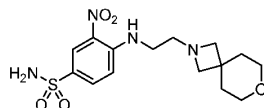
NMR (300 MHz, DMSO- d_6) δ 6.62 (br s, 1H), 3.70 (t, $J=6.9$ Hz, 2H), 3.40 (s, 2H), 3.04-2.98 (m, 2H), 2.40-2.25 (m, 4H), 1.64 (t, $J=7.5$ Hz, 2H), 1.56-1.40 (m, 4H), 1.37 (s, 9H), 1.24 (s, 2H).

[0300] Step 2: To a stirred solution of **Intermediate 4-1** (500 mg, 1.76 mmol) in DCM (20 mL) was added HCl (4 M in dioxane, 10 mL) at 0 °C. The reaction was warmed to rt, stirred for 2 h, concentrated and triturated with Et₂O to afford 2-(2-oxa-8-azaspiro[4.5]decan-8-yl)ethanamine dihydrochloride (**Intermediate 4-2**) (300 mg, 66%) as an off white solid which was used for the next step without further purification. ¹H NMR (300 MHz, DMSO- d_6) δ 10.84 (br s, 1H), 8.38 (br s, 3H), 3.85-3.70 (m, 2H), 3.59-3.40 (m, 8H), 3.12-2.90 (m, 2H), 2.05-1.60 (m, 6H).

[0301] Step 3: A solution of **Intermediate 4-2** (300 mg, 1.17 mmol) in CH₃CN (15 mL) was treated with 4-chloro-3-nitrobenzenesulfonamide (276 mg, 1.17 mmol) followed by DIPEA (0.82 mL, 4.68 mmol) and then heated to 80 °C. After 16 h, the reaction was cooled to rt and concentrated. The crude product was purified by column chromatography (SiO₂, MeOH(0.1% triethylamine)/DCM) to afford **Intermediate 4** (300 mg, 66%) as a yellow solid. LC/MS (ESI) m/z 385.3 [M+H]⁺.

Intermediate 5

2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)ethanamine dihydrochloride



[0302] Step 1: *tert*-butyl 2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)ethylcarbamate (**Intermediate 5-1**) was prepared following the procedure described in Step 1 for **Intermediate 4** using 7-oxa-2-azaspiro[3.5] nonane hemioxalic acid in place of 2-oxa-8-azaspiro[4.5] decane hydrochloride ¹H NMR (300 MHz, DMSO- d_6) δ 6.94 (br s, 1H), 3.74 (br s, 4H), 3.51-3.42 (m, 4H), 3.10 (br s, 4H), 1.76 (br s, 4H), 1.39 (s, 9H).

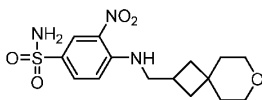
[0303] Step 2: 2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)ethanamine dihydrochloride (**Intermediate 5-2**) was prepared following the procedure described in Step 2 for **Intermediate 4** using **Intermediate 5-1** in place of **Intermediate 4-1**. ¹H NMR (300 MHz,

DMSO-*d*₆) δ 11.42 (br s, 1H), 8.3 (br s, 3H), 4.05-3.99 (m, 2H), 3.92-3.86 (m, 2H), 3.57-3.54 (m, 4H), 3.49-3.40 (m, 4H), 3.10-3.05 (m, 2H), 1.88 (br s, 2H), 1.72 (br s, 2H).

[0304] Step 3: A solution of **Intermediate 5-2** (250 mg, 1.03 mmol) in CH₃CN (13 mL) was treated with 4-fluoro-3-nitrobenzenesulfonamide (226.8 mg, 1.03 mmol) followed by triethylamine (0.58 mL, 4.12 mmol) at rt. After 16 h, the reaction was concentrated to afford the crude product, which was purified by column chromatography (SiO₂, MeOH (containing 7N NH₃)/DCM) to obtain **Intermediate 5** (200 mg, 52%) as a yellow solid. LC/MS (ESI) *m/z* 371.3 [M+H]⁺.

Intermediate 6

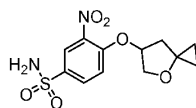
4-(7-Oxaspiro[3.5]nonan-2-yl-methylamino)-3-nitrobenzenesulfonamide



[0305] A solution of 7-oxaspiro[3.5]nonan-2-yl-methanamine (100 mg, 0.64 mmol) in THF (2 mL) was treated with 4-fluoro-3-nitrobenzenesulfonamide (157.6 mg, 0.72 mmol) and Et₃N (0.18 mL, 1.29 mmol) and the mixture was stirred at rt. After 16 h, the reaction was concentrated, and the residue was purified by column chromatography (SiO₂, MeOH/DCM) to provide **Intermediate 6** (126 mg, 55%) as a yellow solid. LC/MS (ESI) *m/z* 356.1 [M+H]⁺.

Intermediate 7

4-((4-oxaspiro[2.4]heptan-6-yl)oxy)-3-nitrobenzenesulfonamide



[0306] Step 1: To a stirred solution of 1-(3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)propyl)cyclopropanol (prepared according to CN106565706) and triphenyl phosphine (9.10 g, 34.7 mmol) in THF (50 mL), was added diethyl azodicarboxylate (DEAD) (5.44 mL, 34.7 mmol) dropwise at rt. After 16 h, the reaction mixture was quenched with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL), dried over Na₂SO₄ and concentrated. The crude product was purified by column

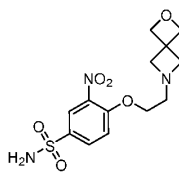
chromatography (SiO₂, EtOAc/pet. ether) to obtain 6-(tetrahydro-2*H*-pyran-2-yloxy)-4-oxaspiro[2.4]heptane (**Intermediate 7-1**) (3.2 g, 69% yield) as a clear yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.65-4.63 (m, 1H), 4.59-4.56 (m, 1H), 4.02-3.85 (m, 3H), 3.53-3.48 (m, 1H), 2.25-1.95 (m, 2H), 1.89-1.76 (m, 1H), 1.72-1.68 (m, 1H), 1.62-1.49 (m, 4H), 0.92-0.89 (m, 1H), 0.81-0.75 (m, 1H), 0.65-0.53 (m, 1H), 0.48-0.39 (m, 1H).

[0307] Step 2: To a stirred solution of **Intermediate 7-1** (3.2 g, 16.1 mmol) in MeOH (32 mL) was added pyridinium p-toluenesulfonate (811 mg, 3.23 mmol) and stirred at 40 °C for 5 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain 4-oxaspiro[2.4]heptan-6-ol (**Intermediate 7-2**) (1.0 g, 54% yield) as colorless oil. GC/MS *m/z* 114.1 [M]⁺.

[0308] Step 3: To a stirred solution of **Intermediate 7-2** was added sodium hydride (63% dispersion in oil, 1.05 g, 26.3 mmol) at 0 °C. After 30 min, a solution of 4-fluoro-3-nitrobenzenesulfonamide (1.92 g, 8.76 mmol) in THF (5 mL) was added dropwise at 0 °C. The reaction was warmed to rt and stirred for 6 h. The reaction was cooled to 0 °C and quenched with sat. aq. NH₄Cl and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was triturated with Et₂O and *n*-pentane to afford **Intermediate 7** (700 mg, 25% yield) as a white solid. LC/MS (ESI) *m/z* 313.0 [M-H]⁻.

Intermediate 8

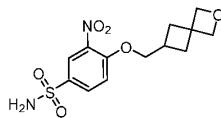
4-(2-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)ethoxy)-3-nitrobenzenesulfonamide



[0309] **Intermediate 8** was prepared following the procedure described in Step 3 for **Intermediate 7** by using 2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)ethanol in place of **Intermediate 7-2**. LC/MS (ESI) *m/z* 344.2 [M+H]⁺.

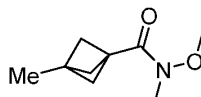
Intermediate 9

4-(2-oxaspiro[3.3]heptan-6-ylmethoxy)-3-nitrobenzenesulfonamide



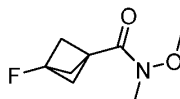
[0310] **Intermediate 9** was prepared following the procedure described in Step 3 for the synthesis of **Intermediate 7** by using 2-oxaspiro[3.3]heptan-6-ylmethanol in place of **Intermediate 7-2**. LC/MS (ESI) m/z 327.4 $[M-H]^-$.

Intermediate 10

N-methoxy-*N*,3-dimethylbicyclo[1.1.1]pentane-1-carboxamide

[0311] To a stirred solution of 3-methylbicyclo[1.1.1]pentane-1-carboxylic acid (3 g, 23.8 mmol) in DCM (100 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (3.48 g, 35.7 mmol) and Et₃N (11.6 mL, 83.2 mmol) at rt. The mixture was then cooled to 0 °C and T₃P (50 wt.% in EtOAc, 6.43 g, 40.4 mmol) was added dropwise and reaction was warmed to rt. After 16 h, the reaction was quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (SiO₂, EtOAc/pet. ether) to provide **Intermediate 10** as an oil (2.5 g, 62% yield). ¹H NMR (300 MHz, CDCl₃) δ 3.65 (s, 3H), 3.17 (s, 3H), 1.98 (s, 6H), 1.18 (s, 3H).

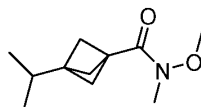
Intermediate 11

3-Fluoro-*N*-methoxy-*N*-methylbicyclo[1.1.1]pentane-1-carboxamide

[0312] **Intermediate 11** was prepared following the procedure described for the synthesis of **Intermediate 10** by using 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid in place of 3-methylbicyclo[1.1.1]pentane-1-carboxylic acid. LC/MS (ESI) m/z 174.3 $[M+H]^+$.

Intermediate 12

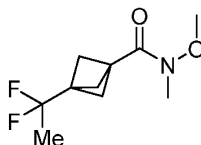
3-isopropyl-N-methoxy-N-methylbicyclo[1.1.1]pentane-1-carboxamide



[0313] **Intermediate 12** was prepared following the procedure described for the synthesis of **Intermediate 10** by using 3-isopropylbicyclo[1.1.1]pentane-1-carboxylic acid in place of 3-methylbicyclo[1.1.1]pentane-1-carboxylic acid. LC/MS (ESI) m/z 198.4 $[M+H]^+$.

Intermediate 13

3-(1,1-Difluoroethyl)-N-methoxy-N-methylbicyclo[1.1.1]pentane-1-carboxamide



[0314] Step 1: To a stirred solution of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (10 g, 58.8 mmol), *N,O*-dimethylhydroxylamine hydrochloride (6.88 g, 42.4 mmol) and triethylamine (12.3 mL, 176.4 mmol) in DCM (200 mL) at 0 °C was added T₃P (50% solution in EtOAc, 18.8 g, 58.8 mmol). The resulting reaction mixture warmed to rt and stirred for 16 h. The reaction mixture was quenched with water (250 mL) and extracted with DCM (3 x 250 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to provide methyl-3-(methoxy(methyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (**Intermediate 13-1**) (9.5 g, 76% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.69 (s, 3H), 3.68 (s, 3H), 3.19 (s, 3H), 2.38 (s, 6H).

[0315] Step 2: To a stirred solution of **Intermediate 13-1** (5 g, 23.5 mmol) in THF (100 mL) at -78 °C was added MeMgBr (3M in Et₂O, 31.3 mL, 93.8 mmol). After stirring for 2 h at -78 °C, the reaction was quenched with sat. aq. NH₄Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄,

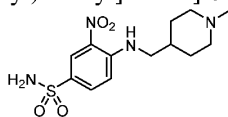
filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to provide methyl-3-acetylbicyclo[1.1.1]pentane-1-carboxylate (**Intermediate 13-2**) (2 g, 51% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 3H), 2.29 (s, 6H), 2.14 (s, 3H).

[0316] Step 3: A solution of the **Intermediate 13-2** (2.3 g, 13.6 mmol) in DCM (50 mL) at -78 °C was treated dropwise with DAST (6.62 g, 41.0 mmol). After the addition, the temperature was raised to rt. After 16 h, the reaction mixture was cooled to -78 °C and carefully quenched with sat. aq. NaHCO₃ (100 mL). The mixture was extracted with DCM (3 x 100 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by chromatography chromatography (SiO₂, EtOAc/pet. ether) to provide methyl-3-(1,1-difluoroethyl)bicyclo[1.1.1]pentane-1-carboxylate (**Intermediate 13-3**) (1.8 g, 69% yield) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 3H), 2.12 (s, 6H), 1.55 (t, *J*=18.0 Hz, 3H).

[0317] Step 4: To a stirred solution of **Intermediate 13-3** (1.8 g, 9.46 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (0.923 g, 9.46 mmol) in anhydrous THF (40 mL) at -78 °C was added *i*-PrMgCl (2M in THF, 18.9 mL, 37.8 mmol). The reaction mixture was warmed -50 °C and stirred for 2 h. The reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to provide **Intermediate 13** (1.7 g, 82% yield) as a clear oil. LC/MS (ESI) *m/z* 220.4 [M+H]⁺.

Intermediate 14

4-[[[(1-Methyl-4-piperidinyl)methyl]amino]-3-nitrobenzenesulfonamide

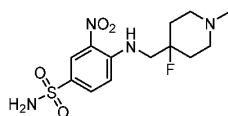


[0318] To a solution of (1-methylpiperidin-4-yl)methanamine (1 g, 7.80 mmol) in THF (75 mL), was added 4-fluoro-3-nitrobenzenesulfonamide (1.71 g, 7.80 mmol) followed by triethylamine (3.15 g, 31.2 mmol) and the reaction was stirred at rt. After 16 h, the

reaction was concentrated, diluted with water (50 mL) and extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (C18, 0.1% HCO₂H(aq)/MeCN) to obtain 650 mg of 4-((1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide as the formate salt. The compound was dissolved in 10% MeOH in DCM (50 mL) and washed with sat. aq. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford **Intermediate 14** as a yellow solid (510 mg, 20% yield). LC/MS (ESI) *m/z* 329.2 [M+H]⁺.

Intermediate 15

4-(((4-fluoro-1-methylpiperidin-4-yl)methyl)amino)-3-nitrobenzenesulfonamide



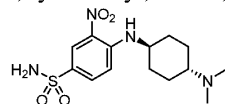
[0319] Step 1: To a stirred solution of *tert*-butyl 4-(aminomethyl)-4-fluoropiperidine-1-carboxylate (2.00 g, 8.61 mmol) in THF (30 mL), was added 4-fluoro-3-nitrobenzenesulfonamide (2.08 g, 9.47 mmol) followed by triethylamine (4.8 mL, 34.45 mmol). The resulting reaction mixture was stirred at rt for 16 h. The reaction was then concentrated, and the resulting residue was diluted with 10% MeOH-DCM (50 mL) and washed with ice-cold water (5 x 50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by trituration with Et₂O to afford *tert*-butyl 4-fluoro-4-(((2-nitro-4-sulfamoylphenyl)amino)methyl)piperidine-1-carboxylate (**Intermediate 15-1**) (1.6 g, 43% yield). LC/MS (ESI) *m/z* 333.10 [M - C₅H₉O₂ + H]⁺.

[0320] Step 2: To a stirred solution of **Intermediate 15-1** (1.6 g, 3.70 mmol) in 1,4-dioxane (10 mL) at 0 °C was added HCl (4M HCl in 1,4-dioxane, 20 mL). The reaction was warmed to rt and stirred for 6 h. The reaction was concentrated and trituated with Et₂O to afford 4-(((4-fluoropiperidin-4-yl)methyl)amino)-3-nitrobenzenesulfonamide hydrochloride (**Intermediate 15-2**) (1.3g, 96%) as a yellow solid. LC/MS (ESI) *m/z* 333.1 [C₁₂H₁₇FN₄O₄S+H]⁺.

[0321] Step 3: To a stirred solution of **Intermediate 15-2** (430 mg, 1.35 mmol) in MeOH (15 mL) was added paraformaldehyde (81 mg, 2.71 mmol) at 0 °C. After 15 min, NaCNBH₃ (128 mg, 2.03 mmol) was added and the reaction was warmed to rt. After 18h, the reaction was quenched sat. aq. NaHCO₃ (15 mL) and the reaction was extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was triturated with Et₂O followed by 1:1 EtOAc/Hexane to afford **Intermediate 15** (340 mg, 25% yield) as a yellow solid. LC/MS (ESI) *m/z* 347.1 [M+H]⁺.

Intermediate 16

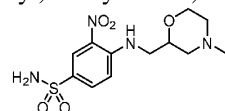
4-(((1*r*,4*r*)-4-(dimethylamino)cyclohexyl)amino)-3-nitrobenzenesulfonamide



[0322] To a stirred solution of trans-*N*^{*l*},*N*^{*l*}-dimethylcyclohexane-1,4-diamine dihydrochloride (350 mg, 1.39 mmol) in THF (10 mL) was added 4-fluoro-3-nitrobenzenesulfonamide (322 mg, 1.39 mmol) followed by triethylamine (844 mg, 8.34 mmol). After stirring for 16 h at rt, the reaction was concentrated and triturated with EtOAc and Et₂O to provide the crude product. The product was further purified by HPLC (75:25 to 1:99 10mM NH₄OAc(aq):CH₃CN) to provide **Intermediate 16** as a yellow solid. LC/MS (ESI) *m/z* 343.1 [M+H]⁺.

Intermediate 17

4-((4-Methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

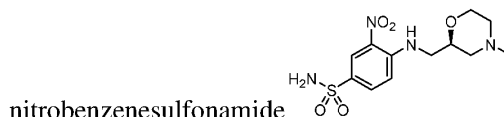


[0323] To a stirred solution of (4-methylmorpholin-2-yl)methanamine (400 mg, 3.07 mmol) in THF (25 mL) was added 4-fluoro-3-nitrobenzenesulfonamide (609 mg, 2.76 mmol) followed by triethylamine (1.24 g, 12.28 mmol). After stirring at rt for 16 h, the reaction was concentrated and the resulting crude was diluted with 10% MeOH-DCM (50 mL), and washed with ice-cold water (3 x 50 mL). The organic layer was dried over Na₂SO₄,

filtered and concentrated. The crude product was triturated with Et₂O/pentane to afford **Intermediate 17** (600 mg, 65% yield) as a yellow solid. LC/MS (ESI) *m/z* 331.2 [M+H]⁺.

Intermediate 17A

(R)-4-(((4-methylmorpholin-2-yl)methyl)amino)-3-



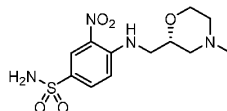
[0324] Racemic

4-((4-Methylmorpholin-2-yl)methylamino)-3-

nitrobenzenesulfonamide (400 mg) was subjected to chiral SFC separation (Chiralpak AD-H (250 x 30 mm), 5 μ, 30% MeOH) to afford 4-((4-Methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide (160 mg) as the first eluted peak (RT = 3.06 min) with 99.6% ee. LC/MS (ESI) *m/z* 331.2 [M+H]⁺. The absolute stereochemistry was arbitrarily assigned for **Intermediate 17A**.

Intermediate 17B

(S)-4-(((4-methylmorpholin-2-yl)methyl)amino)-3-nitrobenzenesulfonamide



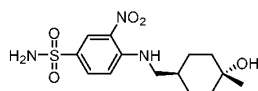
[0325] Racemic

4-((4-Methylmorpholin-2-yl)methylamino)-3-

nitrobenzenesulfonamide (400 mg) was subjected to chiral SFC separation (Chiralpak AD-H (250 x 30 mm), 5 μ, 30% MeOH) to afford 4-((4-Methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide (150 mg) as the second eluted peak (RT = 3.64 min) with 99.8% ee. LC/MS (ESI) *m/z* 331.2 [M+H]⁺. The absolute stereochemistry was arbitrarily assigned for **Intermediate 17B**.

Intermediate 18

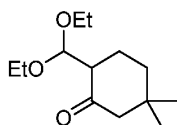
4-(((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrobenzenesulfonamide



[0326] **Intermediate 18** was prepared following a procedure described in WO2014/165044A1. LC/MS (ESI) m/z 344.1 $[M+H]^+$.

Intermediate 19

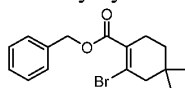
2-(Diethoxymethyl)-5,5-dimethylcyclohexan-1-one



[0327] To a solution of triethyl orthoformate (1.32 L, 7.923 mol) in DCM (8.0 L) at $-30\text{ }^{\circ}\text{C}$ was added $\text{BF}_3 \cdot \text{OEt}_2$ (1.244 L, 9.9 mmol) dropwise over 30 min. The reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$ and stirred for 30 min. The reaction mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ and 3,3-dimethylcyclohexanone (500 g, 3.96 mol) and N,N -diisopropylethylamine (2.08 L, 11.9 mol) were added dropwise and the reaction was stirred for 2 h at the same temperature. The reaction was then carefully poured into a mixture of sat. aq. NaHCO_3 (25 L) and DCM (10 L). The resulting mixture was stirred for 15 min at rt and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 10 L) and the combined organic layers were washed with 10% NaCl(aq.) (5 L), dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to afford **Intermediate 19** (750 g, 83 % yield) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.83 (d, $J=6.0$ Hz, 1H), 3.73-3.57 (m, 4H), 2.56-2.53 (m, 1H), 2.20-2.14 (m, 2H), 2.11-2.10 (m, 1H), 1.81 (m, 1H), 1.62-1.56 (m, 2H), 1.21-1.17 (m, 6H), 1.01 (s, 3H), 0.91 (s, 3H).

Intermediate 20

Benzyl 2-bromo-4,4-dimethylcyclohex-1-ene-1-carboxylate



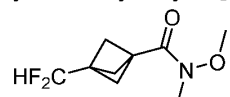
[0328] Step 1: A solution of NaClO_2 (11.08 g, 122.5 mmol) in water (100 mL) was added drop wise to a stirring mixture of 2-bromo-4,4-dimethylcyclohex-1-ene-1-carbaldehyde (19 g, 87.5 mmol), CH_3CN (100 mL), NaH_2PO_4 (2.72 g, 22.75 mmol), water (40 mL) and 30% $\text{H}_2\text{O}_2\text{(aq.)}$ (15 mL) at $10\text{ }^{\circ}\text{C}$. Upon completion, the reaction, was poured

into sat. aq. Na_2CO_3 (200 mL) and washed with Et_2O (200 mL). The aqueous phase was poured into 1N HCl solution (500 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude compound was further washed with water and dried to obtain 2-bromo-4,4-dimethylcyclohex-1-ene-1-carboxylic acid (**Intermediate 20-1**) (15 g, 73% yield) as a white solid. LC/MS (ESI) m/z 231.0 [M-H].

[0329] Step 2: To a stirred solution of **Intermediate 20-1** (10 g, 42.9 mmol) in DMF (100 mL) was added K_2CO_3 (17.79 g, 128.7 mmol) followed by benzyl bromide (14.67 g, 85.8 mmol) at 0 °C and the reaction was warmed to rt. After 16 h, water (200 mL) was added and the reaction was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (3 x 200 mL), dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to afford **Intermediate 20** (11 g, 79% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.32 (m, 5H), 5.22 (s, 2H), 2.45-2.38 (m, 4H), 1.44 (t, $J=5.6$ Hz, 2H), 0.97 (s, 6H); GC/MS m/z 322.1 [M] $^+$.

Intermediate 21

3-(difluoromethyl)-N-methoxy-N-methylbicyclo[1.1.1]pentane-1-carboxamide

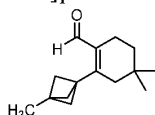


[0330] Step 1: A stirring solution of methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (7.5 g, 48.7 mmol) in DCM (100 mL) was cooled to -78 °C, and treated with DAST (19.3 mL, 146.1 mmol) drop wise and warmed to rt. After 6 h, the reaction mixture was cooled to -78 °C and quenched with sat. aq. NaHCO_3 (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to afford methyl 3-(difluoromethyl) bicyclo[1.1.1] pentane-1-carboxylate (**Intermediate 21-1**) (7 g) as a viscous oil. This was used in the next step without further purification. ^1H NMR (300 MHz, CDCl_3) δ 5.71 (t, $J=56.1$ Hz, 1H), 3.70 (s, 3H), 2.15 (s, 6H).

[0331] Step 2: To a stirred solution of **Intermediate 21-1** (7 g, 39.74 mmol) in anhydrous THF (70 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (3.89 g, 39.74 mmol) at -78 °C, followed by *i*-PrMgCl (2M in THF, 79.5 mL, 159 mmol). The reaction was warmed to -50 °C and stirred for 2 h. The reaction mixture was then quenched with sat. aq. NH₄Cl solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to afford **Intermediate 21** (4 g, 40% yield over two steps). ¹H NMR (400 MHz, CDCl₃) δ 5.72 (t, *J*=56.4 Hz, 1H), 3.68 (s, 3H), 3.19 (s, 3H), 2.20 (s, 6H); LC/MS (ESI) *m/z* 206.1 [M+H]⁺.

Intermediate 22

4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde



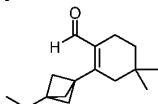
[0332] Step 1: A solution of 1-iodo-3-methylbicyclo[1.1.1]pentane (30 g, 144.20 mmol) in THF (225 mL) was cooled to -78 °C and sec-butyllithium (1.4M in cyclohexane, 154.50 mL, 216.30 mmol) was added drop wise over 1 h. The resulting pale yellow suspension was stirred at -78 °C for 10 min and then warmed to 0 °C and stirred for 80 min. The reaction mixture was then cooled to -78 °C, and a solution of **Intermediate 19** (24.67 g, 108.15 mmol) in THF (75 mL) was added drop wise over 20 min. After 10 min, the reaction was warmed to 0 °C for 1 h. The reaction mixture was then quenched with sat. aq. NH₄Cl (300 mL) and extracted with Et₂O (2 x 450 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford 2-(diethoxymethyl)-5,5-dimethyl-1-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohexan-1-ol (**Intermediate 22-1**) (31 g, crude) as a pale yellow oil. This was used in the next step without further purification.

[0333] Step 2: A solution of **Intermediate 22-1** (62 g, 199.69 mmol) in 1,4-dioxane (1.24 L), was treated with 2N HCl(aq.) (299.5 mL, 599.2 mmol) at rt and then warmed to 70 °C. After 16 h, the reaction was cooled to rt, poured into water (1.24 L) and extracted with Et₂O (2 X 750 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂,

EtOAc/pet. ether) to provide **Intermediate 22** (23 g, 36 % yield over 2 steps) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 10.28 (s, 1H), 2.25-2.22 (m, 2H), 1.94 (s, 6H), 1.92 (br s, 2H), 1.35-1.32 (m, 2H), 1.19 (s, 3H), 0.90 (s, 6H).

Intermediate 23

2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-ene-1-carbaldehyde



[0334] Step 1: To a stirred solution of [1.1.1]propellane (0.19M in Et_2O /pentane), 128.6 mmol) at -78°C was added EtI (18.7 g, 257.38 mmol). The reaction was warmed to rt and stirred for 3 days in the dark. The reaction was then concentrated at 0°C to afford 1-ethyl-3-iodobicyclo[1.1.1]pentane (**Intermediate 23-1**) (21.2 g, 74% yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 2.17 (s, 6H), 1.52 (q, $J=8.0$ Hz, 2H), 0.84 (t, $J=7.2$ Hz, 3H).

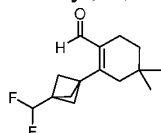
[0335] Step 2: To a stirred solution of **Intermediate 23-1** (10.90 g, 49.1 mmol) in Et_2O (75 mL) at -78°C was added *sec*-BuLi (1.4 M in cyclohexane, 50 mL, 70.0 mmol). After 10 min, the reaction was warmed to rt and stirred for 1 h. The reaction mixture was then cooled to -78°C and treated with a solution of 2-(diethoxymethyl)-5,5-dimethylcyclohexan-1-one (8 g, 35.0 mmol) in Et_2O (25 mL). After 1 h, the reaction was warmed to 0°C and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layers were then dried over Na_2SO_4 , filtered and concentrated to provide 8.5 g of crude 2-(diethoxymethyl)-1-(3-ethylbicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohexan-1-ol (**Intermediate 23-2**). This was used in the next step without further purification.

[0336] Step 3: A solution of **Intermediate 23-2** (8.5 g, crude) in acetone (80 mL), was treated with 2N HCl(aq.) (20 mL) at rt and then warmed to 75°C . After 24 h, the reaction was concentrated and then diluted with water (50 mL) and extracted with Et_2O (3 X 250 mL). The combined organic layers were washed with sat. aq. NaHCO_3 , dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2 , Et_2O /pet. ether) to provide **Intermediate 23** (3.9 g, 48 % yield over 2 steps) as a brown oil. ^1H NMR

(400 MHz, CDCl₃) δ 10.30 (s, 1H), 2.26-2.22 (m, 2H), 1.93-1.92 (m, 2H), 1.89 (s, 6H), 1.49 (q, $J=7.2$ Hz, 2H), 1.33 (t, $J=6.4$ Hz, 2H), 0.89 (s, 6H), 0.87 (t, $J=7.6$ Hz, 3H).

Intermediate 24

2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-ene-1-carbaldehyde



[0337] Step 1: Preparation of CF₂HI (based on a procedure from Cao, P. et. al. *J. Chem. Soc., Chem. Commun.* 1994, 737-738): performed in two parallel batches: A mixture of KI (94 g, 568 mol), MeCN (228 ml) and water (18 mL) was heated to 45 °C and treated with, 2,2-difluoro-2-(fluorosulfonyl)acetic acid (50 g, 284 mmol) in MeCN (50 mL) dropwise over 4 h. The reaction mixture was then cooled to 0 °C, and diluted with pentane (150 mL) and water (125 mL). The aqueous layer was washed with pentane (150 mL), and the combined organic layers from both reactions were washed with sat. aq. NaHCO₃ (200 mL), and dried over Na₂SO₄ to obtain 500 mL of difluoromethyl iodide solution. The solution was washed with additional water (2 x 200 mL) to remove residual acetonitrile, and dried over Na₂SO₄ to obtain difluoroiodomethane (**Intermediate 24-1**) (0.15 M in pentane, 400 mL, 11% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.67 (t, $J=56.0$ Hz, 1H).

[0338] Step 2: To a stirred solution of [1.1.1]propellane (0.53 M in Et₂O, 52 mL, 27.56 mmol) at -40 °C was added **Intermediate 24-1** (0.15 M in pentane, 200 mL, 30 mmol). The reaction mixture was warmed to rt, protected from light, and stirred for 2 days. The reaction was then concentrated at 0 - 10 °C to obtain 1-(difluoromethyl)-3-iodobicyclo[1.1.1]pentane (**Intermediate 24-2**) (5 g, 20.5 mmol, 74% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.65 (t, $J=56.0$ Hz, 1H), 2.40 (s, 6H).

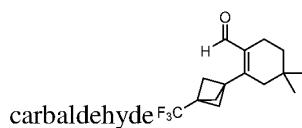
[0339] Step 3: A solution of **Intermediate 24-2** (30 g, 122.94 mmol) in THF (225 mL) was cooled to -78 °C and sec-butyllithium (1.4M in cyclohexane, 219 mL, 306.7 mmol) was added drop-wise for 1 h. The resulting pale yellow suspension was stirred at -78 °C for 10 min and temperature was raised to 0 °C and stirred for 80 min. The reaction mixture was then cooled to -78 °C, and a solution of **Intermediate 19** (21 g, 92.20 mmol) in THF (75

mL) was added drop wise to the reaction over 20 min. After 10 min, the reaction was warmed to 0 °C for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl (450 mL) and extracted with Et₂O (2 x 300 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford 2-(diethoxymethyl)-1-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohexan-1-ol (**Intermediate 24-3**) (31 g, crude) as pale yellow oil. The crude product was used in the next step without further purification.

[0340] Step 4: **Intermediate 24** was prepared following the procedure described in Step 2 for **Intermediate 22** using **Intermediate 24-3** in place of **Intermediate 22-1** (38% over 2 steps). ¹H NMR (400 MHz, CDCl₃): δ 10.26 (s, 1H), 5.73 (t, *J*=56.0 Hz, 1H), 2.29-2.25 (m, 2H), 2.18 (s, 6H), 1.94-1.93 (m, 2H), 1.37 (t, *J*=6.8 Hz, 2H), 0.91 (s, 6H).

Intermediate 25

4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-



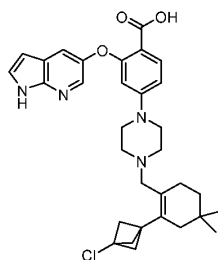
[0341] Step 1: To a stirred solution of 1-iodo-3-(trifluoromethyl)bicyclo[1.1.1]pentane (5.00 g, 19.1 mmol) in Et₂O (100 mL) at -78 °C was added *sec*-BuLi (1.4 M in cyclohexane, 13.63 mL, 19.08 mmol). After 10 minutes at -78 °C, the reaction was warmed to 0 °C and stirred for 1 h. The reaction mixture was then cooled to -78 °C and then a solution of **Intermediate 19** (3.63 g, 15.90 mmol) in Et₂O (50 mL) was added. After 1 h, the reaction was warmed to 0 °C and stirred for 2 h and then warmed to rt for 1h. The reaction mixture was quenched with sat. aq. NH₄Cl (100 mL) and extracted with Et₂O (3 x 150 mL). The organic layers were then dried over Na₂SO₄, filtered and concentrated to provide 2-(diethoxymethyl)-5,5-dimethyl-1-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohexanol (**Intermediate 25-1**) (7 g, crude) as a brown oil. The crude product was used in the next step without further purification.

[0342] Step 2: **Intermediate 25** was prepared following the procedure described in Step 3 for **Intermediate 23** using **Intermediate 25-1** in place of **Intermediate 23-2**. ¹H

NMR (400 MHz, CDCl_3) δ 10.23 (s, 1H), 2.29 (s, 6H), 2.28-2.26 (m, 2H), 1.92 (t, $J=2.0$ Hz, 2H), 1.36 (t, $J=6.8$ Hz, 2H), 0.91 (s, 6H).

Intermediate 26

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0343] Step 1: A solution of 5-iodo-4,4-dimethylpent-1-ene (9.85 g, 44.0 mmol) in pentane (100 mL) was treated with *t*-BuLi (64.6 mL, 1.7 M in *n*-pentane, 109.9 mmol) at -78°C under inert atmosphere. After 1 h, a solution of **Intermediate 1** (5 g, 26.4 mmol) in THF (20 mL) was added and the mixture was stirred at -78°C for 1 h. The reaction was then warmed to -30 °C over 30 min. and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl at -30°C, warmed to rt and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water, dried over Na_2SO_4 , filtered and concentrated. The product was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to provide 1-(3-chlorobicyclo[1.1.1] pentan-1-yl)-3,3-dimethylhex-5-en-1-one (**Intermediate 26-1**) (7 g, 70%) as an oil. ^1H NMR (300 MHz, CDCl_3) δ 5.83-5.69 (m, 1H), 5.05-4.96 (m, 2H), 2.36 (s, 6H), 2.30 (s, 2H), 2.09 (d, $J=7.5$ Hz, 2H), 0.98 (s, 6H).

[0344] Step 2: A solution of **Intermediate 26-1** (3.1 g, 13.7 mmol) and acrylonitrile (2.18 g, 41.0 mmol) in degassed DCM (120 mL) was treated dropwise over 2 h with a solution of Hoveyda-Grubbs CatalystTM 2nd Generation (343 mg, 0.55 mmol) in DCM (5 mL) at 45 °C. The reaction was stirred at 45°C for 48 h, cooled to rt, concentrated and absorbed onto Celite. The residue was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to afford 7-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxohept-2-enenitrile (**Intermediate 26-2**) as mixture of E/Z isomers (1.3 g, 38%) as a clear colorless oil. LC/MS (ESI) m/z 252.1 $[\text{M}+\text{H}]^+$.

[0345] Step 3: A solution of **Intermediate 26-2** (700 mg, 2.78 mmol) in MeOH (20 mL) was treated with Pd/C (10 wt %, 170 mg) and stirred under an atmosphere of H₂ (1 atm) for 2 h. The reaction was purged with N₂ and the reaction mixture was filtered over Celite and concentrated to provide 7-(3-chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxoheptanenitrile (**Intermediate 26-3**) (550 mg, 77%) as a clear colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 2.37 (s, 6H), 2.35-2.30 (m, 4H), 1.66-1.55 (m, 2H), 1.52-1.44 (m, 2H), 0.98 (s, 6H).

[0346] Step 4: A solution of **Intermediate 26-3** (1.1 g, 4.34 mmol, 1 eq) in THF (20 mL) was treated with 4 Å molecular sieves (100 mg) and 15-Crown-5 (956 mg, 4.34 mmol) and was placed in a preheated 70 °C oil bath. After 2 min, the reaction was treated with t-BuONa (2.09 g, 21.7 mmol) in a single portion. After 5 h, the reaction was cooled to rt and poured into a stirring solution of sat. aq. NH₄Cl. The aqueous phase was washed with DCM (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to afford 2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbonitrile (**Intermediate 26-4**) (800 mg, 39%) as a clear colorless oil. LC/MS (ESI) *m/z* 236.3 [M+H]⁺.

[0347] Step 5: To a stirred solution of **Intermediate 26-4** (400 mg, 1.70 mmol) in anhydrous DCM (20 mL) at -78 °C was added DIBAL-H (2.55 mL, 1M in toluene, 2.55 mmol). The reaction was warmed to rt. After 4 h, the reaction was cooled to 0 °C, quenched with 2M HCl(aq.) (40 mL) and warmed to rt. The reaction mixture was diluted with water, and extracted with DCM (2 x 40 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated to provide 2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl cyclohex-1-enecarbaldehyde (**Intermediate 26-5**) (400 mg, quantitative). This compound was used directly in the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 10.19 (s, 1H), 2.44 (s, 6H), 2.30-2.22 (m, 2H), 1.90 (s, 2H), 1.35 (t, *J*=6 Hz, 2H), 0.90 (s, 6H).

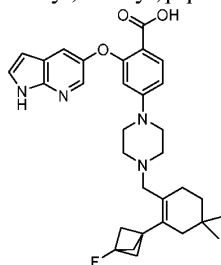
[0348] Step 6: To a stirred solution of **Intermediate 26-5** (300 mg, 1.26 mmol) in DCM (10 mL) was added **Intermediate 2** (544 mg, 1.38 mmol) and NaBH(OAc)₃ (347 mg, 1.64 mmol) at rt. After 16 h, additional NaBH(OAc)₃ (347 mg, 1.64 mmol) was added. After 48 h, the reaction was quenched with MeOH (0.2 mL) at 0 °C, warmed to rt and

concentrated. The residue was diluted with DCM and washed with sat. aq. NaHCO_3 . The aqueous layer was washed with DCM (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to afford *tert*-butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl-oxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 26-6**) (220 mg, 44.6 mmol; 28%) as a white solid. LC/MS (ESI) m/z 617.3 $[\text{M}+\text{H}]^+$.

[0349] Step 7: To a solution of **Intermediate 26-6** (125 mg, 0.20 mmol) in DCM (2 mL) at 0 °C was added TFA (139 mg, 1.22 mmol). The mixture was warmed to rt and stirred for 3 h and concentrated to provide the TFA salt of 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl-oxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-yl)methyl)piperazin-1-yl)benzoic acid (140 mg, quantitative) as a white solid LC/MS (ESI) m/z 561.3 $[\text{C}_{32}\text{H}_{37}\text{ClN}_4\text{O}_3+\text{H}]^+$.

Intermediate 27

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0350] Step 1: 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-3,3-dimethylhex-5-en-1-one (**Intermediate 27-1**) was prepared following the procedure described in Step 1 for **Intermediate 26** using **Intermediate 11** in place of **Intermediate 1**. ^1H NMR (300 MHz, CDCl_3) δ 5.84-5.69 (m, 1H), 5.06-4.96 (m, 2H), 2.34 (s, 2H), 2.29 (d, $J=2.4$ Hz, 6H), 2.10 (d, $J=7.2$ Hz, 2H), 0.99 (s, 6H).

[0351] Step 2: *E/Z*-7-(3-fluorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxohept-2-enenitrile (**Intermediate 27-2**) was prepared following the procedure described in Step 2

for **Intermediate 26** using **Intermediate 27-1** in place of **Intermediate 26-1**. LC/MS (ESI) m/z 236.3 [M+H]⁺.

[0352] Step 3: 7-(3-fluorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxoheptanenitrile (**Intermediate 27-3**) was prepared following the procedure described in Step 3 for **Intermediate 26** using **Intermediate 27-2** in place of **Intermediate 26-2**. ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 2H), 2.32 (t, $J=6.8$ Hz, 2H), 2.31 (d, $J=2.8$ Hz, 6H), 1.64-1.58 (m, 2H), 1.51-1.47 (m, 2H), 0.99 (s, 6H).

[0353] Step 4: 2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbonitrile (**Intermediate 27-4**) was prepared following the procedure described in Step 4 for **Intermediate 26** using **Intermediate 27-3** in place of **Intermediate 26-3**. LC/MS (ESI) m/z 220.4 [M+H]⁺.

[0354] Step 5: 2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbaldehyde (**Intermediate 27-5**) was prepared following the procedure described in Step 5 for **Intermediate 26** using **Intermediate 27-4** in place of **Intermediate 26-4**. ¹H NMR (300 MHz, CDCl₃) δ 10.19 (s, 1H), 2.37-2.34 (m, 6H), 2.30-2.25 (m, 2H), 1.93 (br s, 2H), 1.40-1.35 (m, 2H), 0.91 (s, 6H).

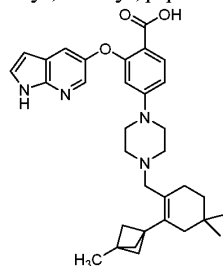
[0355] Step 6: To a stirred solution of **Intermediate 27-5** (100 mg, 0.45 mmol) in EtOH (4 mL) was added **Intermediate 2** (195 mg, 0.49 mmol) and AcOH (*cat.*) at rt and stirred for 15 min. The resulting reaction mixture was cooled to 0 °C and NaCNBH₃ (42 mg, 0.675 mmol) was added and the reaction was warmed to rt. After 16 h, the reaction was concentrated and the residue was diluted with sat. aq. NaHCO₃ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude compound was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain *tert*-Butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl-oxy)-4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 27-6**) as a white solid (40 mg, 15% yield). LC/MS (ESI) m/z 601.7 [M+H]⁺.

[0356] Step 7: 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl-oxy)-4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-yl)methyl)piperazin-1-yl)benzoic acid as the TFA salt was prepared following the procedure described in Step 7 for

Intermediate 26 by reacting **Intermediate 27-6** in place of **Intermediate 26-6**. LC/MS (ESI) m/z 545.4 [$C_{32}H_{37}FN_4O_3+H$] $^+$.

Intermediate 28

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



Route A:

[0357] Step 1: 3,3-dimethyl-1-(3-methylbicyclo[1.1.1]pentan-1-yl)hex-5-en-1-one (**Intermediate 28-1**) was prepared following the procedure described in Step 1 for **Intermediate 26** using **Intermediate 10** in place of **Intermediate 1**. 1H NMR (300 MHz, $CDCl_3$) δ 5.86-5.71 (m, 1H), 5.04-4.97 (m, 2H), 2.28 (s, 2H), 2.09 (d, $J=7.8$ Hz, 2H), 1.85 (s, 6H), 1.12 (s, 3H), 0.97 (s, 6H).

[0358] Step 2: *E/Z*-5,5-dimethyl-7-(3-methylbicyclo[1.1.1]pentan-1-yl)-7-oxohept-2-enenitrile (**Intermediate 28-2**) was prepared following the procedure described in Step 2 for **Intermediate 26** using **Intermediate 28-1** in place of **Intermediate 26-1**. LC/MS (ESI) m/z 232.3 [$M+H$] $^+$.

[0359] Step 3: 5,5-dimethyl-7-(3-methylbicyclo[1.1.1]pentan-1-yl)-7-oxoheptanenitrile (**Intermediate 28-3**) was prepared following the procedure described in Step 3 for **Intermediate 26** using **Intermediate 28-2** in place of **Intermediate 26-2**. 1H NMR (400 MHz, $CDCl_3$) δ 2.33-2.29 (m, 4H), 1.86 (s, 6H), 1.64-1.56 (m, 2H), 1.50-1.45 (m, 2H), 1.18 (s, 3H), 0.98 (s, 6H).

[0360] Step 4: 4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enecarbonitrile (**Intermediate 28-4**) was prepared following the procedure described in Step 4 for **Intermediate 26** using **Intermediate 28-3** in place of **Intermediate 26-3**. LC/MS (ESI) m/z 216.4 [$M+H$] $^+$.

[0361] Step 5: **Intermediate 22** was prepared following the procedure described in Step 5 for **Intermediate 26** using **Intermediate 28-4** in place of **Intermediate 26-4**. LC/MS (ESI) m/z 219.3 $[M+H]^+$.

[0362] Step 6: To a stirred solution of **Intermediate 22** (70 mg, 0.32 mmol) in EtOH (4 mL) was added **Intermediate 2** (190 mg, 0.48 mmol) and AcOH (cat.) at rt. After 15 min, the mixture was cooled to 0 °C, NaCNBH₃ (31 mg, 0.48 mmol) was added and the reaction was warmed to rt. After 16 h, the reaction was concentrated, and the residue was diluted with sat. aq. NaHCO₃ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain *tert*-butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate (**Intermediate 28-5**) (80 mg, 42%) as a white solid. LC/MS (ESI) m/z 597.4 $[M+H]^+$.

[0363] Step 7: 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid trifluoroacetate was prepared following the procedure described in Step 7 for **Intermediate 26** using **Intermediate 28-5** in place of **Intermediate 26-6**. LC/MS (ESI) m/z 541.4 $[C_{33}H_{40}N_4O_3+H]^+$.

Route B:

[0364] Step 1: A solution of *t*-butyl lithium (1.3 M in pentane, 60 mL, 78 mmol) was added dropwise to a solution of 1-iodo-3-methylbicyclo[1.1.1]pentane (6.5 g, 31.2 mmol) in MTBE (60 mL) at -78 °C under N₂. The reaction mixture was stirred for 1 h at -78 °C. Lithium 2-thienylcyanocuprate (0.25M in THF, 125 mL, 31.2 mmol) was added at -78 °C, and the addition was controlled to keep the temperature below -60 °C. After the addition, the reaction mixture was warmed to 0 °C and stirred for 30 min. The reaction was then cooled to -78 °C and **Intermediate 20** (5 g, 15.5 mmol) in MTBE (5 mL) was added followed by BF₃•OEt₂ (3.5 mL, 15.5 mmol). The reaction was stirred for 30 min at -78 °C and then warmed to rt. After 16 h, the reaction was cooled to 0 °C and quenched with sat. aq. NH₄Cl (50 mL) and H₂O (50 mL). MTBE (50 mL) was then added and the reaction mixture was stirred for 20 min at rt. The organic layer was separated, and the aqueous layer was

extracted with MTBE (100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by column chromatography (SiO₂, EtOAc/Heptane) followed by column chromatography (C18, CH₃CN:H₂O) provided benzyl 4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carboxylate (3.6 g, 70%). ¹H NMR (400 MHz, DMSO) δ 7.41-7.34 (m, 5H), 5.13 (s, 2H), 2.17-2.12 (m, 2H), 1.72-1.70 (m, 2H), 1.64 (s, 6H), 1.31-1.27 (m, 2H), 1.08 (s, 3H), 0.86 (s, 6H).

[0365] Step 2: To a stirred solution of benzyl 4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carboxylate (1.1 g, 3.39 mmol) in THF (40 mL) at 0 °C was added lithium aluminum hydride (386.6 mg, 10.2 mmol). The reaction was warmed to rt and stirred for 3 h. The reaction was then cooled to 0 °C, diluted with Et₂O (40 mL) and treated with H₂O (0.386 mL), 0.386 mL of 15% NaOH(aq.) followed by H₂O (1.15 mL). The reaction was warmed to rt, stirred for 15 min, and then treated with anhydrous MgSO₄. After 15 min, the reaction was filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/pet. ether) to provide (4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methanol (1.1 g, 68% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.15 (d, *J*=5.2 Hz, 2H), 2.16-2.12 (m, 2H), 1.81 (s, 6H), 1.68 (s, 2H), 1.32 (t, *J*=6.4 Hz, 2H), 1.15 (s, 3H), 0.86 (s, 6H).

[0366] Step 3: To a stirred solution of (4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methanol (500 mg, 2.27 mmol) in DCM (20 mL) at 0 °C was added SOCl₂ (0.537 mL, 4.54 mmol) drop wise. The reaction mixture was warmed to rt and stirred for 2 h. The reaction was concentrated, diluted with DCM and concentrated once more to obtain 1-(2-(chloromethyl)-5,5-dimethylcyclohex-1-en-1-yl)-3-methylbicyclo[1.1.1]pentane (540 mg, quantitative yield) as a clear oil. This was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 4.19 (s, 2H), 2.15-2.11 (m, 2H), 1.85 (s, 6H), 1.70 (s, 2H), 1.34 (t, *J*=6.4 Hz, 2H), 1.16 (s, 3H), 0.87 (s, 6H).

[0367] Step 4: To a stirred solution of 1-(2-(chloromethyl)-5,5-dimethylcyclohex-1-en-1-yl)-3-methylbicyclo[1.1.1]pentane (540 mg, 2.26 mmol) in acetone (20 mL) was added methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(piperazin-1-yl)benzoate (798 mg, 2.26 mmol), NaI (33.90 mg, 0.22 mmol) and K₂CO₃ (938.9 mg, 6.80 mmol) at rt. The reaction was then heated to reflux for 6 h. The reaction was then cooled to rt, diluted with 50

mL of acetone and filtered. The collected solid was washed with acetone (150 mL) and the combined filtrates were concentrated to provide methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (1.15 g, 91% yield) as a white solid. LC/MS (ESI) *m/z* 555.3 [M+H]⁺.

[0368] Step 5: To a stirred solution of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (1.15 g, 2.075 mmol) in MeOH:THF:H₂O (1:1:1) (36 mL) was added LiOH•H₂O (261.30 mg, 6.23 mmol) at rt. The reaction was heated to 30 °C and stirred for 16 h. The volatile solvents were then removed, and the reaction was neutralized with 1N HCl and extracted with DCM (3 x 70 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to provide **Intermediate 28** (940 mg, 84% yield) as a white solid. LC/MS (ESI) *m/z* 541.3 [M+H]⁺.

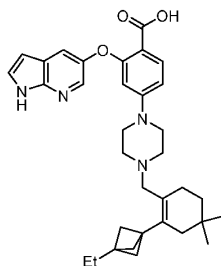
Route C:

[0369] Step 1: A solution of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(piperazin-1-yl)benzoate (35 g, 99.3 mmol) and **Intermediate 22** (26.0 g, 119.2 mmol) in THF (700 mL) was stirred at rt for 20 min. The reaction was then cooled to 0 °C and NaBH(OAc)₃ (63.15 g, 297.96 mmol) was added. Following the addition, the reaction was warmed to rt. After 16 h, the reaction was poured into ice cold water (1 L), and extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with 10% NaHCO₃ (aq.) (500 mL), and brine (500 mL). The organic layer was then dried over Na₂SO₄, filtered and concentrated. The crude product was first purified by column chromatography (SiO₂, EtOAc/pet. ether) and then triturated with MeOH and filtered to afford methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate as an off white solid (38g, 70%). LC/MS (ESI) *m/z* 555.1 [M+H]⁺.

[0370] Step 2: **Intermediate 28** was prepared following the procedure described in Step 5, Route B for **Intermediate 28**. LC/MS (ESI) *m/z* 541.3 [M+H]⁺.

Intermediate 29

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

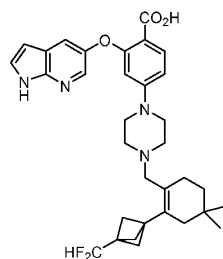


[0371] Step 1: To a solution of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(piperazin-1-yl)benzoate (1.89 g, 5.38 mmol) in DMSO (25 mL) was added a solution of **Intermediate 23** (1.5 g, 6.46 mmol) in THF (25 mL) at rt and the reaction was stirred for 1 h. The reaction was then cooled to 0 °C and treated with Na(OAc)₃BH (3.42 g, 16.14 mmol) and warmed to rt. After 24 h, the reaction was diluted with sat. aq. NaHCO₃, and extracted with 10% MeOH in DCM (4 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, Et₂O/*n*-pentane) to afford methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 29-1**) (1.4 g, 46% yield) as an off white solid. LC/MS (ESI) *m/z* 569.4 [M+H]⁺.

[0372] Step 2: **Intermediate 29** was prepared following the procedure described in Step 5, Route B for **Intermediate 28** using **Intermediate 29-1** in place of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. LC/MS (ESI) *m/z* 555.3 [M+H]⁺.

Intermediate 30

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

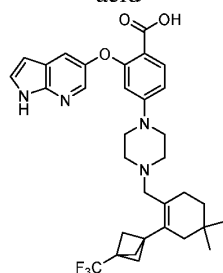


[0373] Step 1: Methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 30-1**) was prepared following the procedure described in Step 1, Route C for **Intermediate 28** using **Intermediate 24** in place of **Intermediate 22**. LC/MS (ESI) m/z 591.2 [M+H]⁺.

[0374] Step 2: **Intermediate 30** was prepared following the procedure described in Step 5, Route B for **Intermediate 26** using **Intermediate 30-1** in place of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. LC/MS (ESI) m/z 577.5[M+H]⁺.

Intermediate 31

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



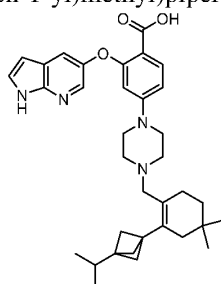
[0375] Step 1: Representative procedure (reaction was performed in 3 parallel batches): To a stirred solution of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(piperazin-1-yl)benzoate (2 g, 5.68 mmol) in DMSO (0.2 M, 30 mL) was added a solution of **Intermediate 25** (1.72 g, 6.22 mmol) in THF (30 mL) at rt. After 1 h, the reaction mixture was cooled to 0 °C, and treated with NaBH(OAc)₃ (1.70 g, 17.04 mmol). The reaction was

warmed to rt and stirred for 24 h. The reaction mixture was diluted with sat. aq. NaHCO₃, and extracted with 10% MeOH in DCM (4 x 150 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂ EtOAc/pet. ether) to afford methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate (**Intermediate 31-1**) (8.7 g, 14.29 mmol, 84% combined for three batches) as a white solid. LC/MS (ESI) *m/z* 609.3 [M+H]⁺.

[0376] Step 2: To a stirred solution of **Intermediate 31-1** (8.3 g, 13.65 mmol) in MeOH:THF:H₂O (1:1:1) (100 mL) was added LiOH•H₂O (1.7 g, 40.95 mmol) at rt. The reaction mixture was then heated to 35 °C and stirred for 16 h. The reaction mixture was concentrated, diluted with water and neutralized with 1N HCl. The product was then extracted with 10% MeOH-DCM (3 x 150 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to provide **Intermediate 31** (7.6 g, 90% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.91 (br s, 1H), 11.59 (s, 1H), 7.98 (d, *J*=2.4 Hz, 1H), 7.70 (d, *J*=8.8 Hz, 1H), 7.43 (t, *J*=2.8 Hz, 1H), 7.37 (d, *J*=2.4 Hz, 1H), 6.73-6.71 (m, 1H), 6.36-6.34 (m, 2H), 3.14-3.05 (m, 4H), 2.94 (s, 2H), 2.40-2.28 (m, 4H), 2.12 (s, 6H), 2.09-1.99 (m, 2H), 1.68 (s, 2H), 1.29-1.19 (m, 2H), 0.84 (s, 6H); ¹⁹F NMR (376 MHz, DMSO-*d*₆, unreferenced) δ -71.55; LC/MS (ESI) *m/z* 595.3 [M+H]⁺.

Intermediate 32

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((2-(3-isopropylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0377] Step 1: 3,3-dimethyl-1-(3-isopropylbicyclo[1.1.1]pentan-1-yl)hex-5-en-1-one (**Intermediate 32-1**) was prepared following the procedure described in Step 1 from **Intermediate 26** using **Intermediate 12** in place of **Intermediate 1**. ¹H NMR (400 MHz,

CDCl_3) δ 5.81-5.74 (m, 1H), 5.04-4.97 (m, 2H), 2.31 (s, 2H), 2.10 (d, $J=7.6$ Hz, 2H), 1.76 (s, 6H), 1.69-1.65 (m, 1H), 0.99 (s, 6H), 0.83 (d, $J=6.8$ Hz, 6H).

[0378] Step 2: *E/Z*-7-(3-isopropylbicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxohept-2-enenitrile (**Intermediate 32-2**) was prepared following the procedure described in Step 2 from **Intermediate 26** using **Intermediate 32-1** in place of **Intermediate 26-1**. LC/MS (ESI) m/z 260.4 $[\text{M}+\text{H}]^+$.

[0379] Step 3: 7-(3-Isopropylbicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxoheptanenitrile (**Intermediate 32-3**) was prepared following the procedure described in Step 3 from **Intermediate 26** using **Intermediate 32-2** in place of **Intermediate 26-2**. ^1H NMR (400 MHz, CDCl_3) δ 2.34-2.30 (m, 4H), 1.78 (s, 6H), 1.70-1.57 (m, 4H), 1.51-1.46 (m, 1H), 0.98 (s, 6H), 0.84 (d, $J=7.2$ Hz, 6H).

[0380] Step 4: 2-(3-Isopropylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbonitrile (**Intermediate 32-4**) was prepared following the procedure described in Step 4 from **Intermediate 26** using **Intermediate 32-3** in place of **Intermediate 26-3**. LC/MS (ESI) m/z 244.4 $[\text{M}+\text{H}]^+$.

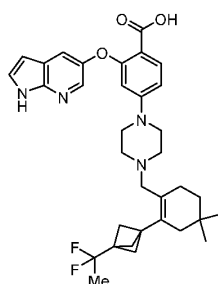
[0381] Step 5: 2-(3-Isopropylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbaldehyde (**Intermediate 32-5**) was prepared following the procedure described in Step 5 from **Intermediate 26** using **Intermediate 32-4** in place of **Intermediate 26-4**. LC/MS (ESI) m/z 247.4 $[\text{M}+\text{H}]^+$.

[0382] Step 6: *tert*-Butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((2-(3-isopropylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate (**Intermediate 32-6**) was prepared following the procedure described in Step 6, Route A for **Intermediate 28** using **Intermediate 32-5** in place of **Intermediate 28-5**. LC/MS (ESI) m/z 625.7 $[\text{M}+\text{H}]^+$.

[0383] Step 7: To a solution of **Intermediate 32-6** (160 mg, 0.26 mmol) in DCM (5 mL) at 0 °C was added TFA (176 mg, 1.54 mmol). The mixture was warmed to rt and stirred for 3 h. The reaction was then diluted with sat. aq. NaHCO_3 (10 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to provide **Intermediate 32** as an off-white solid. LC/MS (ESI) m/z 569.6 $[\text{M}+\text{H}]^+$.

Intermediate 33

2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-((2-(3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid



[0384] Step 1: 1-(3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylhex-5-en-1-one (**Intermediate 33-1**) was prepared following the procedure described in Step 1 for **Intermediate 26** using **Intermediate 13** in place of **Intermediate 1**. ¹H NMR (400 MHz, CDCl₃) δ 5.85-5.69 (m, 1H), 5.03-4.95 (m, 2H), 2.30 (s, 2H), 2.08 (d, *J*=8.0 Hz, 2H), 2.03 (s, 6H), 1.53 (t, *J*=18.0 Hz, 3H), 0.97 (s, 6H).

[0385] Step 2: *E/Z*-7-(3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxohept-2-enenitrile (**Intermediate 33-2**) was prepared following the procedure described in Step 2 for **Intermediate 26** using **Intermediate 33-1** in place of **Intermediate 26-1**. LC/MS (ESI) *m/z* 282.5 [M+H]⁺.

[0386] Step 3: 7-(3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethyl-7-oxoheptanenitrile (**Intermediate 33-3**) was prepared following the procedure described in Step 3 for **Intermediate 26** using **Intermediate 33-2** in place of **Intermediate 26-2**. ¹H NMR (400 MHz, CDCl₃) δ 2.34-2.31 (m, 4H), 2.06 (s, 6H), 1.66-1.57 (m, 2H), 1.55 (t, *J*=18.0 Hz, 3H), 1.51-1.46 (m, 2H), 0.99 (s, 6H).

[0387] Step 4: 2-(3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbonitrile (**Intermediate 33-4**) was prepared following the procedure described in Step 4 for **Intermediate 26** using **Intermediate 33-3** in place of **Intermediate 26-3**. LC/MS (ESI) *m/z* 266.1 [M+H]⁺.

[0388] Step 5: 2-(3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enecarbaldehyde (**Intermediate 33-5**) was prepared following the

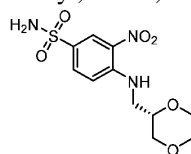
procedure described in Step 5 for **Intermediate 26** using **Intermediate 33-4** in place of **Intermediate 26-4**. LC/MS (ESI) m/z 269.5 $[M+H]^+$.

[0389] Step 6: *tert*-butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((2-(3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate (**Intermediate 33-6**) was prepared following the procedure described in Step 6, Route A for **Intermediate 28** using **Intermediate 33-5** in place of **Intermediate 28-5**. LC/MS (ESI) m/z 647.3 $[M+H]^+$.

[0390] Step 7: **Intermediate 33** was prepared following the procedure described in Step 7 for **Intermediate 32** using **Intermediate 33-6** in place of **Intermediate 32-6**. LC/MS (ESI) m/z 591.3 $[M+H]^+$.

Intermediate 34

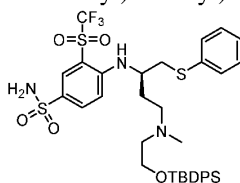
(S)-4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrobenzenesulfonamide



[0391] A solution of (S)-(1,4-dioxan-2-yl)methanamine hydrochloride (500 mg, 3.25 mmol) in THF (5 mL) was treated with 4-fluoro-3-nitrobenzenesulfonamide (501 mg, 2.20 mmol) and DIPEA (1.65 g, 13 mmol) and the mixture was heated to 45 °C. After 16 h, the reaction was concentrated, triturated with MeOH, and filtered to provide **Intermediate 34** (500 mg, 48%) as a yellow solid. LC/MS (ESI) m/z 318.4 $[M+H]^+$.

Intermediate 35

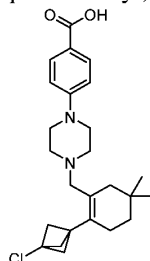
(R)-4-((4-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



[0392] **Intermediate 35** was prepared following a procedure described in WO2012/017251A1. LCMS (ESI) m/z 780.6 $[M+H]^+$.

Intermediate 36

4-(4-((2-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0393] Step 1: To a stirred solution of 3,3-dimethylpent-4-en-1-ol (18.5 g, 162.01 mmol) in DCM (100 mL), was added MsCl (13.54 mL, 175.0 mmol) followed by NEt₃ (33.87 mL, 243.0 mmol) at 0 °C and the reaction was warmed to rt. After 4 h, sat. aq. NaHCO₃ solution (100 mL) was added and the reaction was extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford 3,3-dimethylpent-4-enyl methanesulfonate (**Intermediate 36-1**) (20.0 g, 64% yield) as a clear colorless oil. This was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 5.80-5.72 (m, 1H), 5.01-4.94 (m, 2H), 4.22-4.18 (m, 2H), 2.99 (s, 3H), 1.81-1.77 (m, 2H), 1.06 (s, 6H).

[0394] Step 2: To a pressure flask was added **Intermediate 36-1** (20 g, 104.01 mmol) and NaI (46.77 g, 312.04 mmol) in acetone (100 mL). The flask was sealed and the reaction was stirred at 100 °C for 12 h. The reaction mixture was cooled to rt, diluted with water (250 mL) and extracted with Et₂O (3 x 200 mL). The combined organic layers were washed with sat. aq. Na₂S₂O₃, dried over Na₂SO₄, and evaporated to afford 5-iodo-3,3-dimethylpent-1-ene (**Intermediate 36-2**) (18 g, 77% yield) as a clear colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.75-5.68 (m, 1H), 5.01-4.92 (m, 2H), 3.09-3.05 (m, 2H), 1.99-1.95 (m, 2H), 1.01 (s, 6H).

[0395] Step 3: 1-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylhex-5-en-1-one (**Intermediate 36-3**) was prepared following the procedure described in Step 1 for **Intermediate 26** by reacting **36-2** in place of 5-iodo-4,4-dimethylpent-1-ene. ¹H NMR (400 MHz, CDCl₃) δ 5.71-5.63 (m, 1H), 4.97-4.88 (m, 2H), 2.38 (s, 6H), 2.34-2.30 (m, 2H), 1.57-1.52 (m, 2H), 0.98 (s, 6H).

[0396] Step 4: Ozone gas was bubbled into a solution of **Intermediate 36-3** (1.5 g, 6.63 mmol) in DCM (40 mL) at -78 °C until the solution turned a blue color (~30 min). Then N₂ gas was bubbled into the reaction mixture until it became colorless. PPh₃ (2.6 g, 9.94 mmol) was added in one portion and the reaction was warmed to rt. After 3 h, the reaction mixture was diluted with DCM (100 mL), washed with water (2 x 25 mL), and brine (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to afford 5-(3-chlorobicyclo[1.1.1]pentan-1-yl)-2,2-dimethyl-5-oxopentanal (**Intermediate 36-4**) as a clear colorless oil (800 mg, 53% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 2.39 (s, 6H), 2.38-2.33 (m, 2H), 1.77-1.72 (m, 2H), 1.05 (s, 6H).

[0397] Step 5: To a stirred solution of diethyl cyanomethylphosphonate (619 mg, 3.50 mmol) in toluene (10 mL) at 0 °C was added LiHMDS (1 M in toluene, 3.5 mL, 3.50 mmol). The reaction was then warmed to rt. After 30 min, the solution was added dropwise at -78 °C to a solution of **Intermediate 36-4** (800 mg, 3.50 mmol) in toluene (10 mL). The reaction mixture was warmed to rt and stirred for 16 h at which point it was cooled to 0 °C and quenched with sat. aq. NH₄Cl (20 mL). The organic phase was separated and the aqueous phase was further extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain (*E*)-7-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-7-oxohept-2-enenitrile (**Intermediate 36-5**) as a clear colorless oil (440 mg, 50% yield). LC/MS (ESI) *m/z* 252.4 [M+H]⁺.

[0398] Step 6: A solution of **Intermediate 36-5** (440 mg, 1.75 mmol) in MeOH (10 mL) was treated with Pd/C (25 wt %, 110 mg) and stirred under an atmosphere of H₂ (1 atm) for 2 h. The reaction was then purged with N₂, and filtered over Celite. The Celite plug was washed with MeOH (3 x 25 mL) and the combined organic layers were concentrated to provide 7-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-7-oxoheptanenitrile (**Intermediate 36-6**) as a clear colorless oil (360 mg, 81% yield). ¹H NMR (400 MHz, CDCl₃) 2.41 (s, 6H), δ 2.40-2.36 (m, 2H), 2.30-2.25 (m, 2H), 1.63-1.56 (m, 2H), 1.50-1.46 (m, 2H), 0.89 (s, 6H).

[0399] Step 7: 2-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-ene-1-carbonitrile (**Intermediate 36-7**) was prepared following the procedure described in Step 4 for **Intermediate 26** by reacting **Intermediate 36-6** in place of **Intermediate 26-3**. LC/MS (ESI) m/z 236.4 [M+H]⁺.

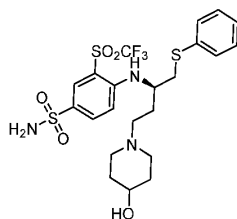
[0400] Step 8: 5,5-Dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde (**Intermediate 36-8**) was prepared following the procedure described in Step 5 for **Intermediate 26** by reacting **Intermediate 36-7** in place of **Intermediate 26-4**. ¹H NMR (400 MHz, CDCl₃) δ 10.17 (s, 1H), 2.46 (s, 6H), 2.44 (s, 2H), 2.03 (t, $J=7.6$ Hz, 2H), 1.42-1.37 (m, 2H), 0.86 (s, 6H).

[0401] Step 9: To a stirred solution of **Intermediate 36-8** (85 mg, 0.361 mmol) in EtOH (3 mL) was added *tert*-Butyl 4-(piperazin-1-yl)benzoate (104 mg, 0.397 mmol) and AcOH (*cat.*). After 15 min, the reaction was cooled to 0 °C, treated with NaCNBH₃ (33.6 mg, 0.535 mmol) and warmed to rt. After 16 h, the reaction was diluted with sat. aq. NaHCO₃ and extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain *tert*-Butyl 4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 36-9**) as a white solid (80 mg, 50% yield). LC/MS (ESI) m/z 485.6 [M+H]⁺.

[0402] Step 10: To a stirred solution of **Intermediate 36-9** (80 mg, 0.165 mmol) in DCM (3 mL) at 0 °C was added TFA (113 mg, 0.99 mmol). The reaction was warmed to rt and stirred for 3h. The reaction was concentrated and then diluted with sat. aq. NaHCO₃ and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to obtain the **Intermediate 36** as an off-white solid (60 mg, 85%). LC/MS (ESI) m/z 429.5 [M+H]⁺.

Intermediate 37

(*R*)-4-(4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide



[0403] Step 1: To a stirred solution of (*R*)-3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(phenylthio)butanoic acid (6.8 g, 15.7 mmol) in DCM (70 mL) and DMF (10 mL) was added HATU (9.5 g, 25.12 mmol) followed by DIPEA (8.3 mL, 47.1 mmol) at 0 °C. After 10 min, 4-hydroxypiperidine (2.4 g, 23.55 mmol) was added and temperature was raised to rt. After 16 h, the reaction was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂ MeOH/DCM) to afford (*R*)-(9*H*-fluoren-9-yl)methyl-4-(4-hydroxypiperidin-1-yl)-4-oxo-1-(phenylthio)butan-2-ylcarbamate (**Intermediate 37-1**) (5.5 g, 68% yield) as a brown oil. LC/MS (ESI) *m/z* 517.6 [M+H]⁺.

[0404] Step 2: To a stirred solution of **Intermediate 37-1** (2.75 g, 5.32 mmol) in CH₃CN (20 mL) at rt was added diethylamine (3.3 mL, 31.92 mmol) and stirred at rt. After 16 h, the reaction was concentrated and purified by column chromatography (neutral alumina, MeOH/DCM) to afford (*R*)-3-amino-1-(4-hydroxypiperidin-1-yl)-4-(phenylthio)butan-1-one (**Intermediate 37-2**) (900 mg, 57% yield) as a brown liquid. LC/MS (ESI) *m/z* 295.1 [M+H]⁺.

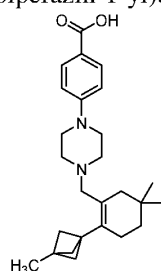
[0405] Step 3: To a stirred solution of **Intermediate 37-2** (0.9 g, 3.06 mmol) in anhydrous THF (12 mL) at 0 °C was added BH₃ (1 M in THF, 9.18 mL, 9.18 mmol) and the temperature was raised to 45 °C. After 16 h, the reaction was cooled to 0 °C and MeOH (30 mL) was added. After 1 hour, the reaction was concentrated and purified by column chromatography (C18, CH₃CN/Water) to afford (*R*)-1-(3-amino-4-(phenylthio)butyl)piperidin-4-ol (**Intermediate 37-3**) (305 mg, 36% yield) as an off-white semi solid. LC/MS (ESI) *m/z* 281.2 [M+H]⁺.

[0406] Step 4: To a stirred solution of **Intermediate 37-3** (100 mg, 0.357 mmol) in DMF (1 mL) was added 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (99 mg,

0.32 mmol) followed by DIPEA (140 mg, 1.07 mmol) and the resulting reaction mixture was stirred at rt. After 16 h, the reaction was concentrated, diluted with water and extracted with 9:1 DCM:MeOH (2 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by trituration with EtOAc/Et₂O to afford **Intermediate 37** (105 mg, 51% yield) as a white solid. LC/MS (ESI) *m/z* 568.1 [M+H]⁺.

Intermediate 38

4-(4-((5,5-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0407] Step 1: 4,4-Dimethyl-1-(3-methylbicyclo[1.1.1]pentan-1-yl)hex-5-en-1-one (**Intermediate 38-1**) was prepared following the procedure described in Step 1 for **Intermediate 26** using **Intermediate 10** and **Intermediate 36-2** in place of **Intermediate 1** and 5-iodo-4,4-dimethylpent-1-ene. ¹H NMR (400 MHz, CDCl₃) δ 5.73-5.66 (m, 1H), 4.95-4.88 (m, 2H), 2.33-2.28 (m, 2H), 1.88 (s, 6H), 1.55-1.51 (m, 2H), 1.21 (s, 3H), 0.99 (s, 6H).

[0408] Step 2: 2,2-dimethyl-5-(3-methylbicyclo[1.1.1]pentan-1-yl)-5-oxopentanal (**Intermediate 38-2**) was prepared following the procedure described in Step 4 for **Intermediate 36** using **Intermediate 38-1** in place of **Intermediate 36-3**. ¹H NMR (300 MHz, CDCl₃) δ 9.41 (s, 1H), 2.36-2.30 (m, 2H), 1.88 (s, 6H), 1.79-1.71 (m, 2H), 1.18 (s, 3H), 1.05 (s, 6H).

[0409] Step 3: 4,4-dimethyl-7-(3-methylbicyclo[1.1.1]pentan-1-yl)-7-oxohept-2-enenitrile (**Intermediate 38-3**) was prepared following the procedure described in Step 5 for **Intermediate 36** using **Intermediate 38-2** in place of **Intermediate 36-4**. LC/MS (ESI) *m/z* 232.5 [M+H]⁺.

[0410] Step 4: 4,4-dimethyl-7-(3-methylbicyclo[1.1.1]pentan-1-yl)-7-oxoheptanenitrile (**Intermediate 38-4**) was prepared following the procedure described in

Step 6 for **Intermediate 36** using **Intermediate 38-3** in place of **Intermediate 36-5**. ^1H NMR (400 MHz, CDCl_3) δ 2.38-2.33 (m, 2H), 2.29-2.25 (m, 2H), 1.90 (s, 6H), 1.62-1.58 (m, 2H), 1.48-1.44 (m, 2H), 1.19 (s, 3H), 0.90 (s, 6H).

[0411] Step 5: 5,5-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbonitrile (**Intermediate 38-5**) was prepared following the procedure described in Step 4 for **Intermediate 26** using **Intermediate 38-4** in place of **Intermediate 26-3**. ^1H NMR (400 MHz, CDCl_3) δ 2.11-2.06 (m, 2H), 2.00-1.98 (m, 2H), 1.93 (s, 6H), 1.35 (t, $J=6.4$ Hz, 2H), 1.18 (s, 3H), 0.90 (s, 6H).

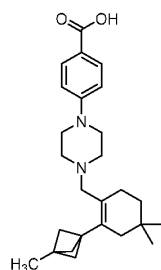
[0412] Step 6: 5,5-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde (**Intermediate 38-6**) was prepared following the procedure described in Step 5 for **Intermediate 26** using **Intermediate 38-5** in place of **Intermediate 26-4**. ^1H NMR (400 MHz, CDCl_3) δ 10.28 (s, 1H), 2.21-2.17 (m, 2H), 2.14 (br s, 2H), 2.00 (s, 6H), 1.35 (t, $J=6.4$ Hz, 2H), 1.20 (s, 3H), 0.88 (s, 6H).

[0413] Step 7: tert-Butyl 4-(4-((5,5-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 38-7**) was prepared following the procedure described in Step 9 from **Intermediate 36** using **Intermediate 38-6** in place of **Intermediate 36-8**. LC/MS (ESI) m/z 465.6 $[\text{M}+\text{H}]^+$.

[0414] Step 8: **Intermediate 38** was prepared following the procedure described in Step 10 from **Intermediate 36** by reacting **Intermediate 38-7** in place of **Intermediate 36-9**. LC/MS (ESI) m/z 409.6 $[\text{M}+\text{H}]^+$.

Intermediate 39

4-(4-((4,4-Dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

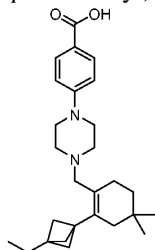


[0415] Step 1: To a stirred solution of methyl 4-(piperazin-1-yl)benzoate (1.68 g, 7.6 mmol) and **Intermediate 22** (2.0 g, 9.15 mmol) in THF (20 mL) was added Na(OAc)₃BH (4.8 g, 22.8 mmol) at rt. After 16 h, the reaction was put in an ice batch and quenched with sat. aq. NaHCO₃ (25 mL). The reaction mixture was extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain methyl 4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 39-1**) as a white solid (1.5 g, 46% yield). LC/MS (ESI) *m/z* 423.2[M+H]⁺.

[0416] Step 2: **Intermediate 39** was prepared following the procedure described in Step 5, Route B for **Intermediate 28** using **Intermediate 39-1** in place of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 7.75 (d, *J*=9.0 Hz, 2H), 6.95 (d, *J*=9.0 Hz, 2H), 3.32-3.25 (m, 4H), 3.03 (s, 2H), 2.45-2.35 (m, 4H), 2.06-2.04 (m, 2H), 1.79 (s, 6H), 1.68 (s, 2H), 1.26 (t, *J*=6.3 Hz, 2H), 1.12 (s, 3H), 0.85 (s, 6H); LC/MS (ESI) *m/z* 409.5 [M+H]⁺.

Intermediate 40

4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

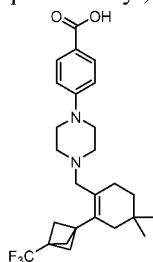


[0417] Step 1: Methyl 4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 40-1**) was prepared following the procedure described in Step 1 for **Intermediate 39** using **Intermediate 23** in place of **Intermediate 22**. LC/MS (ESI) *m/z* 437.3 [M+H]⁺.

[0418] Step 1: **Intermediate 40** was prepared following the procedure described in Step 2 for **Intermediate 39** using **Intermediate 40-1** in place of **Intermediate 39-1**. LC/MS (ESI) m/z 423.3 $[M+H]^+$.

Intermediate 41

4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

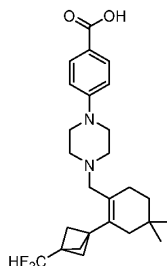


[0419] Step 1: To a stirred solution of **Intermediate 25** (3.5 g, 12.85 mmol) in toluene was added titanium (IV) ethoxide (3.73 g, 16.36 mmol). After 30 min, a solution of methyl 4-(piperazin-1-yl) benzoate (2.35 g, 10.71 mmol) in toluene (20 mL) was added and the resulting reaction mixture was stirred at rt for 1 h. The reaction mixture was then cooled to 0 °C, and Na(OAc)₃BH (6.9 g, 32.72 mmol) was added and the reaction was warmed to rt. After 16 h, the reaction was quenched with water (100 mL) at 0°C, and MTBE (200 mL) was added after 30 min. The reaction mixture was filtered over Celite and the collected solid was washed with DCM (2 x 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated. The crude product was column chromatography (SiO₂, EtOAc/pet. ether) to afford methyl 4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 41-1**) (3.2 g, 63% yield) as a white solid. LC/MS (ESI) m/z 477.3 $[M+H]^+$.

[0420] Step 2: **Intermediate 41** was prepared following the procedure described in Step 2 for **Intermediate 39** by reacting **Intermediate 41-1** in place of **Intermediate 39-1**. LC/MS (ESI) m/z 463.2 $[M+H]^+$.

Intermediate 42

4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

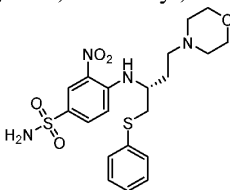


[0421] Step 1: Methyl 4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 42-1**) was prepared following the procedure described in Step 1 for **Intermediate 39** using **Intermediate 24** in place of **Intermediate 22**. ^1H NMR (400 MHz, $\text{DSMO}-d_6$) δ 7.77 (d, $J=8.8$ Hz, 2H), 6.97 (d, $J=8.8$ Hz, 2H), 6.01 (t, $J=56.4$ Hz, 1H), 3.77 (s, 3H), 3.35-3.20 (m, 4H), 3.00 (s, 2H), 2.42 (t, $J=4.4$ Hz, 4H), 2.10-2.01 (m, 2H), 1.90 (s, 6H), 1.71 (s, 2H), 1.27 (t, $J=6.0$ Hz, 2H), 0.86 (s, 6H); LC/MS (ESI) m/z 459.6 $[\text{M}+\text{H}]^+$.

[0422] Step 1: **Intermediate 42** was prepared following the procedure described in Step 2 for **Intermediate 39** using **Intermediate 42-1** in place of **Intermediate 39-1**. LC/MS (ESI) m/z 445.6 $[\text{M}+\text{H}]^+$.

Intermediate 43

(R)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-nitrobenzenesulfonamide

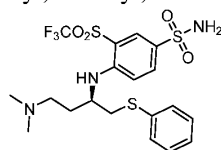


[0423] To a solution of (R)-4-morpholino-1-(phenylthio)butan-2-amine dihydrochloride (900 mg, 2.6 mmol) in DMF (10 mL) was added 4-fluoro-3-nitrobenzenesulfonamide (56 mg, 2.53 mmol) followed by DIPEA (5.8 mL, 33.8 mmol) at rt. The reaction was then heated to 50 °C for 4 h. The reaction was cooled to rt, quenched with ice cold water (150 mL) and stirred at rt for 15 min. The mixture was then filtered and the

collected solid was washed with *n*-pentane to afford **Intermediate 43** (800 mg, 66%) as a yellow solid. LCMS (ESI) m/z 467.1 $[M+H]^+$.

Intermediate 44

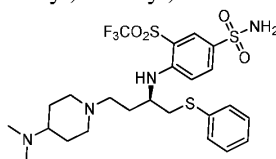
(R)-4-(((4-(dimethylamino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



[0424] **Intermediate 44** was prepared following a procedure described in WO200861208A2. LC/MS (ESI) m/z 512.2 $[M+H]^+$.

Intermediate 45

(R)-4-(((4-(4-(dimethylamino)piperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide

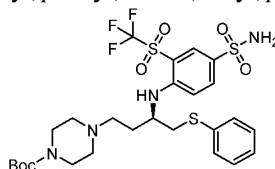


[0425] Step 1: To a stirred solution of *N,N*-dimethylpiperidin-4-amine (462.5 mg, 3.61 mmol), DMAP (367.80 mg, 3.01 mmol), and EDC•HCl (863.75 mg, 4.51 mmol) in DCM (20 mL) was added (R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butanoic acid (prepared following a procedure described in WO2012017251A1) (1.5 g, 3.01 mmol) and Et₃N (0.84 mL, 6.02 mmol) at rt. After 15 min, the reaction was heated to 35 °C and stirred for 16 h. The reaction mixture was then cooled to rt, diluted with DCM (100 mL) and MeOH (10 mL) and washed with 10% CH₃CO₂H (aq.) (2 x 20 mL). The organic layer was then washed with 5% NaHCO₃ (aq.) (20 mL) and 5% NaCl(aq.) (20 mL) and concentrated. The crude product was purified by column chromatography (C18, CH₃CN/H₂O) to provide (R)-4-(((4-(4-(dimethylamino)piperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (**Intermediate 45-1**) (686 mg, 37% yield) LC/MS (ESI) m/z 609.3 $[M+H]^+$.

[0426] Step 2: To a stirred solution of **Intermediate 45-1** (800 mg, 1.31 mmol) in THF (15 mL) was added $\text{BH}_3 \cdot \text{THF}$ (1M in THF, 6.57 mL, 6.57 mmol) at rt. The resulting reaction mixture was heated to 55 °C for 24 h in a sealed tube. The reaction was then cooled to rt, and treated with MeOH (8 mL) and conc. HCl (2 mL) and heated to 65 °C. After 10 h. the reaction was concentrated, diluted with 2N NaOH solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (C18, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$) to afford **Intermediate 45** (490 mg, 62% yield). LC/MS (ESI) m/z 595.3 $[\text{M}+\text{H}]^+$.

Intermediate 46

tert-butyl (R)-4-(4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)piperazine-1-carboxylate

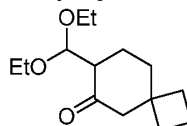


[0427] Step 1: (*R*)-tert-Butyl 4-(4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)-amino)butanoyl)piperazine-1-carboxylate (**Intermediate 46-1**) was prepared following the procedure described in Step 1 for **Intermediate 45** using *tert*-butyl piperazine-1-carboxylate in place of *N,N*-dimethylpiperidin-4-amine. LC/MS (ESI) m/z 665.4 $[\text{M}-\text{H}]^-$.

[0428] Step 2: **Intermediate 46** was prepared following the procedure described in Step 2 for **Intermediate 45** using **Intermediate 46-1** in place of **Intermediate 45-1**. LC/MS (ESI) m/z 653.2 $[\text{M}+\text{H}]^+$.

Intermediate 47

7-(Diethoxymethyl)spiro[3.5]nonan-6-one

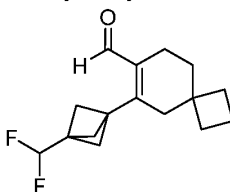


[0429] To a solution of triethyl orthoformate (7.28 mL, 43.79 mmol) in DCM (10 mL) at -30 °C was added $\text{BF}_3 \cdot \text{OEt}_2$ (6.75 mL, 54.72 mmol) dropwise over 20 min. The reaction mixture was warmed to 0 °C and stirred for 20 min. The reaction mixture was then

cooled to -78°C and spiro[3.5]nonan-6-one (3.0 g, 21.89 mmol) and *N,N*-diisopropylethylamine (11.4 mL, 35.7 mmol) were added and stirred for 90 min at the same temperature. The reaction was then carefully poured into a mixture of sat. aq. NaHCO_3 (20 mL) and DCM (30 mL). The resulting mixture was stirred for 15 min at rt and the organic layer was separated. The organic layer was washed with cold 1M H_2SO_4 (2 x 20 mL) and water. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , Et_2O /pet. ether) to afford **Intermediate 47** (3.00 g, 57 % yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.78 (d, $J=6.4$ Hz, 1H), 3.72-3.56 (m, 4H), 2.48-2.45 (m, 1H), 2.38 (d, $J=1.2$ Hz, 1H), 2.35 (d, $J=0.8$ Hz, 1H), 1.90-1.64 (m, 10H), 1.18 (t, $J=6.8$ Hz, 6H).

Intermediate 48

7-(Diethoxymethyl)-6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]nonan-6-ol



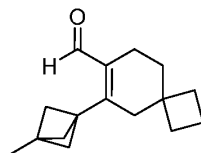
[0430] Step 1: To a stirred solution of **Intermediate 24-2** (4.67 g, 19.15 mmol) in Et_2O (30 mL) under argon was added *sec*-BuLi (1.4 M in cyclohexane, 20.8 mL, 29.12 mmol) at -78°C and the reaction was stirred for 10 minutes at the same temperature. The temperature was then warmed to 0°C and stirred for 1 h. The reaction was cooled to -78°C and a solution of **Intermediate 47** (2 g, 8.32 mmol) in Et_2O (20 mL) was added dropwise for 5 minutes. The reaction was stirred at -78°C for 1 h, and then warmed to 0°C and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) at 0°C , and extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to provide 7-(diethoxymethyl)-6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]nonan-6-ol (**Intermediate 48-1**) (1.5 g, crude) as a yellow oil. This was used in the next step without further purification.

[0431] Step 2: To a stirred solution of **Intermediate 48-1** (1.5 g crude, 4.18 mmol) in 1,4-dioxane (30 mL) was added 2N HCl (aq.) (7 mL) and the resulting reaction

mixture was stirred at 65-70 °C for 16 h. The reaction mixture was diluted with ice cold water (15 mL) and extracted with Et₂O (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The product was purified by column chromatography (SiO₂, Et₂O/pet. ether) to afford **Intermediate 48** (1 g, 45% yield over 2 steps) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ 10.21(s, 1H), 5.74 (t, *J*=56.4 Hz, 1H), 2.22-2.19 (m, 2H), 2.18 (s, 6H), 1.93-1.86 (m, 4H), 1.83-1.65 (m, 4H), 1.63-1.56 (m, 2H).

Intermediate 49

7-(diethoxymethyl)-6-(3-methylbicyclo[1.1.1]pentan-1-yl)spiro[3.5]nonan-6-ol

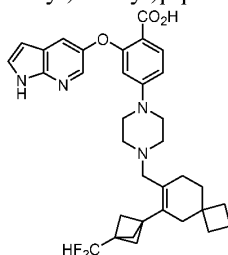


[0432] Step 1: 7-(diethoxymethyl)-6-(3-methylbicyclo[1.1.1]pentan-1-yl)spiro[3.5]nonan-6-ol (**Intermediate 49-1**) was prepared following the procedure described in Step 1 for **Intermediate 48** using 1-iodo-3-methylbicyclo[1.1.1]pentane in place of **Intermediate 24-2**.

[0433] Step 2: **Intermediate 49** was prepared following the procedure described in Step 2 for **Intermediate 49** using **Intermediate 49-1** in place of **Intermediate 48-1**. ¹H NMR (400 MHz, CDCl₃) δ 10.23 (s, 1H), 2.23-2.20 (m, 2H), 1.96 (s, 6H), 1.89-1.71 (m, 8H), 1.58-1.55 (m, 2H), 1.16 (s, 3H).

Intermediate 50

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzoic acid

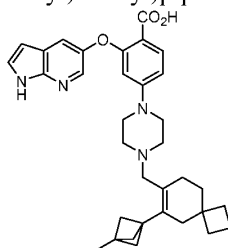


[0434] Step 1: Methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 50-1**) was prepared following the procedure described in Step 1, Route C for **Intermediate 28** using **Intermediate 48** in place of **Intermediate 22**. LC/MS (ESI) m/z 603.5 [M+H]⁺.

[0435] Step 2: **Intermediate 50** was prepared following the procedure described in Step 5, Route B for **Intermediate 28** using **Intermediate 50-1** in place of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. LC/MS (ESI) m/z 589.3.

Intermediate 51

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((6-(3-methylbicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzoic acid

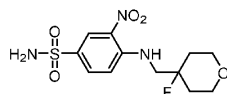


[0436] Step 1: Methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((6-(3-methylbicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzoate: (**Intermediate 51-1**) was prepared following the procedure described in Step 1, Route C for **Intermediate 28** using **Intermediate 49** in place of **Intermediate 22**. LC/MS (ESI) m/z 567.3 [M+H]⁺.

[0437] Step 2: **Intermediate 50** was prepared following the procedure described in Step 5, Route B for **Intermediate 28** using **Intermediate 51-1** in place of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. LC/MS (ESI) m/z 553.3.

Intermediate 52

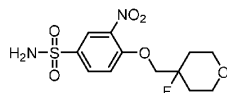
4-(((4-fluorotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrobenzenesulfonamide



[0438] To a stirred solution of (4-fluorotetrahydro-2*H*-pyran-4-yl)methanamine (450 mg, 3.38 mmol) in THF (25 mL) was added 4-fluoro-3-nitrobenzenesulfonamide (669 mg, 3.04 mmol) followed by triethylamine (1.37 g, 13.52 mmol) at rt. After 16 h, the reaction was concentrated and triturated with EtOAc and Et₂O. The crude product was purified by column chromatography (C18, 0.1 μM NH₄CO₃H(aq.):CH₃CN) to provide **Intermediate 52** (220 mg, 21% yield) as a yellow solid. LC/MS (ESI) *m/z* 334.3[M+H]⁺.

Intermediate 53

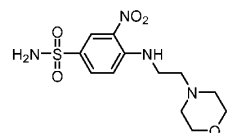
4-((4-fluorotetrahydro-2*H*-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide



[0439] **Intermediate 53** was prepared following the procedure described in Step 3 for **Intermediate 7** by using (4-fluorotetrahydro-2*H*-pyran-4-yl)methanol in place of **Intermediate 7-2**. LC/MS (ESI) *m/z* 333.5 [M-H]⁻.

Intermediate 54

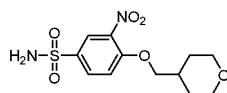
4-((2-morpholinoethyl)amino)-3-nitrobenzenesulfonamide



[0440] **Intermediate 54** was prepared following a procedure described in a WO2010/065824. LC/MS (ESI) *m/z* 331.2 [M+H]⁺.

Intermediate 55

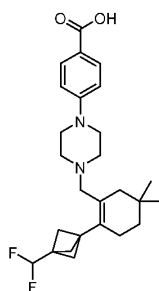
3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzenesulfonamide



[0441] **Intermediate 55** was prepared following the procedure described in Step 3 for **Intermediate 7** by using (tetrahydro-2*H*-pyran-4-yl)methanol in place of **Intermediate 7-2**. LC/MS (ESI) m/z 315.1 [M-H]⁻.

Intermediate 56

4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0442] Step 1: 2-(diethoxymethyl)-1-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohexanol (**Intermediate 56-1**) was prepared following the procedure described in Step 1, for **Intermediate 25** using **Intermediate 24-2** in place of i-iodo-3(trifluoromethyl)bicyclo[1.1.1]pentane and 2-(diethoxymethyl)-4,4-dimethylcyclohexanone in place of **Intermediate 19**. The crude product was used in the next step without purification.

[0443] Step 2: 2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-enecarbaldehyde (**Intermediate 56-2**) was prepared following the procedure described in Step 2 for **Intermediate 22**, using **Intermediate 56-1** in place of **Intermediate 22-1**. ¹H NMR (400 MHz, CDCl₃) δ 10.25 (br s, 1H), 5.74 (t, *J*=56.0 Hz, 1H), 2.23-2.21 (m, 2H), 2.20 (s, 6H), 2.03 (br s, 2H), 1.38 (t, *J*=6.4 Hz, 2H), 0.89 (s, 6H).

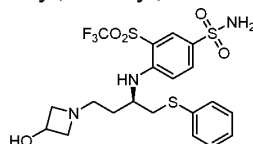
[0444] Step 3: To a stirred solution of methyl 4-(piperazin-1-yl)benzoate (389 mg, 1.77 mmol) in THF (10 mL) was added a solution of **Intermediate 56-2** (450 mg, 1.77 mmol) in THF (5 mL) at rt. The reaction was stirred for 1h, treated with Na(OAc)₃BH (1.12 g, 5.31 mmol) at 0 °C, and then warmed to rt. After 16 h, MeOH (10 mL) was added and the reaction was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure, dissolved in DCM (20 mL) and washed with sat. aq. NaHCO₃ (3×10 mL). The

organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to afford methyl 4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 56-3**) (400 mg, 49% yield) as an off-white solid. LC/MS (ESI) m/z 459.2 $[\text{M}+\text{H}]^+$.

[0445] Step 4: **Intermediate 56** was prepared following the procedure described in Step 5, Route B for **Intermediate 28** using **Intermediate 56-3** in place of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. LC/MS (ESI) m/z 445.4 $[\text{M}+\text{H}]^+$.

Intermediate 57

(*R*)-4-((4-(3-hydroxyazetidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



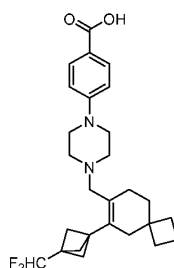
[0446] Step 1: To a solution of (*R*)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butanoic acid (1.5 g, 3.01 mmol) and O-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (1.09 g, 3.41 mmol) in DCM (3 mL) at 0 °C was added *N*-methylmorpholine (1.3 mL, 9.3 mmol) and DMF (1.5 mL). The reaction was warmed to rt and stirred for 0.5 h. The reaction mixture was then cooled to 0 °C, and azetidin-3-ol (264 mg, 3.61 mmol) was added and the reaction was warmed to rt. After 16h, the reaction was quenched with sat. aq. NaHCO_3 (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , MeOH/DCM) to afford (*R*)-4-((4-(3-hydroxyazetidin-1-yl)-4-oxo-1-(phenylthio)butan-2-yl)amino)-3-((trifluoro-methyl)sulfonyl)benzenesulfonamide (**Intermediate 57-1**) (1.00 g, 60% yield) as an off-white solid. LC/MS (ESI) m/z 554.1.

[0447] Step 2: To a stirred solution of **Intermediate 57-1** (1.0 g, 1.80 mmol) in THF (20 mL) at 0 °C was added $\text{BH}_3 \cdot \text{THF}$ (1 M in THF, 5.0 mL, 5 mmol) and the reaction

was warmed to rt. After 1 h, the reaction mixture was heated to 55 °C and stirred for 16 h in a sealed tube. The reaction mixture was then cooled to 0 °C, quenched with NH₃ (7.0 M in MeOH, 5 mL) at 0 °C and warmed to rt. After 16 h, the reaction was concentrated and purified by column chromatography (SiO₂, MeOH/DCM) to afford **Intermediate 57** (500 mg, 51% yield) as an off-white solid. LC/MS (ESI) *m/z* 540.3 [M+H]⁺.

Intermediate 58

4-(4-((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzoic acid

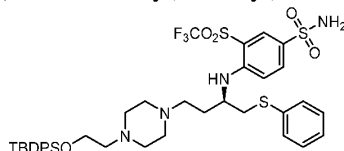


[0448] Step 1: Methyl 4-(4-((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 58-1**) was prepared following the procedure described in Step 3, for **Intermediate 56** using **Intermediate 48** in place of **Intermediate 56-2**. LC/MS (ESI) *m/z* 471.3 [M+H]⁺.

[0449] Step 2: **Intermediate 58** was prepared following the procedure described in Step 5, Route B for **Intermediate 28** using **Intermediate 58-1** in place of methyl 2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate. LC/MS (ESI) *m/z* 457.5 [M+H]⁺.

Intermediate 59

(R)-4-((4-(4-(2-((tert-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide

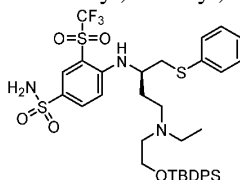


[0450] Step 1: (*R*)-4-((4-(4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)-4-oxo-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (**Intermediate 59-1**) was prepared following the procedure described in Step 1 for **Intermediate 45** using 1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazine in place of *N,N*-dimethylpiperidin-4-amine. LC/MS (ESI) m/z 849.3 [M+H]⁺.

[0451] Step 2: **Intermediate 59** was prepared following the procedure described in Step 2, for **Intermediate 57** using **Intermediate 59-1** in place of **Intermediate 57-1**. LC/MS (ESI) m/z 835.0 [M+H]⁺.

Intermediate 60

(*R*)-4-((4-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



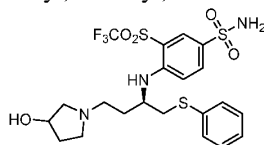
[0452] Step 1: 2-((*tert*-butyldiphenylsilyl)oxy)-*N*-ethylethanamine (**Intermediate 60-1**) was prepared following a procedure described in WO2012/017251A1. LC/MS (ESI) m/z 328.4 [M+H]⁺.

[0453] Step 2: To a stirred solution of (*R*)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butanoic acid (500 mg, 1.0 mmol) in CH₃CN (10 mL) at 0 °C was added **Intermediate 60-1** (328 mg, 1.01 mmol) in CH₃CN (2 mL), followed by *N*-methyl imidazole (250 mg, 3.1 mmol) and *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (308 mg, 1.1 mmol). The reaction was warmed to rt and stirred for 16 h. The reaction was then diluted with water and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 x 20 mL), water (2 x 10 mL) and then brine (2 x 20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to afford (*R*)-*N*-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-*N*-ethyl-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butanamide (**Intermediate 60-2**) (500 mg, 65% yield) as a yellow oil. LC/MS (ESI) m/z 808.4 [M+H]⁺.

[0454] Step 2: **Intermediate 60** was prepared following the procedure described in Step 2, for **Intermediate 57** using **Intermediate 60-2** in place of **Intermediate 57-1**. LC/MS (ESI) m/z 794.8 $[M+H]^+$.

Intermediate 61

4-(((2*R*)-4-(3-Hydroxypyrrolidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide

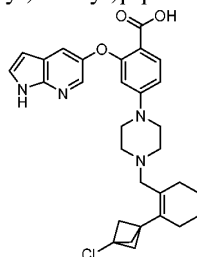


[0455] Step 1: 4-(((2*R*)-4-(3-Hydroxypyrrolidin-1-yl)-4-oxo-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (**Intermediate 61-1**) was prepared following the procedure described in Step 1, for **Intermediate 45** using pyrrolidin-3-ol in place of *N,N*-dimethylpiperidin-4-amine. LC/MS (ESI) m/z 568.1 $[M+H]^+$.

[0456] Step 2: **Intermediate 61** was prepared following the procedure described in Step 2, for **Intermediate 57** using **Intermediate 61-1** in place of **Intermediate 57-1**. LC/MS (ESI) m/z 554.4 $[M+H]^+$.

Intermediate 62

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid



[0457] Step 1: 1-(3-Chlorobicyclo[1.1.1]pentan-1-yl)hex-5-en-1-one (**Intermediate 62-1**) was prepared following the procedure described in Step 1 for **Intermediate 26** using 5-bromopent-1-ene in place of 5-iodo-3,3-dimethylpent-1-ene. ^1H NMR (300 MHz, CDCl_3) δ 5.84-5.66 (m, 1H), 5.03-4.97 (m, 2H), 2.48 (s, 6H), 2.44 (t, $J=7.2$ Hz, 2H), 2.08-2.01 (m, 2H), 1.71-1.61 (m, 2H).

[0458] Step 2: *E/Z*-7-(3-chlorobicyclo[1.1.1]pentan-1-yl)-7-oxohept-2-enenitrile (**Intermediate 62-2**) was prepared following the procedure described in Step 2 for **Intermediate 26** using **Intermediate 62-1** in place of **Intermediate 26-1**. LC/MS (ESI) *m/z* 236.3 [M+H]⁺.

[0459] Step 3: 7-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-7-oxoheptanenitrile (**Intermediate 62-3**) was prepared following the procedure described in Step 3 for **Intermediate 26** using **Intermediate 62-2** in place of **Intermediate 26-2**. ¹H NMR (400 MHz, CDCl₃) δ 2.47 (t, *J*=7.2 Hz, 2H), 2.40 (s, 6H), 2.35 (t, *J*=6.8 Hz, 2H), 1.70-1.62 (m, 2H), 1.61-1.55 (m, 2H), 1.48-1.41 (m, 2H).

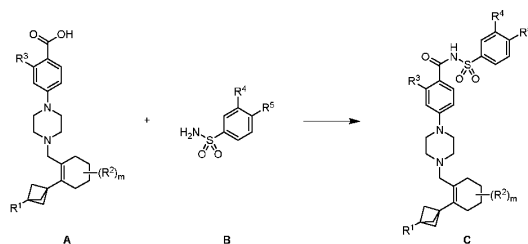
[0460] Step 4: 2-(3-chlorobicyclo[1.1.1]pentan-1-yl)cyclohex-1-enecarbonitrile (**Intermediate 62-4**) was prepared following the procedure described in Step 4 for **Intermediate 26** using **Intermediate 62-3** in place of **Intermediate 26-3**. LC/MS (ESI) *m/z* 208.1 [M+H]⁺.

[0461] Step 5: 2-(3-chlorobicyclo[1.1.1]pentan-1-yl)cyclohex-1-enecarbaldehyde (**Intermediate 62-5**) was prepared following the procedure described in Step 5 for **Intermediate 26** using **Intermediate 62-4** in place of **Intermediate 26-4**. ¹H NMR (300 MHz, CDCl₃) δ 10.16 (s, 1H), 2.46 (s, 6H), 2.23-2.21 (m, 2H), 2.15-2.13 (m, 2H), 1.64-1.54 (m, 4H).

[0462] Step 6: *tert*-butyl 2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate (**Intermediate 62-6**) was prepared following the procedure described in Step 6, Route A for **Intermediate 28** using **Intermediate 62-5** in place of **Intermediate 22**. LC/MS (ESI) *m/z* 589.3 [M+H]⁺.

[0463] Step 7: **Intermediate 62** was prepared following the procedure described in Step 7, for **Intermediate 32**, using **Intermediate 62-6** in place of **Intermediate 32-6**. LC/MS (ESI) *m/z* 533.3 [M+H]⁺.

General Procedure A: Acyl Sulfonamide Formation

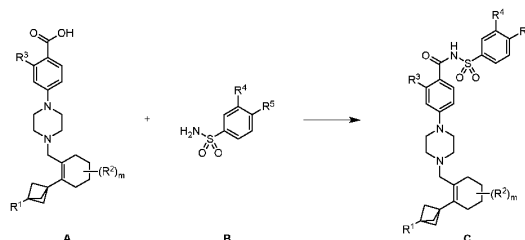


[0464] To a solution of corresponding sulfonamide **B** or acid **A** (1.0-1.2 equiv. Note #1) in DCM (0.01-0.1 M) at 0 °C was added EDC•HCl (1-2.5 equiv.) followed by DMAP (1-2 equiv.). After 10 min, the appropriate acid **A** or sulfonamide **B** (1-1.5 equiv. Note #1) and *N*-methylmorpholine (2-4 equiv. Note #2) were added at 0 °C and the reaction was warmed to rt or to 35 °C. Upon completion as determined by LCMS (or TLC), water was added and the reaction was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product **C** was either purified by 1) column chromatography (SiO₂), 2) HPLC (10 mM NH₄CO₃H(aq): CH₃CN or MeOH) or 3) trituration with an organic solvent.

[0465] Note #1: In some instances, the TFA salt of acid **A** was used.

[0466] Note #2: In some instances, *N*-methylmorpholine was not added.

General Procedure B: Acyl Sulfonamide Formation



[0467] To a solution of corresponding sulfonamide **B** (1.0 equiv) in DCM (0.01-0.1 M) at rt was added EDC•HCl (1.5-1.75 equiv.) and DMAP (1-2.5 equiv.). In a separate flask, the appropriate acid **A** (1-1.1 equiv.) was dissolved in DCM (0.02-0.1M) was treated with Et₃N (2 equiv). Note #1). After 15 min, the acid solution was added to the sulfonamide suspension and either stirred at rt or heated to 35 °C. Upon completion as determined by LCMS, *N,N*-dimethylethylenediamine (2-2.5 equiv., Note #2) was added to the reaction

mixture and the reaction was stirred for 90 min. The reaction mixture was then washed with 10% aq. AcOH (Note #3), 5% NaHCO₃(aq.) and then with 5% NaCl (aq.). The organic layer was concentrated, and crude product **C** was either purified by 1) column chromatography (SiO₂), 2) HPLC (10 mM NH₄CO₃H(aq): CH₃CN or MeOH), or 3) trituration with an organic solvent.

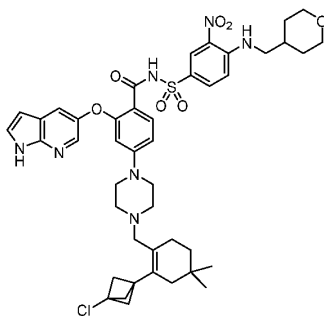
[0468] Note #1: In some instances, Et₃N was added to the flask containing sulfonamide **B**

[0469] Note #2: In some instances, *N,N*-dimethylethylenediamine was not added during the workup.

[0470] Note #3: In some instances, the organic layer was diluted with DCM and MeOH to solubilize the crude product.

Example 1

2-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl-oxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-yl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

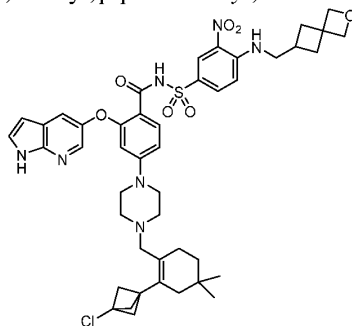


[0471] Representative example of General Procedure A: To a solution of 3-nitro-4-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)benzenesulfonamide (63 mg, 0.20 mmol) in DCM (20 mL) was added EDC•HCl (58 mg, 0.30 mmol) followed by DMAP (49 mg, 0.40 mmol) at 0 °C. After 10 min, **Intermediate 26** (140 mg, 0.20 mmol) and *N*-methylmorpholine (0.07 mL, 0.60 mmol) were added and the reaction was warmed to rt. After 16 h, water was added, and the mixture was extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (10:90 to 99:1 10mM NH₄CO₃H(aq.)/ CH₃CN) to afford **Example 1** (69

mg, 39%) as a yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.68 (br s, 1H), 11.42 (br s, 1H), 8.58 (br s, 1H), 8.53 (s, 1H), 8.03 (d, $J=2.1$ Hz, 1H), 7.77 (d, $J=8.4$ Hz, 1H), 7.54-7.46 (m, 3H), 7.10-7.02 (m, 1H), 6.74-6.68 (m, 1H), 6.38 (s, 1H), 6.25 (s, 1H), 3.89-3.82 (m, 2H), 3.33-3.22 (m, 4H), 3.19-3.05 (m, 4H), 2.90 (s, 2H), 2.33 (br s, 4H), 2.29 (s, 6H), 2.05-1.95 (m, 2H), 1.95-1.82 (m, 1H), 1.69-1.57 (m, 4H), 1.32-1.18 (m, 4H), 0.82 (s, 6H).; LC/MS (ESI) m/z 858.4 $[\text{M}+\text{H}]^+$.

Example 2

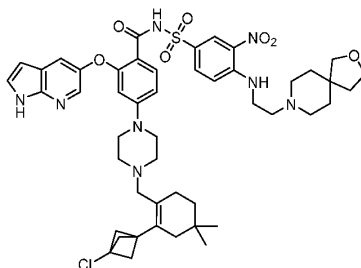
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl-oxy)-*N*-(4-(2-oxaspiro[3.3]heptan-6-yl-methylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-yl)methyl)piperazin-1-yl)benzamide



[0472] **Example 2** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 3**. ^1H NMR (400 MHz, CDCl_3) δ 10.13 (br s, 1H), 8.89 (d, $J=2$ Hz, 1H), 8.82 (br s, 1H), 8.33 (t, $J=5.2$ Hz, 1H), 8.22 (d, $J=2.8$ Hz, 1H), 8.17 (dd, $J=9.4, 1.6$ Hz, 1H), 7.98 (d, $J=9.6$ Hz, 1H), 7.72 (d, $J=2.4$ Hz, 1H), 7.44 (br s, 1H), 6.88 (d, $J=9.2$ Hz, 1H), 6.59-6.56 (m, 2H), 6.02 (s, 1H), 4.74 (s, 2H), 4.63 (s, 2H), 3.32 (t, $J=5.2$ Hz, 2H), 3.15-3.05 (m, 4H), 2.89 (s, 2H), 2.55-2.45 (m, 2H), 2.38-2.28 (m, 4H), 2.25 (s, 6H), 2.08-1.95 (br s, 4H), 1.64 (s, 2H), 1.33-1.25 (m, 2H), 0.84 (s, 6H); LC/MS (ESI) m/z 870.6 $[\text{M}+\text{H}]^+$.

Example 3

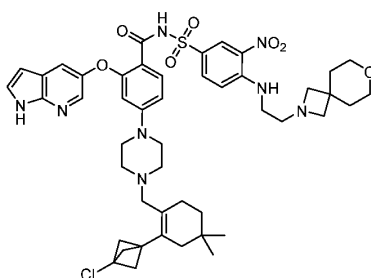
2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-*N*-((4-((2-(2-oxa-8-azaspiro[4.5]decan-8-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0473] **Example 3** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 4**. ¹H NMR (300 MHz, CDCl₃) δ 10.18 (br s, 1H), 9.21 (br s, 1H), 8.99 (br s, 1H), 8.88 (d, *J*=2.1 Hz, 1H), 8.21 (d, *J*=2.1 Hz, 1H), 8.16 (dd, *J*=9.0, 1.8 Hz, 1H), 7.97 (d, *J*=8.7 Hz, 1H), 7.71 (d, *J*=2.1 Hz, 1H), 7.45 (t, *J*=3.0 Hz, 1H), 6.86 (d, *J*=9.0 Hz, 1H), 6.60-6.54 (m, 2H), 6.03 (d, *J*=1.8 Hz, 1H), 3.85 (t, *J*=7.2 Hz, 2H), 3.57 (s, 2H), 3.42-3.36 (m, 2H), 3.10 (br s, 4H), 2.89 (s, 2H), 2.71 (t, *J*=5.7 Hz, 2H), 2.58-2.38 (m, 4H), 2.38-2.29 (m, 4H), 2.24 (s, 6H), 2.06-1.95 (m, 2H), 1.77-1.63 (m, 8H), 1.27-1.23 (m, 2H), 0.83 (s, 6H); LC/MS (ESI) *m/z* 927.6 [M+H]⁺.

Example 4

2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-*N*-(4-(2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)ethyl)amino)-3-nitrophenylsulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

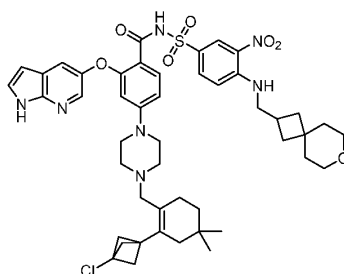


[0474] **Example 4** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 5**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.60 (s, 1H), 8.50 (br s, 1H), 8.46 (s, 1H), 7.97 (d, *J*=2.4 Hz, 1H), 7.75 (d, *J*=8.8 Hz, 1H), 7.57 (d, *J*=8.8 Hz,

1H), 7.45 (t, $J=2.4$ Hz, 1H), 7.38 (br s, 1H), 6.93 (d, $J=9.2$ Hz, 1H), 6.69 (dd, $J=9.4$, 2.0 Hz, 1H), 6.34 (dd, $J=3.2$, 2.0 Hz, 1H), 6.28 (d, $J=2.0$ Hz, 1H), 3.60-3.38 (m, 10H), 3.16-2.95 (m, 6H), 2.89 (s, 2H), 3.38-2.30 (m, 4H), 2.29 (s, 6H), 2.05-1.98 (m, 2H), 1.71-1.66 (m, 6H), 1.23 (t, $J=6.4$ Hz, 2H), 0.82 (s, 6H), one NH proton not observed; ^1H NMR (400 MHz, DMSO- d_6) LC/MS (ESI) m/z 913.5 $[\text{M}+\text{H}]^+$.

Example 5

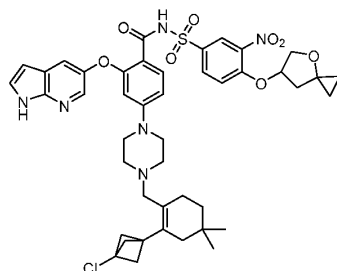
2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-*N*-(((4-(((7-oxaspiro[3.5]nonan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0475] **Example 5** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 6**. ^1H NMR (400 MHz, CDCl_3) δ 10.13 (br s, 1H), 8.88 (d, $J=2.4$ Hz, 1H), 8.81 (br s, 1H), 8.37 (t, $J=4.8$ Hz, 1H), 8.21 (d, $J=2.4$ Hz, 1H), 8.17 (dd, $J=9.6$, 2.4 Hz, 1H), 7.97 (d, $J=9.2$ Hz, 1H), 7.71 (d, $J=2.8$ Hz, 1H), 7.44 (t, $J=2.8$ Hz, 1H), 6.88 (d, $J=9.6$ Hz, 1H), 6.59-6.54 (m, 2H), 6.01 (d, $J=2.0$ Hz, 1H), 3.64 (t, $J=4.8$ Hz, 2H), 3.56 (t, $J=5.2$ Hz, 2H), 3.39-3.36 (m, 2H), 3.10 (br s, 4H), 2.89 (s, 2H), 2.70-2.65 (m, 1H), 2.32 (br s, 4H), 2.24 (s, 6H), 2.14-2.09 (m, 2H), 2.01 (br s, 2H), 1.68 (t, $J=5.2$ Hz, 2H), 1.63-1.56 (m, 6H), 1.25 (t, $J=6.0$ Hz, 2H), 0.83 (s, 6H); LC/MS (ESI) m/z 898.4 $[\text{M}+\text{H}]^+$.

Example 6

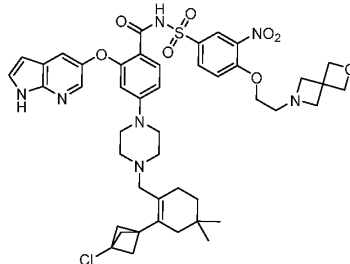
2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-*N*-(((4-(((4-oxaspiro[2.4]heptan-6-yl)oxy)-3-nitrophenyl)sulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0476] **Example 6** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 7**. LC/MS (ESI) m/z 857.4 [M+H]⁺.

Example 7

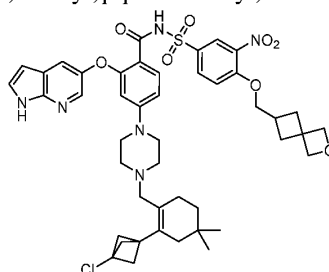
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-*N*-(4-(2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)ethoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide



[0477] **Example 7** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 8**. LC/MS (ESI) m/z 886.5 [M+H]⁺.

Example 8

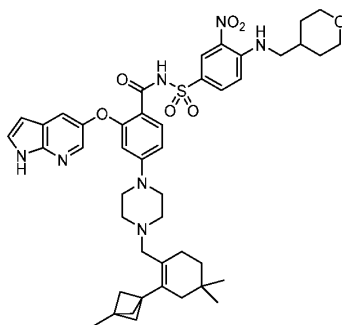
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-*N*-(4-(2-oxaspiro[3.3]heptan-6-ylmethoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide



[0478] **Example 8** was prepared following General Procedure A using **Intermediate 26** and **Intermediate 9**. LC/MS (ESI) m/z 871.6 $[M+H]^+$.

Example 9

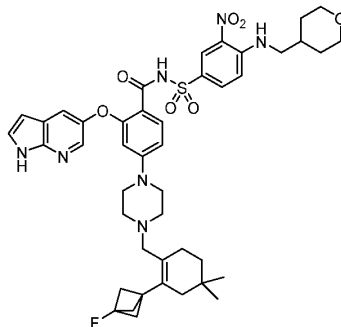
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)phenylsulfonyl)benzamide



[0479] **Example 9** was prepared following General Procedure A using **Intermediate 28** and 3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)benzenesulfonamide. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.68 (s, 1H), 11.42 (br s, 1H), 8.58 (br s, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.80-7.76 (m, 1H), 7.53-7.48 (m, 3H), 7.12-7.05 (m, 1H), 6.74-6.70 (m, 1H), 6.38 (s, 1H), 6.25 (s, 1H), 3.85-3.83 (m, 2H), 3.30-3.23 (m, 4H), 3.19-3.05 (m, 4H), 2.99 (br s, 2H), 2.38-2.32 (m, 4H), 2.05-1.95 (m, 2H), 1.93-1.85 (m, 1H), 1.75 (s, 6H), 1.67-1.58 (m, 4H), 1.30-1.20 (m, 4H), 1.10 (s, 3H), 0.81 (s, 6H); LC/MS (ESI) m/z 838.5 $[M+H]^+$.

Example 10

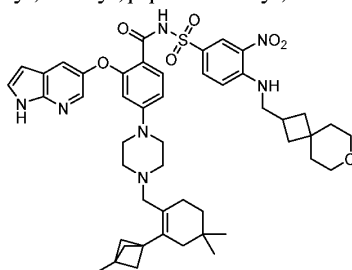
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)phenylsulfonyl)benzamide



[0480] Example 10 was prepared following General Procedure A using **Intermediate 27** and 3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)benzenesulfonamide. ¹H NMR (300 MHz, CDCl₃) δ 10.20 (br s, 2H), 9.09 (br s, 1H), 8.90 (d, *J*=2.4 Hz, 1H), 8.52 (t, *J*=5.7 Hz, 1H), 8.22-8.15 (m, 2H), 7.98 (d, *J*=9.3 Hz, 1H), 7.71 (d, *J*=9.3 Hz, 1H), 7.45 (t, *J*=3.0 Hz, 1H), 6.92 (d, *J*=9.3 Hz, 1H), 6.60-6.54 (m, 2H), 6.03-6.01 (m, 1H), 4.03 (dd, *J*=11.5, 3.9 Hz, 2H), 3.46-3.38 (m, 2H), 3.27 (t, *J*=6.0 Hz, 2H), 3.12-3.09 (m, 4H), 2.91 (s, 2H), 2.35-2.33 (m, 4H), 2.15 (d, *J*=2.4 Hz, 6H), 2.09-1.95 (m, 3H), 1.77-1.62 (m, 4H), 1.51-1.38 (m, 2H), 1.27 (t, *J*=6.3 Hz, 2H), 0.84 (s, 6H); LC/MS (ESI) *m/z* 842.4 [M+H]⁺.

Example 11

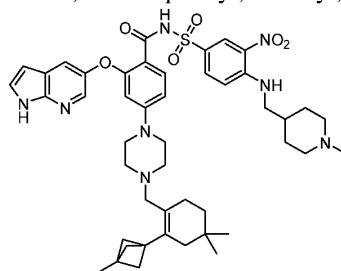
2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-*N*-((4-(((7-oxaspiro[3.5]nonan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0481] **Example 11** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 6**. ^1H NMR (400 MHz, CDCl_3) δ 10.15 (br s, 1H), 9.16 (br s, 1H), 8.88 (d, $J=2.0$ Hz, 1H), 8.37 (t, $J=4.8$ Hz, 1H), 8.22 (d, $J=2.4$ Hz, 1H), 8.17 (dd, $J=9.0, 2.0$ Hz, 1H), 7.97 (d, $J=9.2$ Hz, 1H), 7.71 (d, $J=2.0$ Hz, 1H), 7.45 (t, $J=2.8$ Hz, 1H), 6.89 (d, $J=9.6$ Hz, 1H), 6.60-6.54 (m, 2H), 6.02 (d, $J=2.0$ Hz, 1H), 3.64 (t, $J=5.2$ Hz, 2H), 3.56 (t, $J=5.2$ Hz, 2H), 3.38 (dd, $J=7.0, 5.2$ Hz, 2H), 3.10 (t, $J=4.8$ Hz, 4H), 3.00 (s, 2H), 2.71-2.64 (m, 1H), 2.35 (t, $J=4.8$ Hz, 4H), 2.15-2.09 (m, 2H), 2.01-1.98 (m, 2H), 1.73 (s, 6H), 1.68 (t, $J=5.2$ Hz, 2H), 1.66-1.56 (m, 6H), 1.24 (t, $J=6.4$ Hz, 2H), 1.10 (s, 3H), 0.82 (s, 6H); LC/MS (ESI) m/z 878.6 $[\text{M}+\text{H}]^+$

Example 12

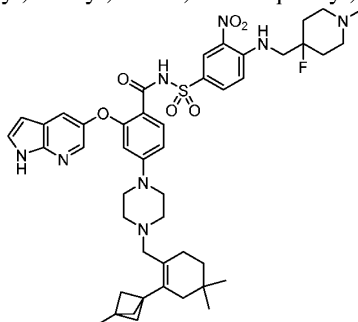
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0482] To a stirred solution of **Intermediate 28** (150 mg, 0.277 mmol) in DMF (1 mL) at 0 °C was added EDC•HCl (106.2 mg, 0.554 mmol) and 1-hydroxy-7-azabenzotriazole (75.4 mg, 0.554 mmol). After 10 min, **Intermediate 14** (92 mg, 0.277 mmol) and DIPEA (108 mg, 0.83 mmol) were added and the reaction was warmed to rt. After 48 h, water (10 mL) was added and the reaction was extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude product was purified by HPLC (30:70 to 1:99, 10mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$: CH_3CN) to afford **Example 12** as a yellow solid (6 mg, 3% yield). LC/MS (ESI) m/z 851.4 $[\text{M}+\text{H}]^+$

Example 13

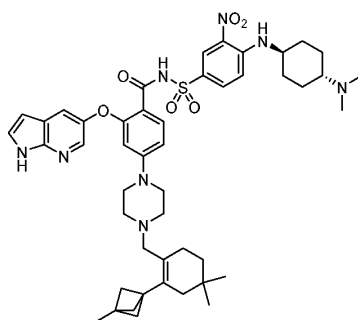
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-(((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((4-fluoro-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0483] **Example 13** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 15**. ¹H NMR (400 MHz, CDCl₃) δ 9.07 (br s, 1H), 8.90 (d, *J*=2.4 Hz, 1H), 8.66 (t, *J*=5.2, 1H), 8.17 (d, *J*=2.4 Hz, 1H), 8.10 (dd, *J*=9.2, 1.6 Hz, 1H), 7.96 (d, *J*=9.2 Hz, 1H), 7.69 (d, *J*=2.4 Hz, 1H), 7.44 (d, *J*=3.2 Hz, 1H), 6.92 (d, *J*=9.2 Hz, 1H), 6.59 (dd, *J*=9.2, 2.4 Hz, 1H), 6.54 (dd, *J*=3.6, 2.0 Hz, 1H), 6.04 (d, *J*=2.4 Hz, 1H), 3.52 (dd, *J*=19.6, 6.0 Hz, 2H), 3.11 (t, *J*=4.8 Hz, 4H), 2.99 (s, 2H), 2.82-2.75 (m, 2H), 2.41-2.31 (m, 8H), 2.06-1.97 (m, 4H), 1.74 (s, 6H), 1.65 (s, 2H), 1.33-1.22 (s, 5H), 1.10 (s, 3H), 0.82 (s, 6H). One NH proton not observed; LC/MS (ESI) *m/z* 869.5 [M+H]⁺.

Example 14

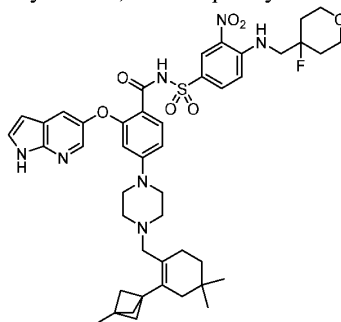
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-(((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((1r,4r)-4-(dimethylamino)cyclohexyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0484] **Example 14** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 16**. LC/MS (ESI) m/z 865.5 $[M+H]^+$.

Example 15

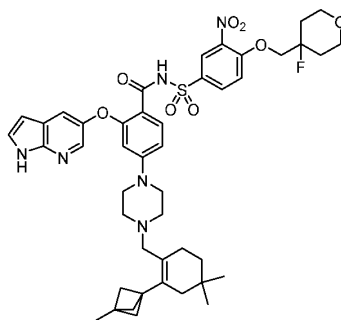
2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-fluorotetrahydro-2*H*-pyran-4-yl)methylamino)-3-nitrophenylsulfonyl)benzamide



[0485] **Example 15** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 52**. ^1H NMR (400 MHz, CDCl_3) δ 10.16 (br s, 1H), 8.97 (br s, 1H), 8.91 (d, $J=2.0$ Hz, 1H), 8.67 (t, $J=5.6$ Hz, 1H), 8.22 (d, $J=2.4$ Hz, 1H), 8.19 (dd, $J=9.0, 2.4$ Hz, 1H), 7.97 (d, $J=8.8$ Hz, 1H), 7.71 (d, $J=2.4$ Hz, 1H), 7.45 (t, $J=2.8$ Hz, 1H), 6.98 (d, $J=9.2$ Hz, 1H), 6.59 (dd, $J=9.0, 2.4$ Hz, 1H), 6.55 (dd, $J=3.2, 2.0$ Hz, 1H), 6.02 (d, $J=2.4$ Hz, 1H), 3.89 (dd, $J=11.8, 4.0$ Hz, 2H), 3.79-3.72 (m, 2H), 3.55 (dd, $J=19.6, 6.0$ Hz, 2H), 3.11-3.09 (m, 4H), 3.00 (s, 2H), 2.36-2.33 (m, 4H), 2.05-1.95 (m, 2H), 1.94-1.75 (m, 4H), 1.74 (s, 6H), 1.64 (s, 2H), 1.24 (t, $J=6.4$ Hz, 2H), 1.10 (s, 3H), 0.82 (s, 6H); LC/MS (ESI) m/z 856.5 $[M+H]^+$.

Example 16

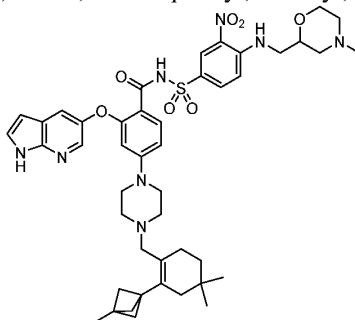
2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-fluorotetrahydro-2*H*-pyran-4-yl)methoxy)-3-nitrophenyl)sulfonyl)benzamide



[0486] **Example 16** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 53**. ^1H NMR (400 MHz, CDCl_3) δ 10.16 (br s, 1H), 8.85 (br s, 1H), 8.58 (d, $J=2.4$ Hz, 1H), 8.38 (dd, $J=9.2$, 2.4 Hz, 1H), 8.22 (d, $J=2.8$ Hz, 1H), 7.95 (d, $J=9.2$ Hz, 1H), 7.70 (d, $J=2.8$ Hz, 1H), 7.45 (t, $J=2.8$ Hz, 1H), 7.18 (d, $J=8.8$ Hz, 1H), 6.60-6.54 (m, 2H), 6.01 (d, $J=2.0$ Hz, 1H), 4.18 (d, $J=18.0$ Hz, 2H), 3.91-3.87 (m, 2H), 3.81-3.74 (m, 2H), 3.12-3.10 (m, 4H), 2.99 (s, 2H), 2.36-2.34 (m, 4H), 2.01-1.83 (m, 6H), 1.74 (s, 6H), 1.65 (s, 2H), 1.24 (t, $J=6.0$ Hz, 2H), 1.10 (s, 3H), 0.82 (s, 6H); LC/MS (ESI) m/z 857.5 $[\text{M}+\text{H}]^+$.

Example 17

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-(((4-methylmorpholin-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide

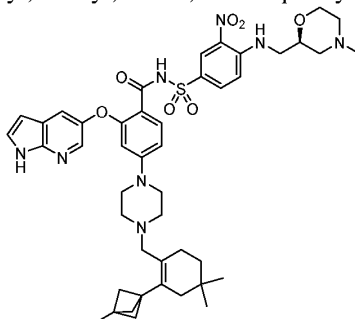


[0487] **Example 17** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 17**. ^1H NMR (400 MHz, CDCl_3) δ 10.16 (br s, 1H), 8.97 (br s, 1H), 8.88 (d, $J=2.0$ Hz, 1H), 8.65 (t, $J=5.6$ Hz, 1H), 8.18 (d, $J=2.4$ Hz, 1H), 8.13 (dd, $J=9.0$, 2.4 Hz, 1H), 7.96 (d, $J=9.2$ Hz, 1H), 7.70 (d, $J=2.4$ Hz, 1H), 7.43 (t, $J=2.8$ Hz, 1H), 6.88 (d, $J=9.2$ Hz, 1H), 6.58 (dd, $J=9.2$, 2.0 Hz, 1H), 6.55 (dd, $J=3.6$, 2.0 Hz, 1H), 6.03 (d,

$J=2.0$ Hz, 1H), 3.95 (d, $J=10.4$ Hz, 1H), 3.90-3.84 (m, 1H), 3.73 (dt, $J=11.4$, 2.4 Hz, 1H), 3.49-3.36 (m, 2H), 3.12-3.09 (m, 4H), 2.99 (s, 2H), 2.77 (d, $J=11.2$ Hz, 1H), 2.67 (d, $J=11.6$ Hz, 1H), 2.36-2.33 (m, 4H), 2.32 (s, 3H), 2.19 (dt, $J=11.4$, 3.2 Hz, 1H), 2.03-1.98 (m, 3H), 1.74 (s, 6H), 1.65 (s, 2H), 1.24 (t, $J=6.4$ Hz, 2H), 1.10 (s, 3H), 0.82 (s, 6H); LC/MS (ESI) m/z 853.5[M+H]⁺.

Example 18

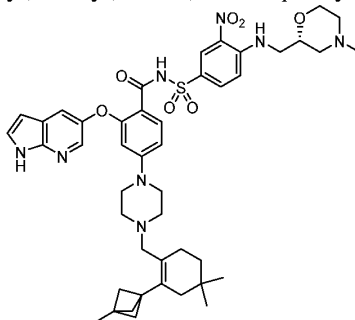
(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-methylmorpholin-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0488] Example 18 was prepared following General Procedure A using **Intermediate 28** and **Intermediate 17A**. LC/MS (ESI) m/z 853.5[M+H]⁺. The absolute stereochemistry was arbitrarily assigned.

Example 19

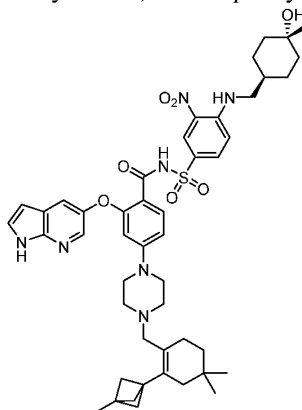
(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-methylmorpholin-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0489] **Example 19** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 17B**. LC/MS (ESI) m/z 853.6[M+H]⁺. The absolute stereochemistry was arbitrarily assigned.

Example 20

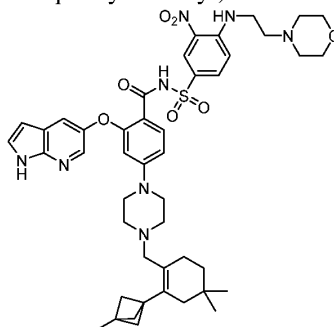
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-(((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrophenylsulfonyl)benzamide



[0490] **Example 19** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 18**. LC/MS (ESI) m/z 866.5 [M+H]⁺

Example 21

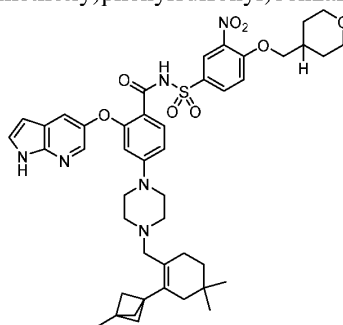
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-(2-morpholinoethylamino)-3-nitrophenylsulfonyl)benzamide



[0491] **Example 21** was prepared following General Procedure A using **Intermediate 28** and **Intermediate 54**. LC/MS (ESI) m/z 853.6 [M+H]⁺.

Example 22

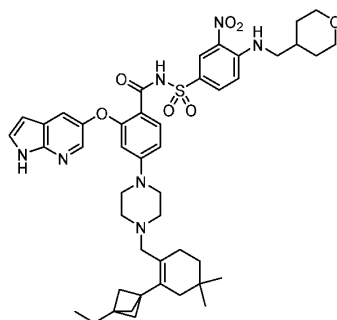
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methoxy)phenylsulfonyl)benzamide



[0492] Representative example of General Procedure B: To a stirred solution of **Intermediate 55** (70.03 mg, 0.22 mmol) in DCM (5 mL) was added DMAP (54.02 mg, 0.44 mmol), and EDC•HCl (63.15 mg, 0.33 mmol) and DCM (5 mL). In a separate flask, **Intermediate 28** (120 mg, 0.222 mmol), Et₃N (0.046 mL, 0.44 mmol) and DCM (3 mL) were combined and stirred for 15 minutes. The solution containing the acid was then slowly added to the suspension of the sulfonamide and the reaction mixture was stirred at rt. After 20 hours, *N,N*-dimethylethylenediamine (0.055 mL) was charged to the reaction mixture, and stirring was continued for 90 min. The reaction mixture was then washed with 10% acetic acid solution (2 x 10 mL). Note: The organic layer was diluted with DCM (10 mL) and MeOH (3 mL), before final separation of the aqueous layer. The organic layer was washed with 5% NaHCO₃(aq.) (10 mL), 5% NaCl(aq.) (10 mL) and the organic layer was concentrated. The crude product was purified by HPLC (30:70 to 1:99 10 mM NH₄CO₃H(aq): CH₃CN) to provide **Example 22** (55 mg, 30% yield) as a white solid. LC/MS (ESI) *m/z* 839.6 [M+H]⁺

Example 23

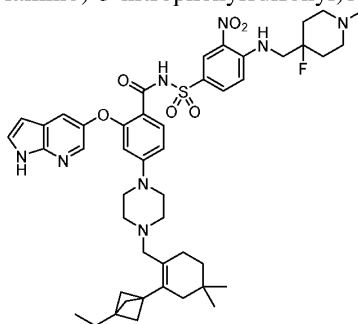
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)phenylsulfonyl)benzamide



[0493] **Example 23** was prepared following General Procedure B using **Intermediate 29** and 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.69 (s, 1H), 11.40 (br s, 1H), 8.59 (br s, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.77 (d, *J*=9.6 Hz, 1H), 7.56-7.48 (m, 3H), 7.07 (d, *J*=8.8 Hz, 1H), 6.72 (d, *J*=8.8 Hz, 1H), 6.37 (s, 1H), 6.26 (s, 1H), 3.85 (d, *J*=11.2 Hz, 2H), 3.33-3.23 (m, 4H), 3.20-3.05 (m, 4H), 3.05-2.94 (m, 2H), 2.41-2.28 (m, 4H), 2.05-1.95 (m, 2H), 1.94-1.81 (m, 1H), 1.70 (s, 6H), 1.66-1.59 (m, 4H), 1.38 (q, *J*=7.6 Hz, 2H), 1.31-1.19 (m, 4H), 0.82 (s, 6H), 0.78 (t, *J*=8.0 Hz, 3H); LC/MS (ESI) *m/z* 852.5 [M+H]⁺.

Example 24

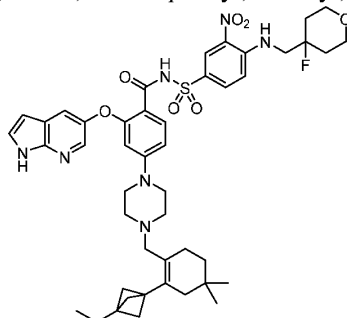
2-(1H-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-((4-fluoro-1-methylpiperidin-4-yl)methylamino)-3-nitrophenylsulfonyl)benzamide



[0494] **Example 24** was prepared following General Procedure B using **Intermediate 29** and **Intermediate 15**. LC/MS (ESI) *m/z* 883.9 [M+H]⁺.

Example 25

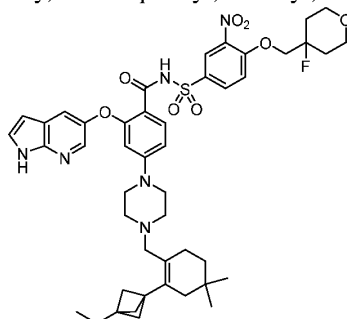
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0495] **Example 25** was prepared following General Procedure B using **Intermediate 29** and **Intermediate 52**. LC/MS (ESI) m/z 870.8 $[M+H]^+$.

Example 26

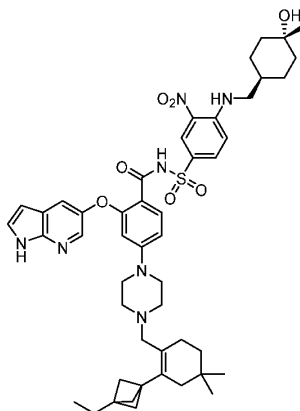
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl)sulfonyl)benzamide



[0496] **Example 26** was prepared following General Procedure B using **Intermediate 29** and **Intermediate 53**. LC/MS (ESI) m/z 871.7 $[M+H]^+$.

Example 27

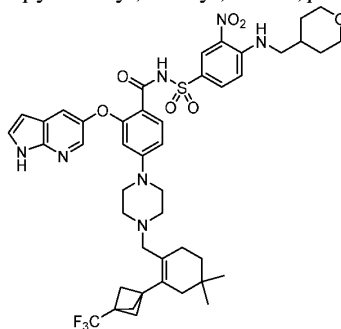
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0497] **Example 27** was prepared following General Procedure B using **Intermediate 29** and **Intermediate 18**. LC/MS (ESI) m/z 880.6 $[M+H]^+$.

Example 28

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide

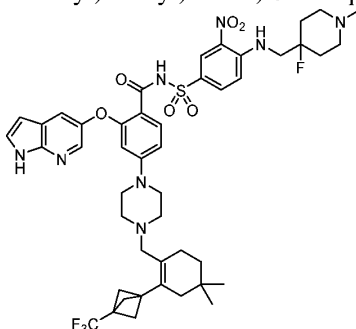


[0498] **Example 28** was prepared following General Procedure A using **Intermediate 31** and 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.68 (s, 1 H), 11.50 (br s, 1H), 8.60 (br s, 1H), 8.55 (s, 1H), 8.42 (d, $J=2.4$ Hz, 1H), 7.82-7.77 (m, 1H), 7.53-7.49 (m, 3H), 7.12-7.08 (m, 1H), 6.73-6.70 (m, 1H), 6.39-6.38 (m, 1H), 6.25-6.23 (m, 1H), 3.87-3.83 (m, 2H), 3.38-3.24 (m, 4H), 3.14-3.09 (m, 4H), 2.94 (br s, 2H), 2.39-2.31 (m, 4H), 2.11 (s, 6H), 2.04-1.98 (m, 2H), 1.90-1.85 (m, 1H), 1.68 (s, 2H), 1.64-1.59 (m, 2H),

1.31-1.22 (m, 4H), 0.83 (s, 6H); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$, unreferenceed) δ -71.53; LC/MS (ESI) m/z 892.6 $[\text{M}+\text{H}]^+$.

Example 29

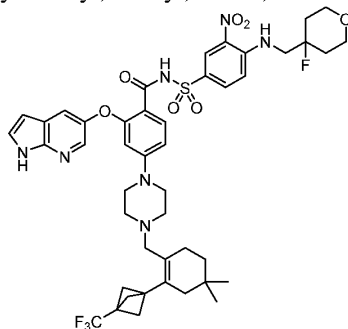
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-(((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-fluoro-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0499] **Example 29** was prepared following General Procedure B using **Intermediate 31** and **Intermediate 15**. LC/MS (ESI) m/z 923.9 $[\text{M}+\text{H}]^+$.

Example 30

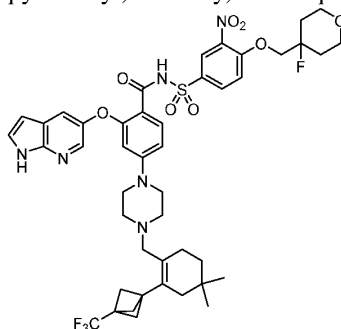
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-(((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0500] **Example 30** was prepared following General Procedure B using **Intermediate 31** and **Intermediate 52**. LC/MS (ESI) m/z 910.6 $[\text{M}+\text{H}]^+$.

Example 31

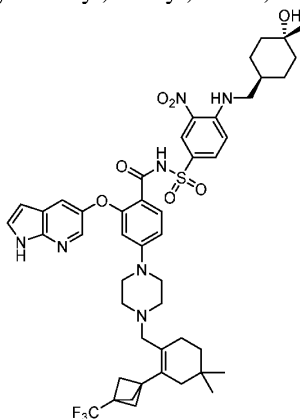
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl)sulfonyl)benzamide



[0501] **Example 31** was prepared following General Procedure B using **Intermediate 31** and **Intermediate 53**. LC/MS (ESI) m/z 911.6 $[M+H]^+$.

Example 32

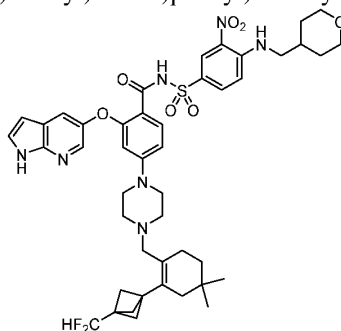
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0502] **Example 32** was prepared following General Procedure B using **Intermediate 31** and **Intermediate 18**. LC/MS (ESI) m/z 920.7 $[M+H]^+$.

Example 33

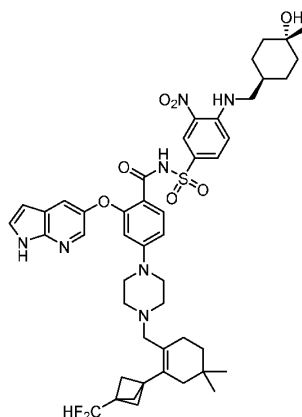
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide



[0503] Example 33 was prepared following General Procedure A using **Intermediate 30** and 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃) δ 10.06 (br s, 1H), 8.94 (br s, 1H), 8.90 (d, *J*=2.0 Hz, 1H), 8.53 (t, *J*=5.6 Hz, 1H), 8.22 (d, *J*=2.4 Hz, 1H), 8.18 (dd, *J*=9.6, 2.0 Hz, 1H), 7.98 (d, *J*=9.2 Hz, 1H), 7.71 (d, *J*=2.0 Hz, 1H), 7.45 (t, *J*=3.2 Hz, 1H), 6.92 (d, *J*=9.6 Hz, 1H), 6.60-6.55 (m, 2H), 6.02 (d, *J*=2.0 Hz, 1H), 5.65 (t, *J*=56.8 Hz, 1H), 4.03 (dd, *J*=11.2, 3.2 Hz, 2H), 3.46-3.39 (m, 2H), 3.27 (t, *J*=6.4 Hz, 2H), 3.12-3.09 (m, 4H), 2.96 (s, 2H), 2.35-2.32 (m, 4H), 2.05-1.98 (m, 3H), 1.96 (s, 6H), 1.76-1.72 (m, 2H), 1.66 (s, 2H), 1.49-1.38 (m, 2H), 1.26 (t, *J*=6.4 Hz, 2H), 0.84 (s, 6H); LC/MS (ESI) *m/z* 874.4 [M+H]⁺.

Example 34

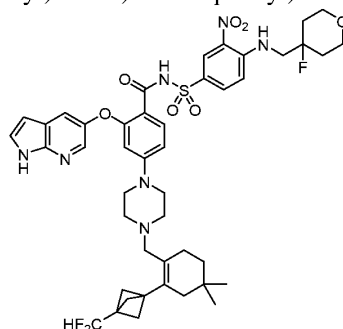
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0504] **Example 34** was prepared following General Procedure A using **Intermediate 30** and **Intermediate 18**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.70 (s, 1H), 11.40 (br s, 1H), 8.59-8.49 (m, 2H), 8.04 (d, $J=2.0$ Hz, 1H), 7.78 (d, $J=8.8$ Hz, 1H), 7.53-7.48 (m, 3H), 7.06 (d, $J=9.2$ Hz, 1H), 6.72 (d, $J=7.2$ Hz, 1H), 6.38 (s, 1H), 6.25 (s, 1H), 5.99 (t, $J=56.8$ Hz, 1H), 4.25 (s, 1H), 3.33-3.25 (m, 2H), 3.18-3.05 (m, 4H), 2.97 (s, 2H), 2.40-2.28 (m, 4H), 2.05-1.95 (m, 2H), 1.94 (s, 6H), 1.71-1.59 (m, 5H), 1.58-1.49 (m, 2H), 1.39-1.28 (m, 2H), 1.27-1.20 (m, 2H), 1.18-1.09 (m, 2H), 1.10 (s, 3H), 0.83 (s, 6H); LC/MS (ESI) m/z 902.6 $[\text{M}+\text{H}]^+$.

Example 35

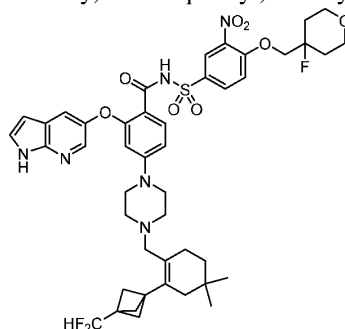
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0505] **Example 35** was prepared following General Procedure A using **Intermediate 30** and **Intermediate 52**. LC/MS (ESI) m/z 892.5 $[\text{M}+\text{H}]^+$.

Example 36

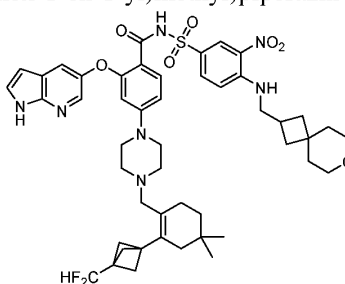
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl)sulfonyl)benzamide



[0506] **Example 36** was prepared following General Procedure A using **Intermediate 30** and **Intermediate 53**. LC/MS (ESI) m/z 893.5 $[M+H]^+$.

Example 37

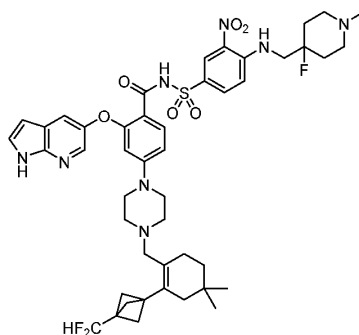
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-(((4-(((7-oxaspiro[3.5]nonan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0507] **Example 37** was prepared following General Procedure A using **Intermediate 30** and **Intermediate 6**. LC/MS (ESI) m/z 914.5 $[M+H]^+$.

Example 38

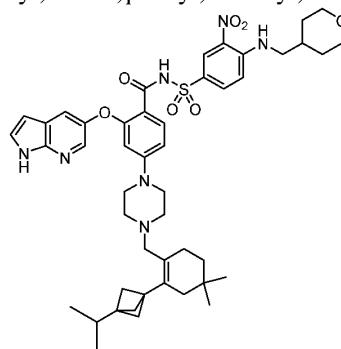
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((4-fluoro-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0508] **Example 38** was prepared following General Procedure A using **Intermediate 30** and **Intermediate 15**. LC/MS (ESI) m/z 905.5 $[M+H]^+$.

Example 39

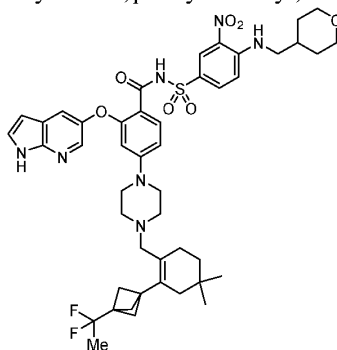
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-isopropylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide



[0509] **Example 39** was prepared following General Procedure A using **Intermediate 32** and 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3) δ 10.18 (br s, 1H), 8.92 (br s, 1H), 8.90 (d, $J=1.6$ Hz, 1H), 8.53 (t, $J=5.6$ Hz, 1H), 8.23 (d, $J=2.8$ Hz, 1H), 8.18 (dd, $J=9.0, 2.4$ Hz, 1H), 7.97 (d, $J=9.2$ Hz, 1H), 7.71 (d, $J=2.4$ Hz, 1H), 7.44 (t, $J=2.8$ Hz, 1H), 6.91 (d, $J=9.6$ Hz, 1H), 6.59 (dd, $J=9.2, 2.4$ Hz, 1H), 6.56 (dd, $J=3.4, 2.4$ Hz, 1H), 6.02 (d, $J=2.0$ Hz, 1H), 4.03 (dd, $J=11.2, 4.0$ Hz, 2H), 3.46-3.39 (m, 2H), 3.27 (t, $J=6.4$ Hz, 2H), 3.12-3.09 (m, 4H), 3.02 (s, 2H), 2.37-2.34 (m, 4H), 2.05-1.95 (m, 3H), 1.78-1.71 (m, 2H), 1.66 (s, 2H), 1.65 (s, 6H), 1.62-1.56 (m, 1H), 1.49-1.39 (m, 2H), 1.25 (t, $J=6.4$ Hz, 2H), 0.83 (s, 6H), 0.78 (d, $J=6.8$ Hz, 6H); LC/MS (ESI) m/z 866.4 $[M+H]^+$.

Example 40

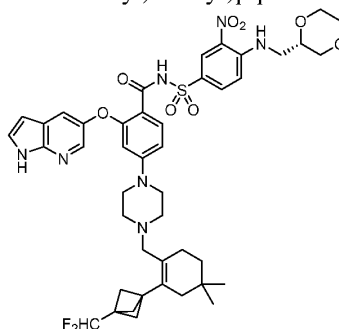
2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)-4-((2-(3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)phenylsulfonyl)benzamide



[0510] Example 40 was prepared following General Procedure B using **Intermediate 33** and 3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)benzenesulfonamide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.70 (s, 1H), 11.50 (br s, 1H), 8.61-8.49 (m, 2H), 8.03 (s, 1H), 7.80-7.70 (m, 1H), 7.54-7.45 (m, 3H), 7.04 (br s, 1H), 6.71 (d, *J*=8.8 Hz, 1H), 6.37 (s, 1H), 6.25 (s, 1H), 3.87-3.83 (m, 2H), 3.33-3.21 (m, 4H), 3.15-3.05 (m, 4H), 2.97 (s, 2H), 2.40-2.25 (m, 4H), 2.04-1.97 (m, 2H), 1.94 (s, 6H), 1.93-1.82 (m, 1H), 1.67-1.57 (m, 4H), 1.53 (t, *J*=18.8 Hz, 3H), 1.30-1.15 (m, 4H), 0.83 (s, 6H); LC/MS (ESI) *m/z* 888.7 [M+H]⁺.

Example 41

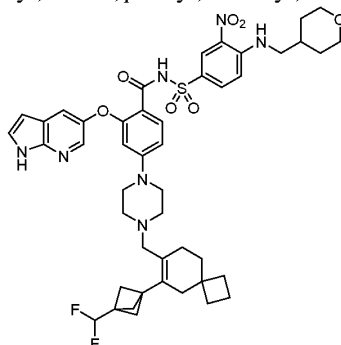
(*S*)-*N*-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0511] **Example 41** was prepared following General Procedure B using **Intermediate 30** and **Intermediate 34**. LC/MS (ESI) m/z 876.5 $[M+H]^+$.

Example 42

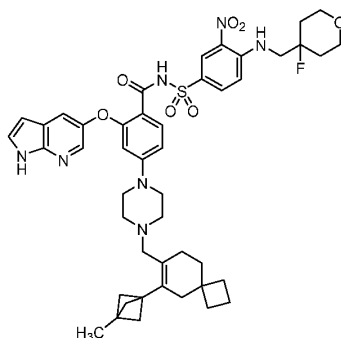
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-(((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide



[0512] **Example 42** was prepared following General Procedure B using **Intermediate 50** and 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.63 (s, 1H), 11.38 (br s, 1H), 8.61-8.54 (m, 2H), 8.04 (d, $J=2.8$ Hz, 1H), 7.78 (dd, $J=9.6$, 1.6 Hz, 1H), 7.53-7.50 (m, 3H), 7.10 (d, $J=9.2$ Hz, 1H), 6.71 (dd, $J=9.2$, 1.6 Hz, 1H), 6.39-6.38 (m, 1H), 6.25-6.24 (m, 1H), 5.99 (t, $J=56.4$ Hz, 1H), 3.84 (dd, $J=11.2$, 3.2 Hz, 2H), 3.32-3.23 (m, 4H), 3.11 (br s, 4H), 2.94 (s, 2H), 2.33 (br s, 4H), 2.09-1.73 (m, 13H), 1.71-1.60 (m, 6H), 1.46 (t, $J=5.6$ Hz, 2H), 1.30-1.20 (m, 2H); LC/MS (ESI) m/z 886.3 $[M+H]^+$.

Example 43

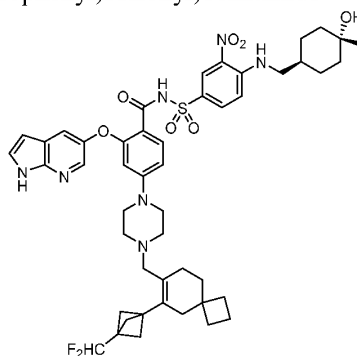
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-(((6-(3-methylbicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)benzamide



[0513] **Example 43** was prepared following General Procedure B using **Intermediate 51** and **Intermediate 52**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.64 (s, 1H), 11.40 (br s, 1H), 8.57-8.53 (m, 2H), 8.01 (d, $J=2.4$ Hz, 1H), 7.78 (d, $J=8$ Hz, 1H), 7.53-7.48 (m, 3H), 7.19-7.17 (m, 1H), 6.70 (dd, $J=8.8$, 1.6 Hz, 1H), 6.36 (br s, 1H), 6.26-6.25 (m, 1H), 3.76-3.68 (m, 4H), 3.55-3.50 (m, 2H), 3.09 (br s, 4H), 2.95 (br s, 2H), 2.32-2.32 (br s, 4H), 1.98-1.92 (m, 4H), 1.83-1.58 (m, 16H), 1.45 (t, $J=5.6$ Hz, 2H), 1.10 (s, 3H); LC/MS (ESI) m/z 868.4 $[\text{M}+\text{H}]^+$.

Example 44

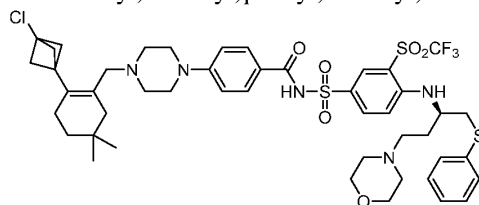
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)-N-((4-(((1R,4R)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0514] **Example 44** was prepared following General Procedure B using **Intermediate 50** and **Intermediate 18**. LC/MS (ESI) m/z 914.5 $[\text{M}+\text{H}]^+$.

Example 45

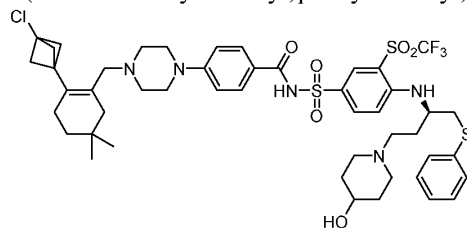
(*R*)-4-(4-((2-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0515] To a stirred solution of **Intermediate 36** (45 mg, 0.105 mmol) in DCM (5 mL) was added EDC•HCl (21 mg, 0.0252 mmol) followed by DMAP (26 mg, 0.21 mmol) at 0 °C. After 10 min, (*R*)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (70 mg, 0.126 mmol) was added and the reaction was warmed to rt. After 48 h, water (10 mL) was added and the reaction mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The product was purified by HPLC (45:55 to 1:99 10mM NH₄CO₃H(aq.)/CH₃CN) to afford **Example 45** (4 mg, 4% yield) as a white solid. LC/MS (ESI) *m/z* 964.4 [M+H]⁺.

Example 46

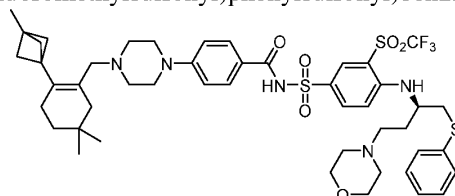
(*R*)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-(4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenyl)sulfonyl)benzamide



[0516] **Example 46** was prepared following the procedure described for **Example 45** by using **Intermediate 37** in place of (*R*)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide. LC/MS (ESI) *m/z* 978.4 [M+H]⁺

Example 47

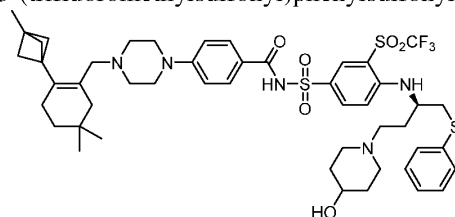
(*R*)-4-(4-((5,5-Dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-(4-morpholino-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[0517] **Example 47** was prepared following the procedure described for **Example 45** by using **Intermediate 38** in place of **Intermediate 36**. ^1H NMR (400 MHz, CDCl_3) δ 8.36 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 9.4, 1.6 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 6.8 Hz, 2H), 7.33-7.26 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 10.0 Hz, 1H), 3.95-3.85 (m, 1H), 3.71-3.60 (m, 4H), 3.36-3.24 (m, 4H), 3.14 (s, 2H), 3.13-2.98 (m, 2H), 2.61-2.50 (m, 4H), 2.49-2.28 (m, 6H), 2.19-2.08 (m, 1H), 1.99-1.92 (m, 2H), 1.86 (s, 2H), 1.81 (s, 6H), 1.71-1.61 (m, 1H), 1.30 (t, J = 6.4 Hz, 2H), 1.13 (s, 3H), 0.86 (s, 6H). One $-\text{NH}$ proton was not observed; LC/MS (ESI) m/z 944.6 $[\text{M}+\text{H}]^+$.

Example 48

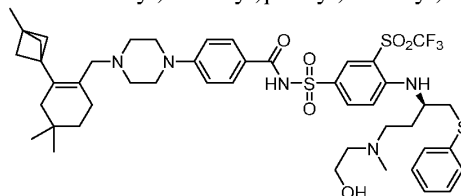
(*R*)-4-(4-((5,5-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-(4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide



[0518] **Example 48** was prepared following the procedure described **Example 46** by using **Intermediate 38** in place of **Intermediate 36**. LC/MS (ESI) m/z 958.3 $[\text{M}+\text{H}]^+$.

Example 49

(R)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

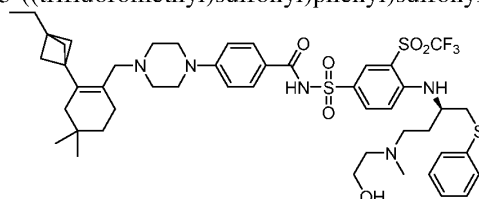


[0519] Step 1: (R)-N-((4-((4-((2-((tert-butyl)diphenylsilyl)oxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (**Example 49-1**) was prepared following General Procedure B using **Intermediate 39** and **Intermediate 35**. LC/MS (ESI) m/z 1170.9 $[M+H]^+$.

[0520] Step 2: To a stirred solution of **Example 49-1** (375 mg, 0.32 mmol) in THF (15 mL) at 0 °C was added TBAF (1M in THF, 0.48 mL). After 5 min the reaction was warmed to rt. After 2 h, the reaction was quenched with water (25 mL) and extracted with 9:1 DCM/MeOH (3 x 35 mL), and concentrated. The crude compound was purified by HPLC (50:50 to 0:100 10mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ / CH_3CN) to obtain **Example 49** as a white solid. LC/MS (ESI) m/z 932.6 $[M+H]^+$

Example 50

(R)-4-(4-((2-(3-Ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



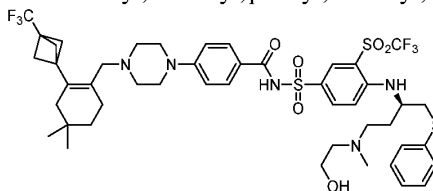
[0521] Step 1: (R)-N-((4-((4-((2-((tert-Butyl)diphenylsilyl)oxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-

dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (**Example 50-1**) was prepared following General Procedure B using **Intermediate 40** and **Intermediate 35**. LC/MS (ESI) m/z 1186.0 $[M+H]^+$

[0522] Step 2: **Example 50** was prepared following the procedure described in Step 2 for **Example 49** by using **Example 50-1** in place of **Example 49-1**. LC/MS (ESI) m/z 946.7 $[M+H]^+$

Example 51

(R)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

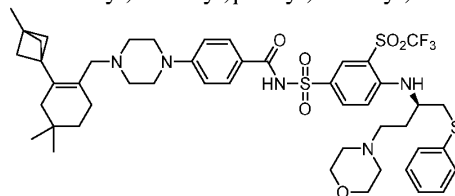


[0523] Step 1: (R)-N-((4-((4-((2-((tert-Butyldiphenylsilyl)oxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (**Example 51-1**) was prepared following General Procedure B using **Intermediate 41** and **Intermediate 35**. LC/MS (ESI) m/z 1225.9 $[M+2H]^+$

[0524] Step 2: To a stirred solution of **Example 51-1** (500 mg, 0.4 mmol) in THF at 0 °C was added TBAF (1M in THF, 0.49 mL). After 5 min the reaction was warmed to rt. After 5 h, the reaction was quenched with water (25 mL) and with 9:1 DCM/MeOH (3 x 50 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na₂SO₄, filtered and concentrated. The crude compound was purified by column chromatography (SiO₂, 7-10% MeOH in DCM) to obtain **Example 51** (101 mg, 20 %, over 2 steps) as a white solid. LC/MS (ESI) m/z 986.7 $[M+H]^+$

Example 52

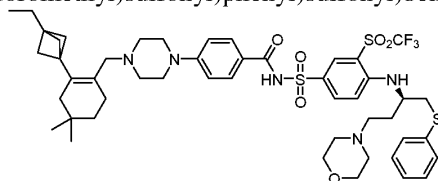
(*R*)-4-(4-((4,4-Dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0525] **Example 52** was prepared following General Procedure B using **Intermediate 39** and (*R*)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide. LC/MS (ESI) *m/z* 944.9 [M+H]⁺.

Example 53

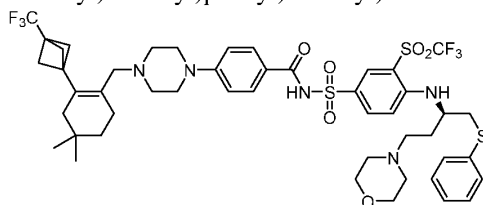
(*R*)-4-(4-((2-(3-Ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0526] **Example 53** was prepared following General Procedure B using **Intermediate 40** and (*R*)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide. LC/MS (ESI) *m/z* 958.8 [M+H]⁺.

Example 54

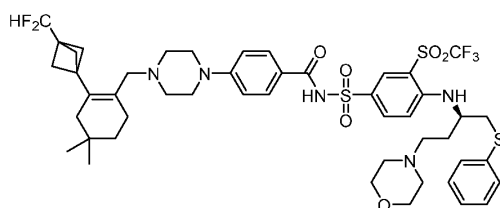
(*R*)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0527] **Example 54** was prepared following General Procedure B using **Intermediate 41** and (*R*)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide. LC/MS (ESI) *m/z* 998.9 [M+H]⁺.

Example 55

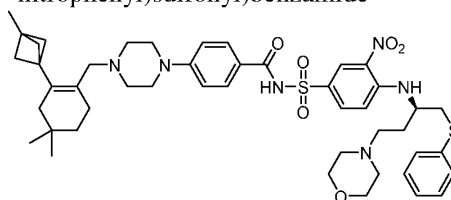
(*R*)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0528] **Example 55** was prepared following General Procedure B using **Intermediate 42** and (*R*)-4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide. LC/MS (ESI) *m/z* 980.9 [M+H]⁺.

Example 56

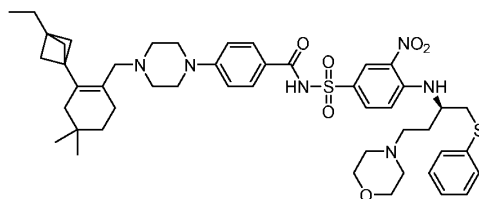
(*R*)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0529] **Example 56** was prepared following General Procedure B using **Intermediate 39** and **Intermediate 43**. LC/MS (ESI) *m/z* 857.8 [M+H]⁺.

Example 57

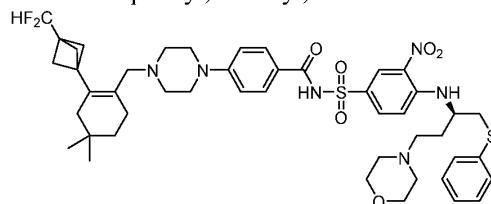
(*R*)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0530] **Example 57** was prepared following General Procedure B using **Intermediate 40** and **Intermediate 43**. LC/MS (ESI) m/z 871.8 $[M+H]^+$.

Example 58

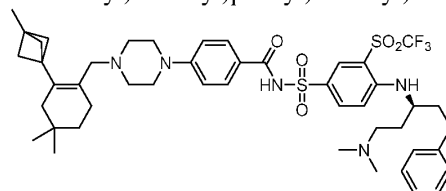
(R)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0531] **Example 58** was prepared following General Procedure B using **Intermediate 42** and **Intermediate 43**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.48 (s, 1H), 8.40-8.30 (m, 1H), 7.78 (d, $J=9.2$ Hz, 1H), 7.73 (d, $J=8.8$ Hz, 2H), 7.31-7.28 (m, 2H), 7.25-7.20 (m, 2H), 7.17-7.13 (m, 1H), 7.05-6.95 (m, 1H), 6.87 (d, $J=8.8$ Hz, 2H), 6.01 (t, $J=56.0$ Hz, 1H), 4.19-4.09 (m, 1H), 3.60-3.45 (m, 4H), 3.30-3.15 (m, 6H), 3.10-2.90 (m, 2H), 2.55-2.10 (m, 10H), 2.10-2.01 (m, 3H), 1.99 (s, 6H), 1.90-1.80 (m, 1H), 1.71 (s, 2H), 1.30-1.21 (m, 2H), 0.86 (s, 6H). One -NH proton was not observed; LC/MS (ESI) m/z 893.6 $[M+H]^+$.

Example 59

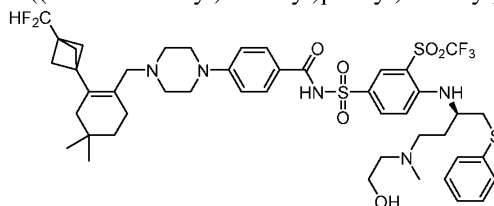
(R)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-(dimethylamino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0532] **Example 59** was prepared following General Procedure B using **Intermediate 39** and **Intermediate 44**. LC/MS (ESI) m/z 902.6 $[M+H]^+$.

Example 60

(*R*)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

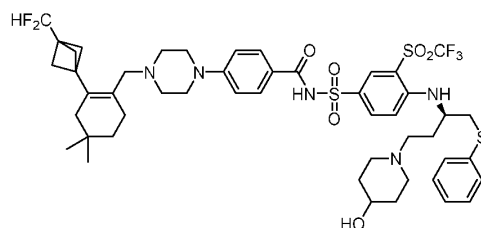


[0533] Step 1: (*R*)-*N*-((4-((4-((2-((tert-butyl)diphenylsilyl)oxy)ethyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (**Example 60-1**) was prepared following General Procedure B using **Intermediate 42** and **Intermediate 35**. LC/MS (ESI) m/z 1206.5 $[M+H]^+$

[0534] Step 2: To a stirred solution of **Example 60-1** (130 mg, 0.10 mmol) in 1,4-dioxane (5 mL) was added HCl (4M in 1,4 dioxane, 1 mL) followed by 3 drops of water at 0 °C. The reaction was warmed to rt, stirred for 16 h, and then concentrated. The crude reaction mixture was diluted with sat. aq. NaHCO₃ and extracted with EtOAc (3 X 25 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, MeOH/DCM) to afford **Example 60** (30 mg, 29% yield) as an off-white colored solid. LC/MS (ESI) m/z 968.2 $[M+H]^+$.

Example 61

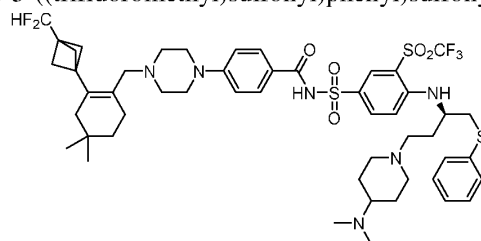
(*R*)-4-(4-((2-(3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0535] **Example 61** was prepared following General Procedure B using **Intermediate 42** and **Intermediate 37**. LC/MS (ESI) m/z 994.6 $[M+H]^+$.

Example 62

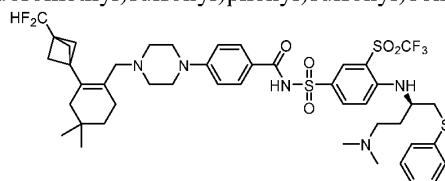
(*R*)-4-(4-((2-(3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-(dimethylamino)piperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0536] **Example 62** was prepared following General Procedure B using **Intermediate 42** and **Intermediate 45**. LC/MS (ESI) m/z 1021.2 $[M+H]^+$.

Example 63

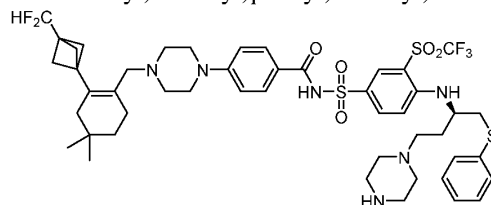
(*R*)-4-(4-((2-(3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((4-(dimethylamino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0537] **Example 63** was prepared following General Procedure B using **Intermediate 42** and **Intermediate 44**. LC/MS (ESI) m/z 938.4 $[M+H]^+$.

Example 64

(R)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

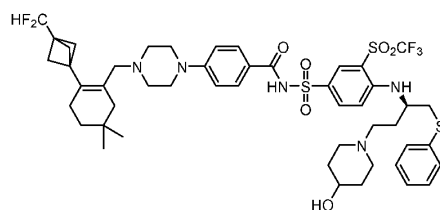


[0538] Step 1: (*R*)-*tert*-Butyl 4-(3-((4-(*N*-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoro-methyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Example 64-1**) was prepared following General Procedure B using **Intermediate 42** and **Intermediate 46**. LC/MS (ESI) *m/z* 1079.3 [M+H]⁺

[0539] Step 2: To a stirred solution of **Example 64-1** (350 mg, 0.32 mmol) in Et₂O (5 mL) at 0 °C, was added HCl (2M in Et₂O, 2.0 mL). The reaction was warmed to rt and stirred for 16 h. The reaction was concentrated, diluted with ice cold water, basified with sat. aq. NaHCO₃ (10 mL) and extracted with 10% MeOH in DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (30:70 to 1:99 10 mM NH₄CO₃H(aq.)/CH₃CN) to provide **Example 64** (14 mg, 4% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 (br s, 2H), 8.02 (s, 1H), 7.91 (d, *J*=8.8 Hz, 1H), 7.68 (d, *J*=8.8 Hz, 2H), 7.34-7.23 (m, 4H), 7.19-7.15 (m, 1H), 6.83-6.75 (m, 3H), 6.66 (d, *J*=8.8 Hz, 1H), 5.97 (t, *J*=56.8 Hz, 1H), 3.97 (br s, 1H), 3.26-3.23 (m, 2H), 3.15-3.10 (m, 4H), 3.02-2.90 (m, 6H), 2.52-2.50 (m, 2H), 2.40-2.23 (m, 8H), 2.10-1.83 (m, 9H), 1.67 (s, 3H), 1.23 (t, *J*=6.4 Hz, 2H), 0.82 (s, 6H); LC/MS (ESI) *m/z* 979.4 [M+H]⁺.

Example 65

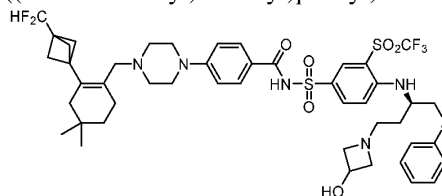
(R)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0540] **Example 65** was prepared following General Procedure B using **Intermediate 56** and **Intermediate 37**. LC/MS (ESI) m/z 994.4 $[M+H]^+$.

Example 66

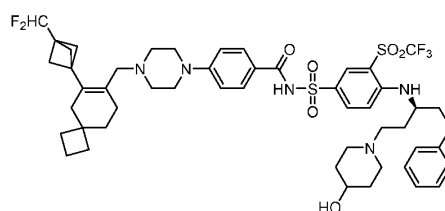
(*R*)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-((4-(3-hydroxyazetidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0541] **Example 66** was prepared following General Procedure B using **Intermediate 42** and **Intermediate 57**. LC/MS (ESI) m/z 966.5 $[M+H]^+$.

Example 67

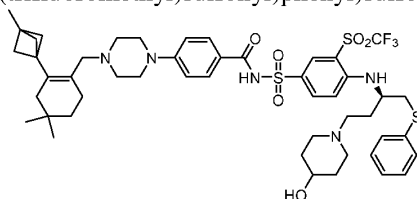
(*R*)-4-(4-((6-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)spiro[3.5]non-6-en-7-yl)methyl)piperazin-1-yl)-N-(((4-((4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0542] **Example 67** was prepared following General Procedure B using **Intermediate 58** and **Intermediate 37**. LC/MS (ESI) m/z 1006.5 $[M+H]^+$.

Example 68

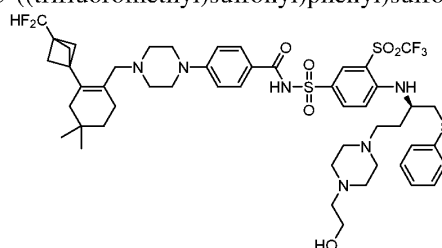
(R)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-(4-hydroxypiperidin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0543] **Example 68** was prepared following General Procedure B using **Intermediate 37** and **Intermediate 39**. LC/MS (ESI) m/z 958.2 $[M+H]^+$.

Example 69

(R)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-(2-hydroxyethyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



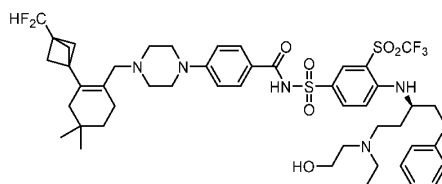
[0544] Step 1: (*R*)-N-((4-((4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (**Example 69-1**) was prepared following General Procedure B using **Intermediate 42** and **Intermediate 59**. LC/MS (ESI) m/z 631.6 $[M+2H]^+$

[0545] Step 2: To a stirred solution of **Example 69-1** (250 mg, 0.198 mmol) in 1,4-dioxane was added HCl (4M in 1,4 dioxane, 1.5 mL) followed by 3 drops of water at 0 °C. The reaction was warmed to rt, stirred for 16 h, and then concentrated. The crude reaction mixture was diluted with sat. aq. NaHCO₃ and extracted with 9:1 DCM:MeOH (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude

product was purified by HPLC (10mM NH₄OAc(aq):CH₃CN) to afford the title compound (22 mg, 11% yield) as an off-white solid. LC/MS (ESI) *m/z* 1023.3 [M+H]⁺.

Example 70

(R)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

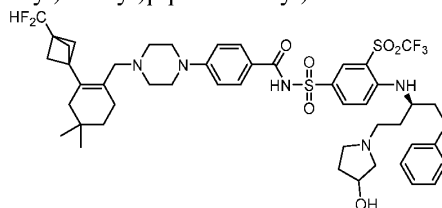


[0546] Step 1: (*R*)-*N*-((4-((4-((2-((tert-butyldiphenylsilyl)oxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (**Example 70-1**) was prepared following General Procedure B using **Intermediate 42** and **Intermediate 60**. LC/MS (ESI) *m/z* 611.3 [M+2H]⁺

[0547] Step 2: **Example 70** was prepared following the procedure described in **Example 69** using **Example 70-1** in place of **Example 69-1**. LC/MS (ESI) *m/z* 982.5 [M+H]⁺.

Example 71

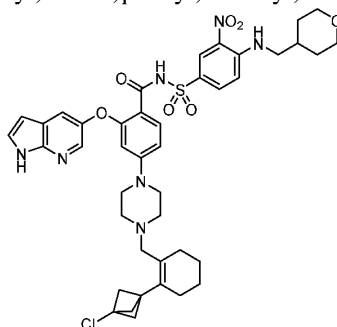
(*R*)-*N*-((4-((4-((2-((tert-butyldiphenylsilyl)oxy)ethyl)(ethyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0548] **Example 71** was prepared following General Procedure B using **Intermediate 42** and **Intermediate 61**. LC/MS (ESI) *m/z* 980.4 [M+H]⁺.

Example 72

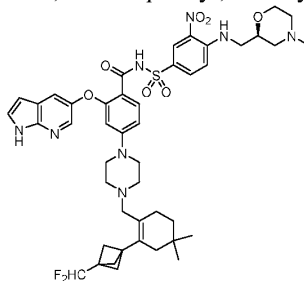
2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide



[0549] **Example 72** was prepared following General Procedure A using **Intermediate 62** and 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide. LC/MS (ESI) m/z 830.8 [M+H]⁺.

Example 73

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-methylmorpholin-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide



[0550] **Example 73** was prepared following General Procedure B using **Intermediate 30** and **Intermediate 17A**. The absolute stereochemistry was arbitrarily assigned. LC/MS (ESI) m/z 445.5 [M+2H]⁺.

Examples 74-97

[0551] **Examples 74-97**, having the chemical names and structures shown in FIGS. 3, 4A and 4B, are prepared in accordance with the methods described herein. Similar results are obtained.

Example A

Bcl-2 Protein Family Binding Assay

[0552] Binding to Bcl-2 proteins Bcl-2, and Bcl-X_L was assessed using the Bcl2scan™ platform: T7 phage strains displaying BCL2 proteins were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis (90-150 minutes). The lysates were centrifuged (5,000 x g) and filtered (0.2µm) to remove cell debris. Streptavidin-coated magnetic beads were treated with biotinylated BIM peptide ligand for 30 minutes at room temperature to generate affinity resins for BCL2 assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific phage binding. Binding reactions were assembled by combining BCL2 proteins, liganded affinity beads, and test compounds in 1x binding buffer (20 % SeaBlock, 0.17x PBS, 0.05 % Tween 20, 6 mM DTT). Test compounds were prepared as 100X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with one DMSO control point. All compounds for Kd measurements were distributed by acoustic transfer in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.9%. All reactions performed in polypropylene 384-well plates. Each was a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 2 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The BCL2 concentration in the eluates was measured by qPCR. Binding constants (Kds) were calculated with a standard dose-response curve using the Hill equation:
$$\text{Response} = \text{Background} + \frac{\text{Signal} - \text{Background}}{1 + (K_d^{\text{Hill Slope}} / \text{Dose}^{\text{Hill Slope}})}$$
 The Hill Slope was set to -1.

Curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm. The results are shown in Table 1.

Table 1

Example	Bcl-2 Kd (nm)	Bcl-X _L Kd (nm)
1	A	C
9	A	C
10	A	C
11	A	C
13	A	C
15	A	C
16	A	C
17	A	B
20	A	C
23	A	C
25	A	C
26	A	C
27	A	C
28	A	C
30	A	C
31	A	C
32	A	C
33	A	C
34	A	C
35	A	C
36	A	B
38	A	B
39	B	C
40	A	C
47	C	B
48	B	B
ABT-199	A	B
ABT-263	B	B

Bcl-2 Binding Assay (Kd): A = a single Kd ≤ 10 nM; B = a single Kd > 10 nM and < 100 nM; C = a single Kd ≥ 100 nM

Example B

Bcl-2/Bcl-X_L Homogeneous Time Resolved Fluorescence (HTRF) Assay

[0553] Binding to Bcl-2 proteins Bcl-2, and Bcl-X_L was also assessed using an HTRF assay. Background: FAM-Bak/Bad binds to surface pocket of the Bcl-2 protein family. This binding can be monitored by HTRF signals between anti-GST-Tb and FAM-peptide

using GST-tagged Bcl proteins. Assay conditions: Bcl-2: 4 nM Bcl-2, 100 nM FAM-Bak peptide, Bcl-X_L: 3 nM Bcl-X_L, 40 nM FAM-Bad peptide in 20 mM K Phosphate, pH 7.5, 50 mM NaCl, 1 mM EDTA, 0.005% Triton X-100 and 1% DMSO (final). Assay procedure: Compounds were tested in 10-dose IC₅₀ mode, in singlicate, with 3-fold serial dilution starting at 10 μM or 1 μM. Compound stock solutions were added to protein solution using Acoustic technology. The compounds were then incubated with protein for 10 min at room temperature. The respective FAM labeled peptide was added and incubated for another 10 min and then anti-GST-Tb was added. After 60 min at rt, the HTRF fluorescence signal ratio was measured. Curve fits were performed in GraphPad Prism 4 with “sigmoidal dose-response (variable slope)”; 4 parameters with Hill Slope. The results are shown in Table 2.

Table 2

Example	Bcl-2 IC ₅₀ (nM)	Bcl-X _L IC ₅₀ (nM)
15	A	C
20	A	C
34	A	B
46	A	A
48	A	A
49	A	A
50	A	A
55	A	A
58	A	A
59	A	A
60	A	A
61	A	A
62	A	A
63	A	A
64	A	A
67	A	A
69	A	A
70	A	A
ABT-199	A	B
ABT-263	A	A

Bcl-2 Binding Assay (IC₅₀): A = a single IC₅₀ ≤ 10 nM; B = a single IC₅₀ > 10 nM and < 100 nM; C = a single IC₅₀ ≥ 100 nM.

Example C

RS4;11 and NCI-H1963 Cell Proliferation Assay

[0554] 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. RS4;11 (ATC, CRL-1873) cells were cultured according to ATCC recommendations and were seeded at 50,000 cells per well. NCI-H1963 cells (ATCC CRL-5982) were cultured according to ATCC recommendations and seeded at 12,000 cells per well.

[0555] 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). Compound treatment (1.0 μ L) was added from the compound dilution plate to the cell plate. The highest compound concentration was 10 μ M (final), with a 0.1% final DMSO concentration. Plates were then incubated at 37 °C, 5% CO₂. After 48 h of compound treatment for RS4;11 or 72 h for NCI-H1963, cell plates were equilibrated at rt for approximately 30 mins. An equi-volume amount of CellTiter-Glo® Reagent (40 μ L) 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 Envision plate reader according to CellTiter-Glo protocol. IC₅₀ of each compound was calculated using GraphPad Prism by nonlinear regression analysis. IC₅₀ values are provided in Table 3.

Table 3

Example#	RS4;11 (nM)	H1963 (nM)	Example#	RS4;11 (nM)	H1963 (nM)
1	A		39	A	
2	A		40	A	
3	B		41		
4	B		42	A	
5	B		43	B	
6	C		44		
7	C		45	C	
8	B		46	B	
9	A		47	C	
10	A		48	B	
11	A		49	B	

Example#	RS4;11 (nM)	H1963 (nM)	Example#	RS4;11 (nM)	H1963 (nM)
12	A		50	B	
13	A		51	B	
14	A		52	B	
15	A		53	C	
16	A		54	C	
17	A		55	B	
18	A		56	C	B
19	A		57	C	C
20	A		58	B	
21	B		59	B	B
22	A		60	A	B
23	A		61	A	A
24	A		62	B	A
25	A		63	A	A
26	A		64	B	C
27	A		65		B
28	A		66		
29	A		67	B	
30	A		68	B	A
31	A		69		B
32	A		70	B	C
33	A		71		B
34	A		72	C	
35	A		73		
36	A		ABT-199	A	C
37	A		ABT-263	A	A
38	A				

For RS4;11 CTG IC₅₀: A = a single IC₅₀ ≤ 100 nM; B = a single IC₅₀ >100 nM and < 1000 nM; C = a single IC₅₀ ≥ 1000 nM. For H1963 CTG IC₅₀: A = a single IC₅₀ ≤ 500 nM; B = a single IC₅₀ >500 nM and < 1000 nM; C = a single IC₅₀ ≥ 1000 nM.

Example D

Measurement of Caspase Release in Mock and HIV-1 (IIIB strain) Infected CD4 Cells

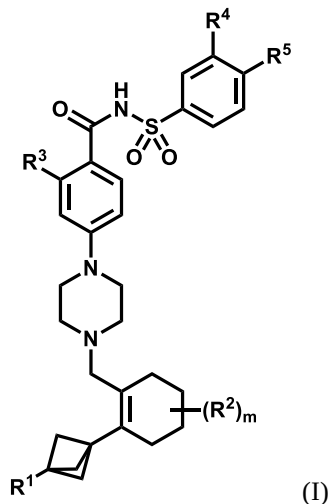
[0556] Primary CD4 T cells were purified by negative selection, using RosetteSep human CD4⁺ T cell enrichment cocktail (Stemcell Technologies) or an EasySep human CD4⁺ T cell isolation kit (Stemcell Technologies) as per the manufacturer's protocol. Primary CD4 T cells were isolated and activated with IL-2 50 IU/mL and phytohaemagglutinin (PHA) 1

µg/mL for 48 hours. Then cells were infected with HIV-1_{IIIb} (NIH AIDS Reagent Program) viral stock for 3-6 hours with 6 µg/mL Polybrene (Sigma-Aldrich), washed, and resuspended with complete RPMI and IL-2 for 48 hours. The cells were treated with compounds as 100 µM and 300 µM DMSO stock solutions or DMSO. Cell death was measured using an IncuCyte system (Essen BioScience) and IncuCyte Caspase 3/7 Green Apoptosis Assay Reagent (catalog number 4440, Essen BioScience). Analysis of the data was done using IncuCyte Zoom software (2018A). Statistical analysis was performed using GraphPad Prism. Results are depicted as standard error (SE). The fold changes for area under the curve analysis were compared by multiple t-tests. *P* values of less than 0.05 were considered statistically significant. The results of this assay are summarized in FIG. 5 and indicate that **Examples 34 and 36** exhibit selectivity in killing HIV vs. mock infected cells.

[0557] 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 invention.

Claims

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

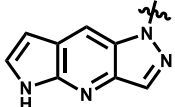
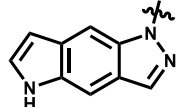


wherein:

R¹ is selected from the group consisting of hydrogen, halogen, a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl, a substituted or unsubstituted C₃-C₆ cycloalkyl, a substituted or unsubstituted C₁-C₆ alkoxy, an unsubstituted mono-C₁-C₆ alkylamine and an unsubstituted di-C₁-C₆ alkylamine;

each R² is independently selected from the group consisting of halogen, a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl; or

when m is 2 or 3, each R² is independently selected from the group consisting of halogen, a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl, or two R² groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C₃-C₆ cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;

R³ is selected from the group consisting of X-R^{3A},  and  ;

R^{3A} is a substituted or unsubstituted 5 to 10 membered heteroaryl;

R⁴ is selected from the group consisting of NO₂, S(O)R⁶, SO₂R⁶, halogen, cyano and an unsubstituted C₁-C₆ haloalkyl;

R⁵ is -X¹-(Alk¹)_n-R⁷;

Alk¹ is selected from an unsubstituted C₁-C₄ alkylene and a C₁-C₄ alkylene substituted with 1, 2 or 3 substituents independently selected from fluoro, chloro, an unsubstituted C₁-C₃ alkyl and an unsubstituted C₁-C₃ haloalkyl;

R⁶ is selected from the group consisting of a substituted or unsubstituted C₁-C₆ alkyl, a substituted or unsubstituted C₁-C₆ haloalkyl and a substituted or unsubstituted C₃-C₆ cycloalkyl;

R⁷ is selected from a substituted or unsubstituted C₃-C₁₀ cycloalkyl and a substituted or unsubstituted 3 to 10 membered heterocyclyl;

m is 0, 1, 2 or 3;

n is selected from 0 and 1;

X¹ is -NH-; and

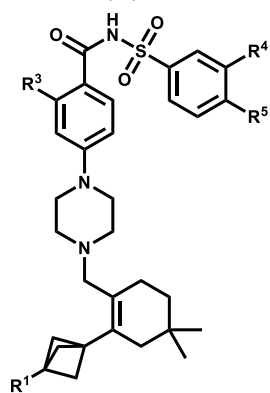
X is selected from the group consisting of -O-, -S- and -NH-.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CH₂F or -CF₃.

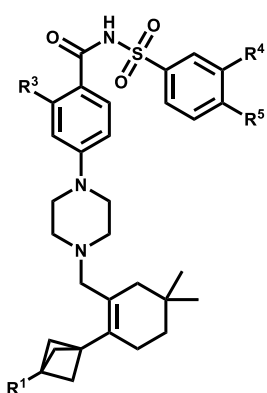
3. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CHF₂.

4. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is not -CH₂F, -CHF₂ or -CF₃.

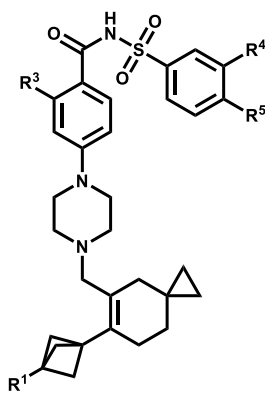
5. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein m is 1.
6. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein m is 2.
7. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein m is 3.
8. The compound of any one of Claims 1-7, or a pharmaceutically acceptable salt thereof, wherein one R^2 is an unsubstituted C_1 - C_6 alkyl and any other R^2 , if present, is independently selected from the group consisting of halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl.
9. The compound of any one of Claims 1-8, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently an unsubstituted C_1 - C_6 alkyl.
10. The compound of any one of Claims 1-4, 8 or 9, or a pharmaceutically acceptable salt thereof, wherein m is 2; and each R^2 is an unsubstituted methyl.
11. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein m is 0.
12. The compound of any one of Claims 1-4 or 6, or a pharmaceutically acceptable salt thereof, wherein two R^2 groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C_3 - C_6 cycloalkyl.
13. The compound of any one of Claims 1-4, 6-7 or 12, or a pharmaceutically acceptable salt thereof, wherein two R^2 groups taken together with the atom to which they are attached form an unsubstituted cyclopropyl.
14. The compound of any one of Claims 1-4 or 6-7, or a pharmaceutically acceptable salt thereof, wherein two R^2 groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted 3 to 6 membered heterocycl.
15. The compound of any one of Claims 1-4, that is also a compound of Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



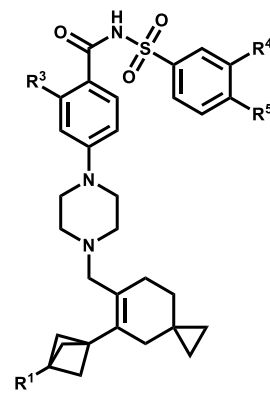
(Ia)



(Ib)



(Ic)

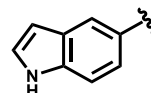


(Id)

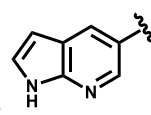
or pharmaceutically acceptable salts of any of the foregoing.

16. The compound of any one of Claims 1-15, wherein R^3 is $X-R^{3A}$.

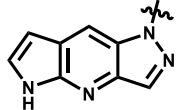
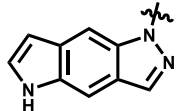
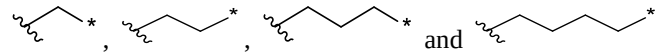
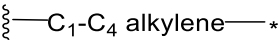
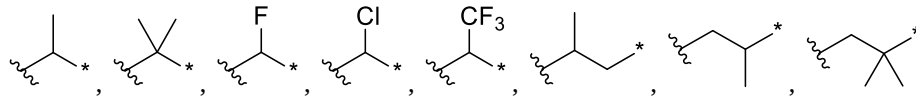
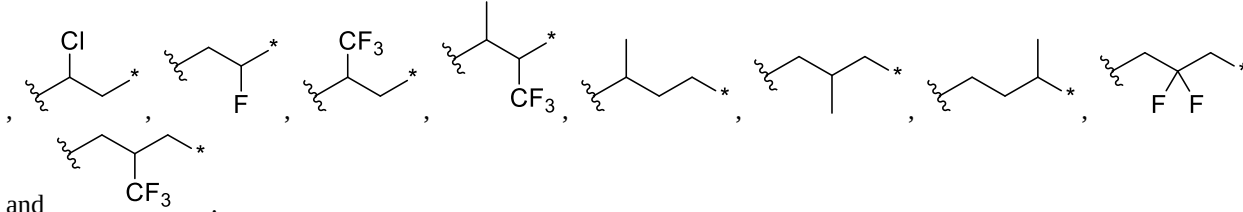
17. The compound of any one of Claims 1-16, wherein R^{3A} is



18. The compound of any one of Claims 1-16, wherein R^{3A} is



19. The compound of any one of Claims 1-16, wherein R^{3A} is a substituted 5 to 10 membered heteroaryl.
20. The compound of any one of Claims 1-19, wherein X is -O-.
21. The compound of any one of Claims 1-19, wherein X is -S-.
22. The compound of any one of Claims 1-19, wherein X is -NH-.

23. The compound of any one of Claims 1-15, wherein R³ is .
24. The compound of any one of Claims 1-15, wherein R³ is .
25. The compound of any one of Claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R⁴ is NO₂.
26. The compound of any one of Claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R⁴ is cyano.
27. The compound of any one of Claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R⁴ is halogen.
28. The compound of any one of Claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R⁴ is an unsubstituted C₁-C₆ haloalkyl.
29. The compound of any one of Claims 1-24 or 28, or a pharmaceutically acceptable salt thereof, wherein R⁴ is -CF₃.
30. The compound of any one of Claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R⁴ is S(O)R⁶.
31. The compound of any one of Claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R⁴ is SO₂R⁶.
32. The compound of any one of Claims 1-24 or 30-31, or a pharmaceutically acceptable salt thereof, wherein R⁶ is a substituted or unsubstituted C₁-C₆ alkyl.
33. The compound of any one of Claims 1-24 or 30-31, or a pharmaceutically acceptable salt thereof, wherein R⁶ is a substituted or unsubstituted C₃-C₆ cycloalkyl.
34. The compound of any one of Claims 1-24 or 30-31, or a pharmaceutically acceptable salt thereof, wherein R⁶ is a substituted or unsubstituted C₁-C₆ haloalkyl.
35. The compound of any one of Claims 30-31 or 34, or a pharmaceutically acceptable salt thereof, wherein R⁶ is -CF₃.
36. The compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, wherein Alk¹ is unsubstituted -(CH₂)₁₋₄-* for which "*" represents the point of attachment to R⁷.
37. The compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, wherein Alk¹ is selected from .
38. The compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, wherein Alk¹ is a substituted * for which "*" represents the point of attachment to R⁷.
39. The compound of any one of Claims 1-35 or 38, or a pharmaceutically acceptable salt thereof, wherein Alk¹ is selected from:
- 
- 
- and
40. The compound of any one of Claims 1-39, or a pharmaceutically acceptable salt thereof, wherein n is 1.

41. The compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, wherein n is 0.

42. The compound of any one of Claims 1-41, or a pharmaceutically acceptable salt thereof, wherein R⁷ is a substituted or unsubstituted C₃-C₁₀ cycloalkyl.

43. The compound of any one of Claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R⁷ is a substituted or unsubstituted C₆-C₁₀ spirocycloalkyl.

44. The compound of any one of Claims 1-41, or a pharmaceutically acceptable salt thereof, wherein R⁷ is a substituted or unsubstituted 3 to 10 membered heterocyclyl.

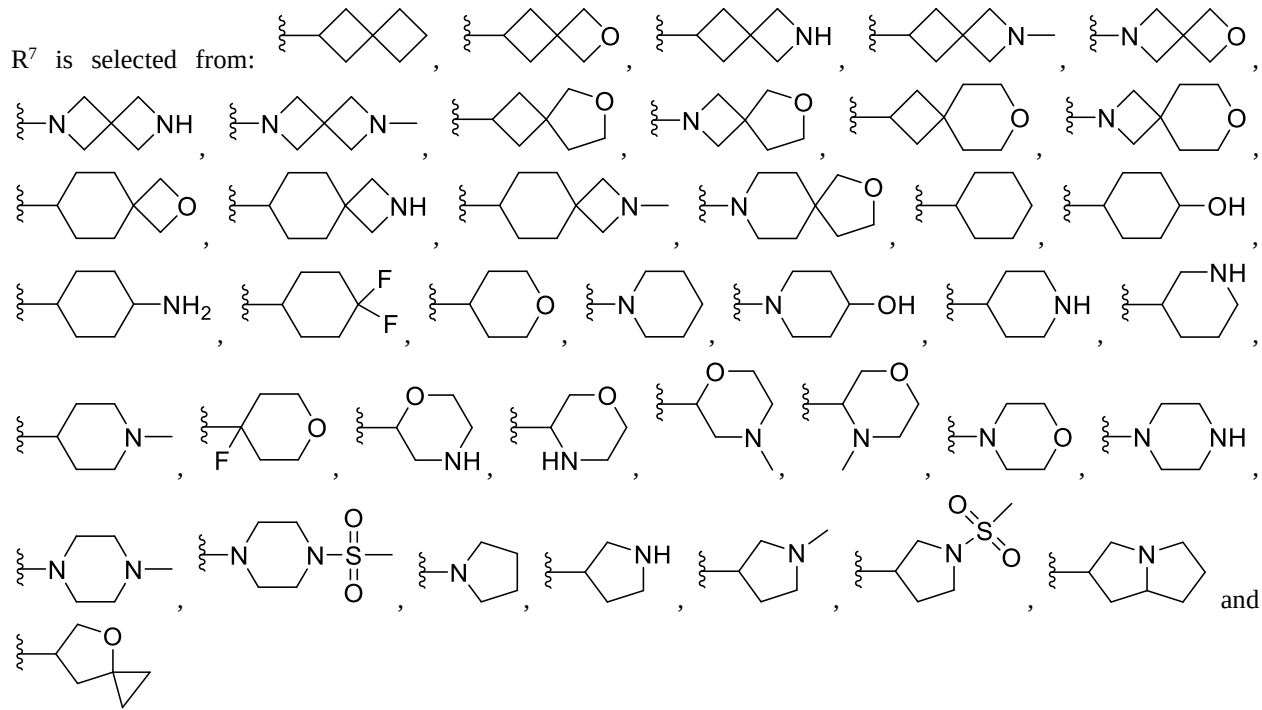
45. The compound of any one of Claims 1-41 or 44, or a pharmaceutically acceptable salt thereof, wherein R⁷ is a substituted or unsubstituted 6 to 10 membered spiro heterocyclyl.

46. The compound of any one of Claims 1-45, or a pharmaceutically acceptable salt thereof, wherein R⁷ is unsubstituted.

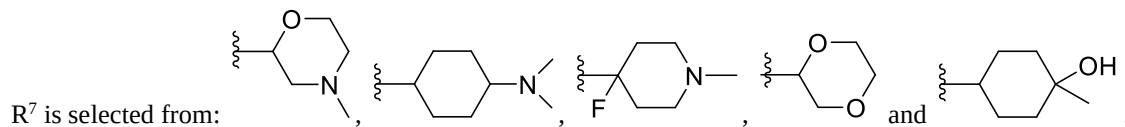
47. The compound of any one of Claims 1-45, or a pharmaceutically acceptable salt thereof, wherein R⁷ is substituted.

48. The compound of any one of Claims 1-45 or 47, or a pharmaceutically acceptable salt thereof, wherein R⁷ is substituted with 1 or 2 substituents independently selected from an unsubstituted C₁-C₆ alkyl, an unsubstituted C₁-C₆ alkoxy, fluoro, chloro, hydroxy and -SO₂-(unsubstituted C₁-C₆ alkyl).

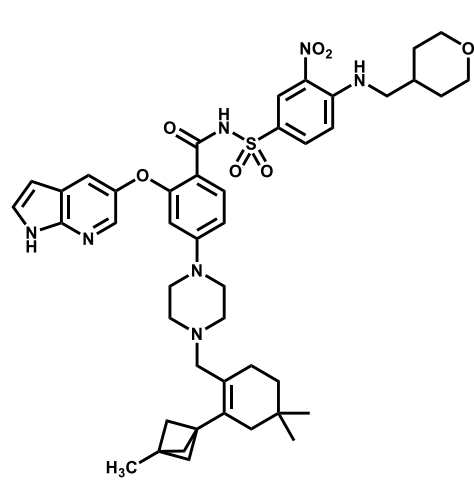
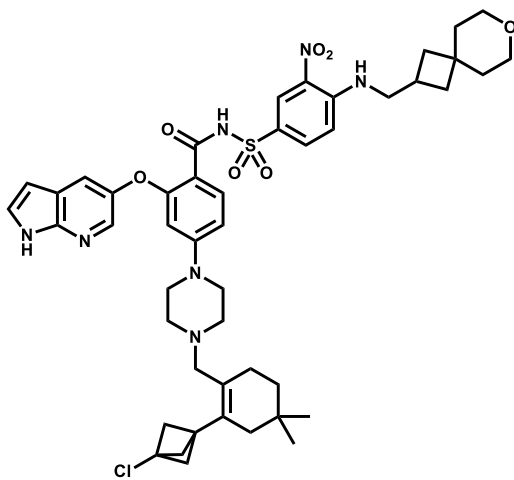
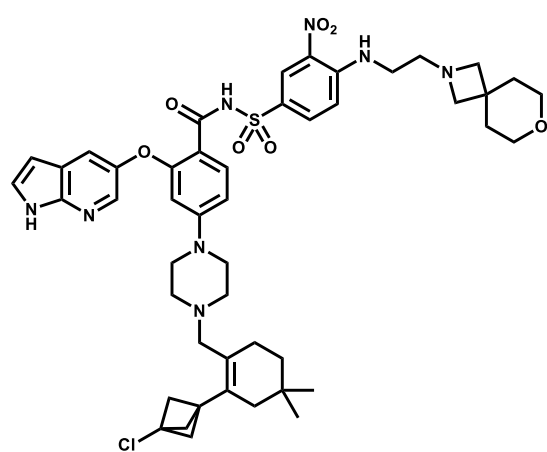
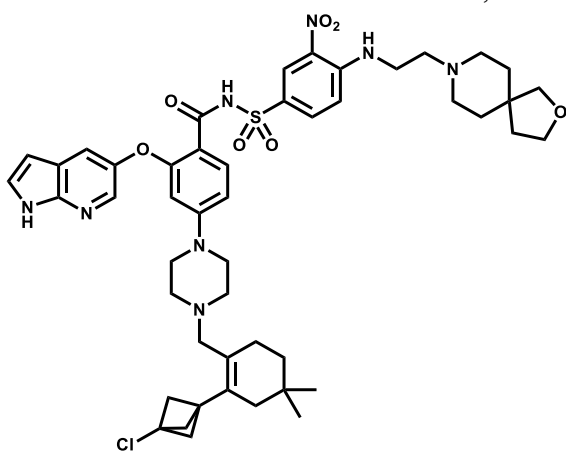
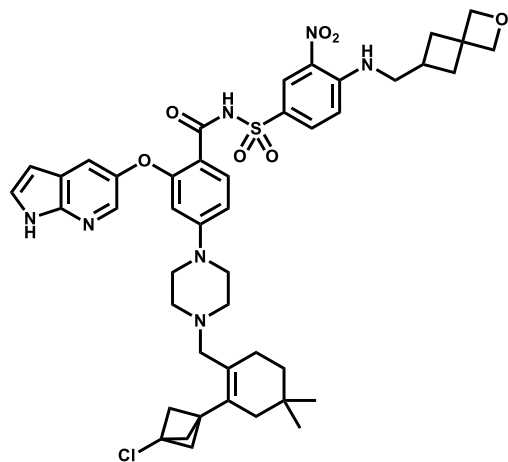
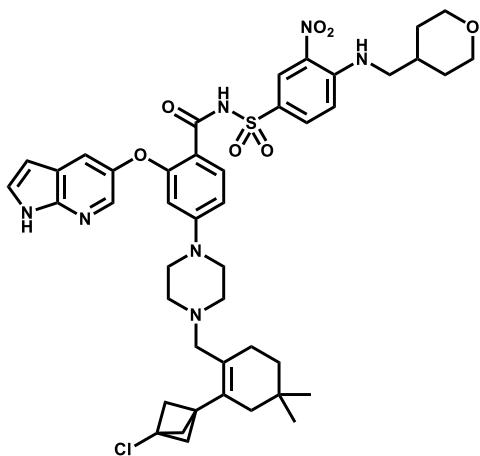
49. The compound of any one of Claims 1-41, or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from:

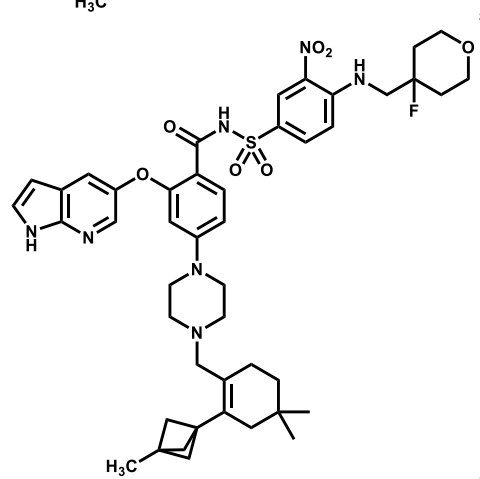
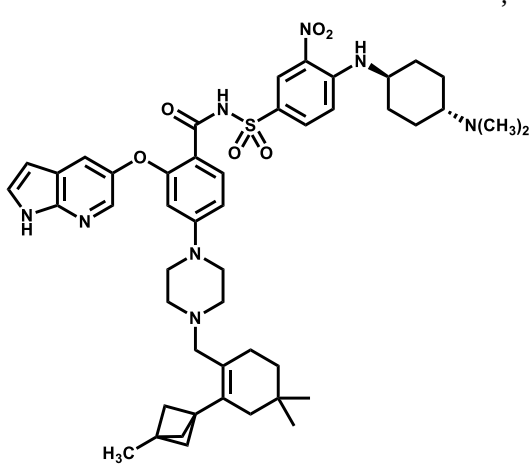
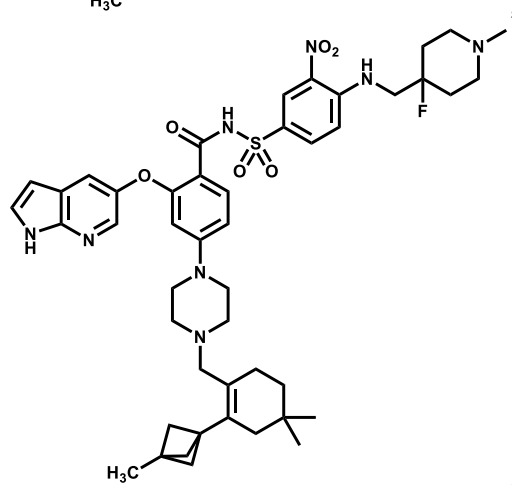
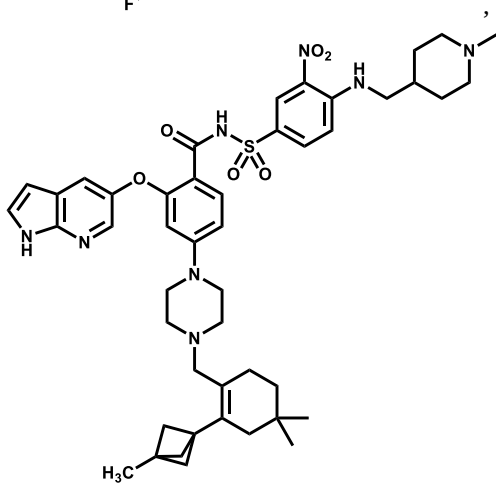
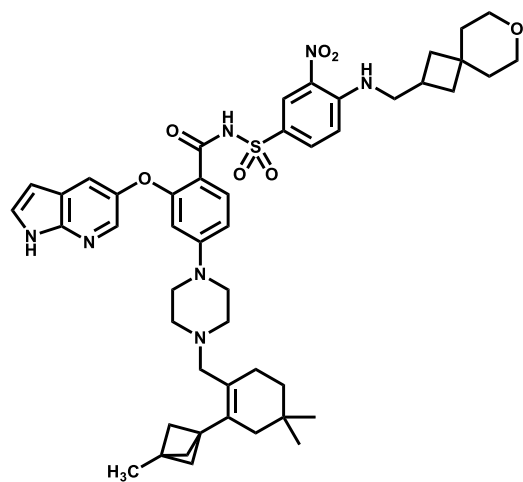
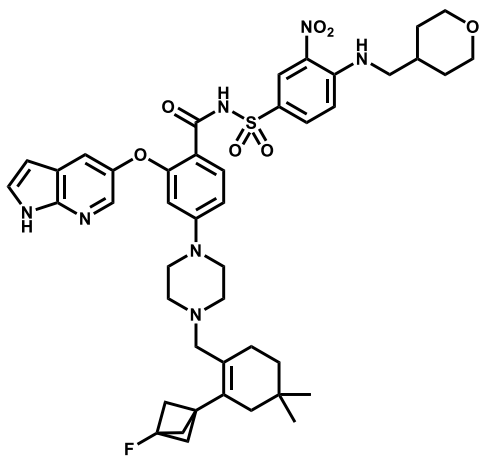


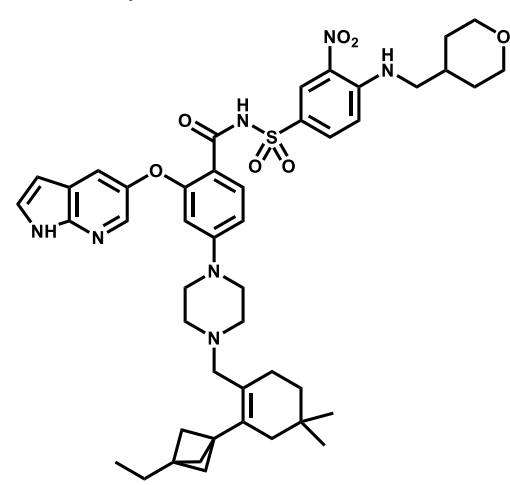
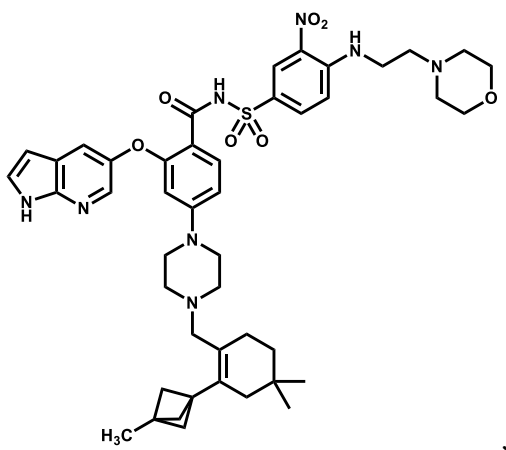
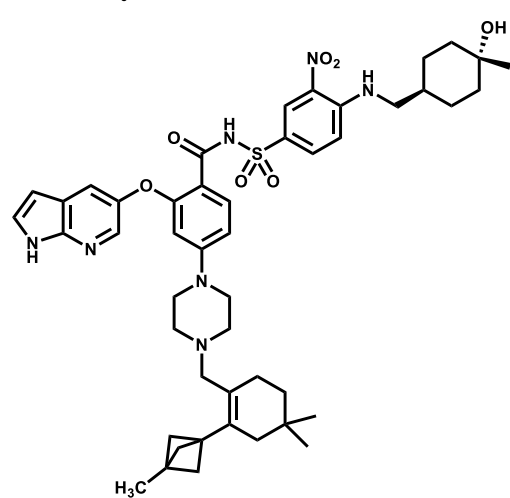
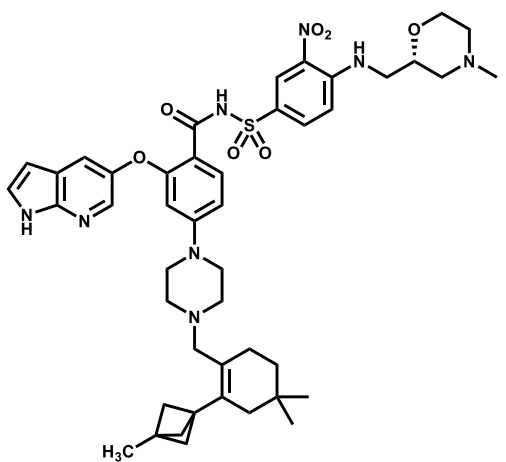
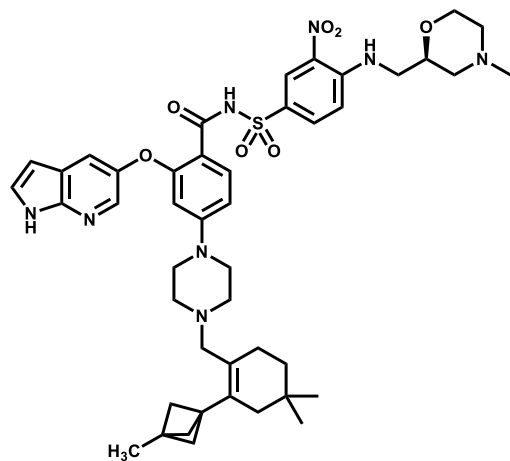
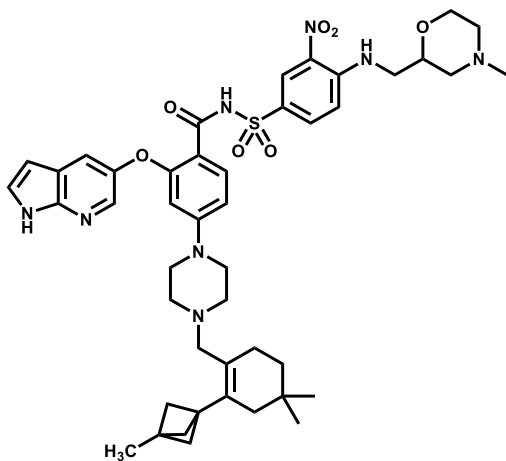
50. The compound of any one of Claims 1-41, or a pharmaceutically acceptable salt thereof, wherein

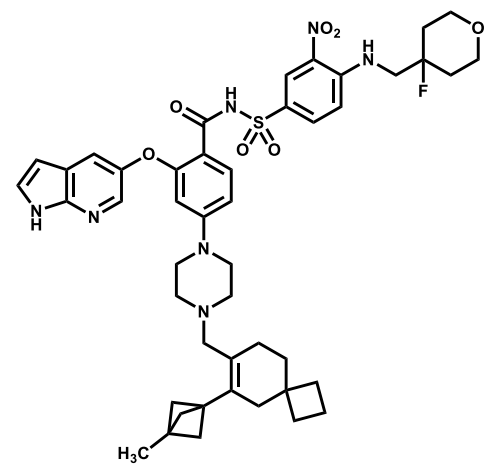
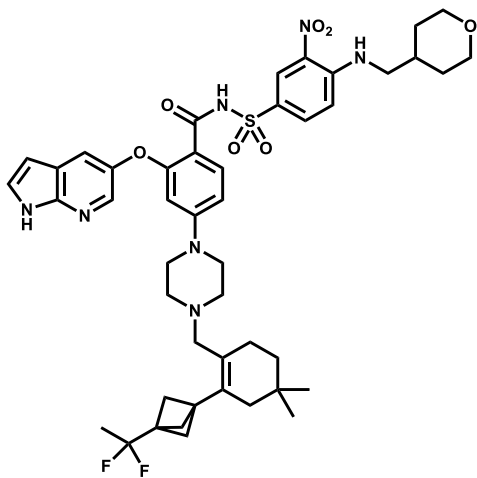
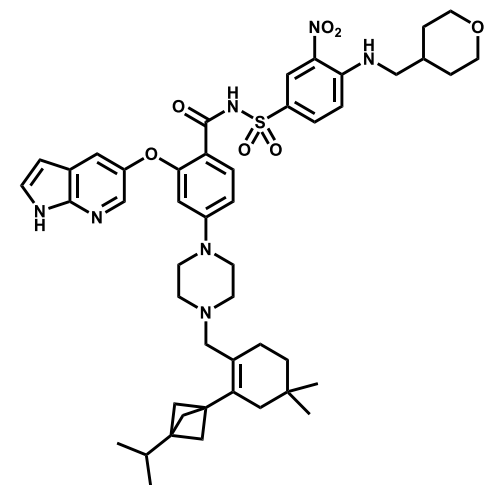
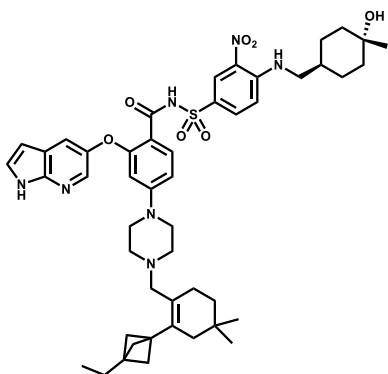
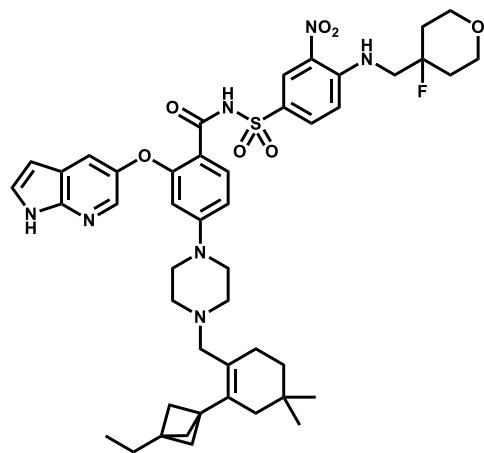
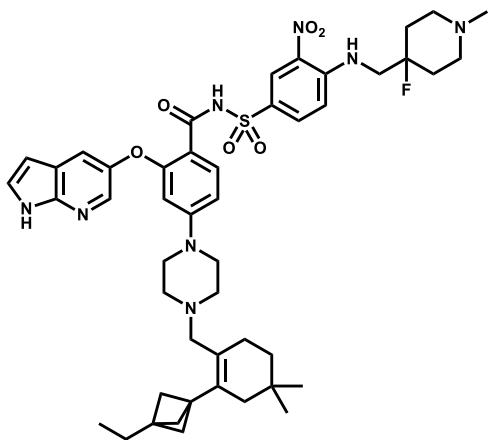


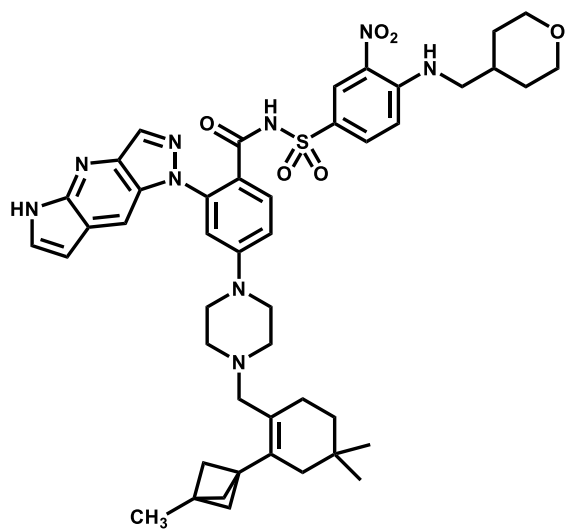
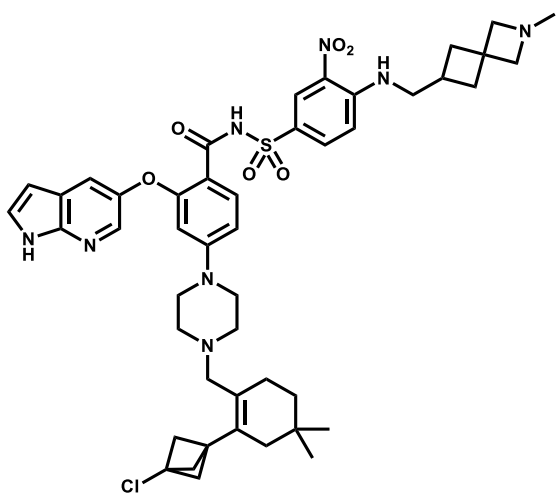
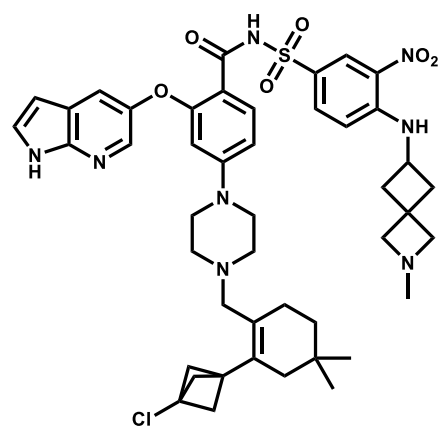
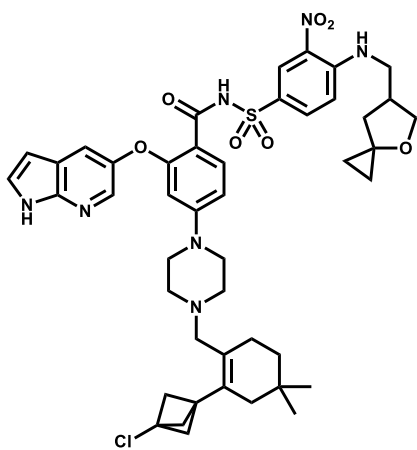
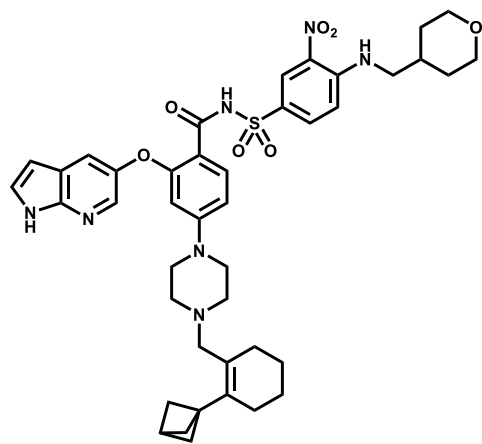
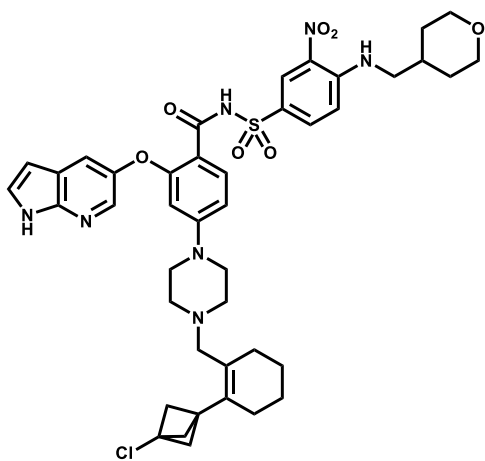
51. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

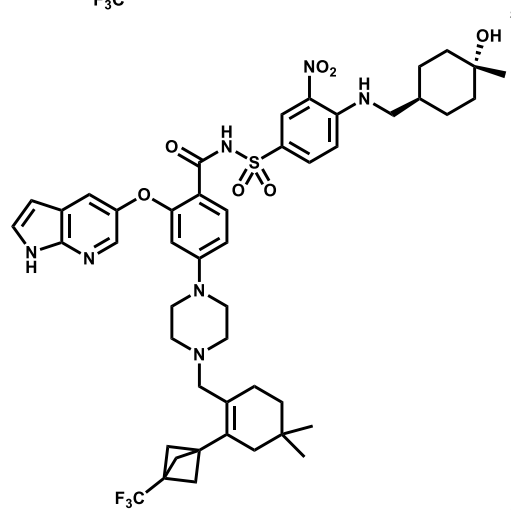
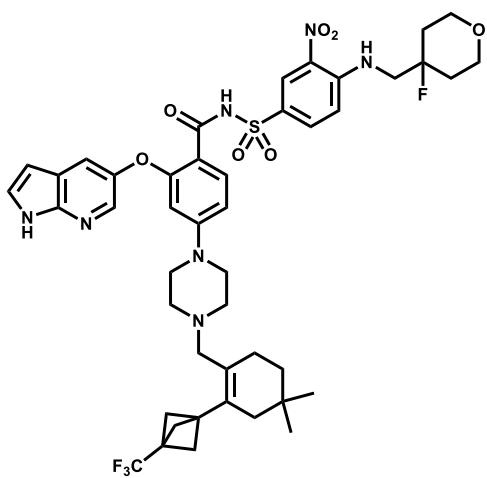
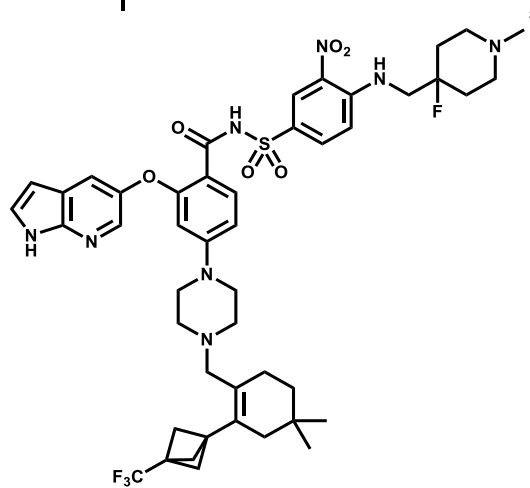
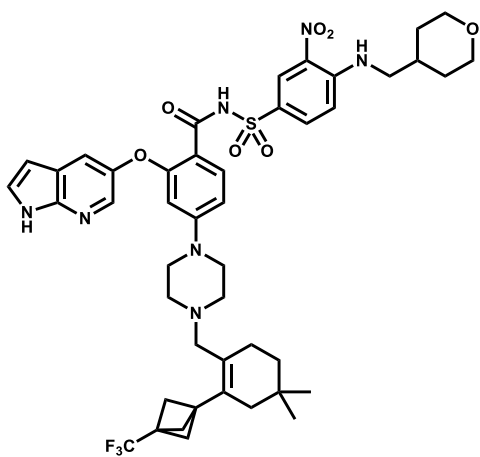
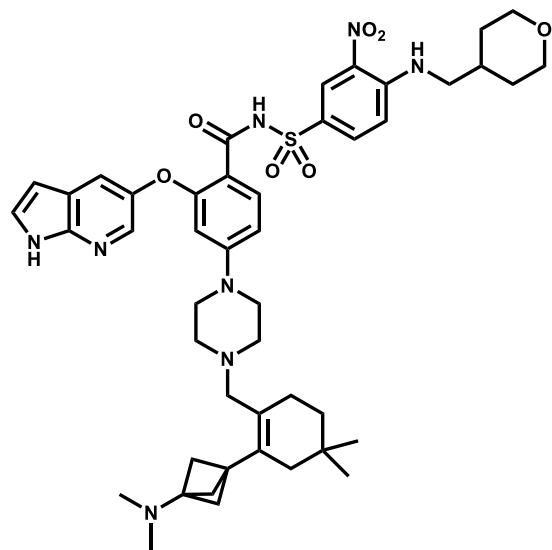
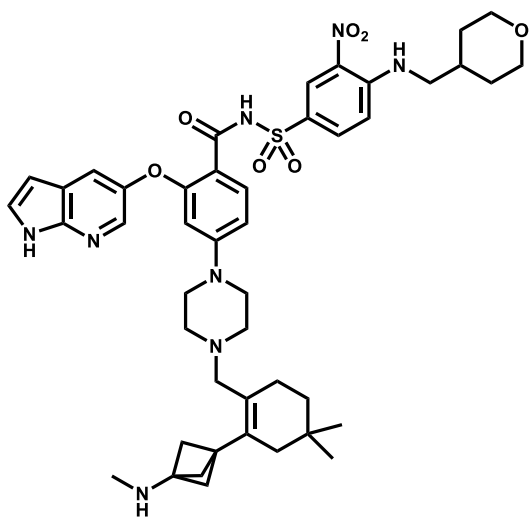


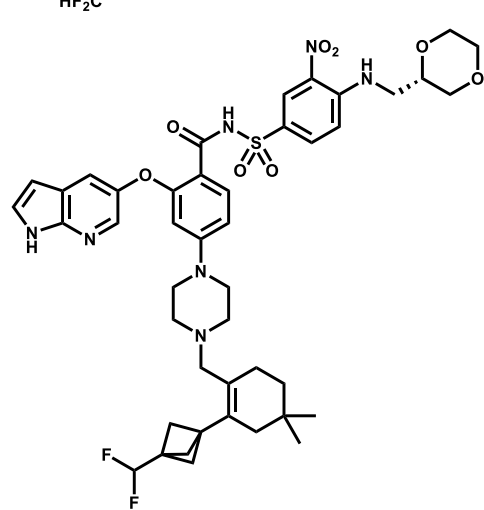
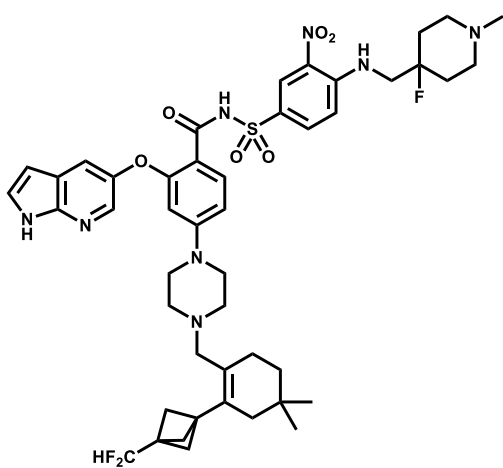
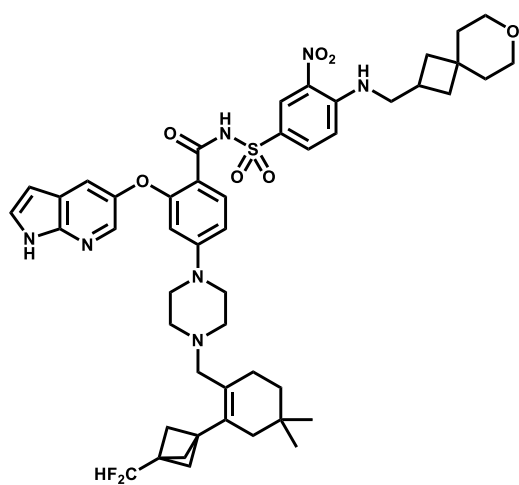
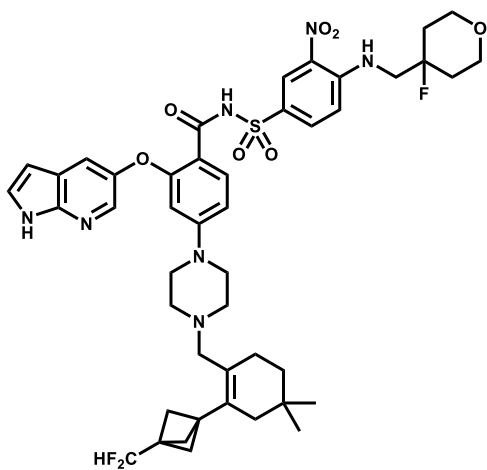
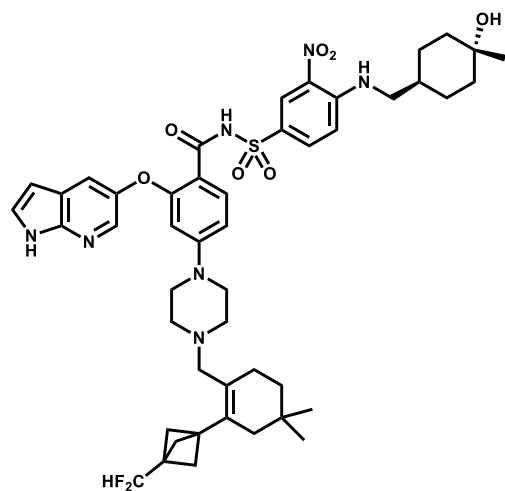
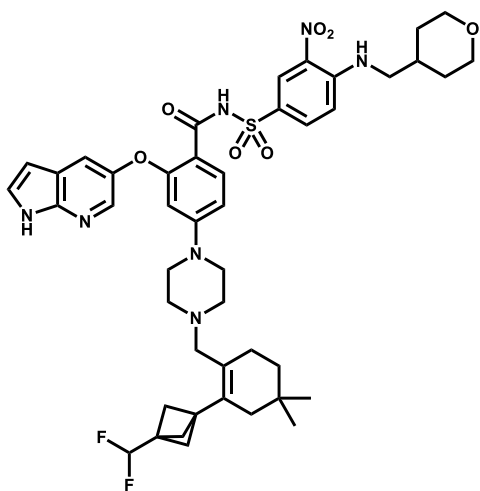


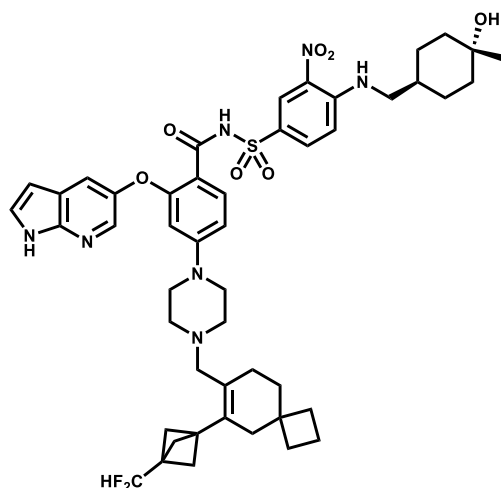
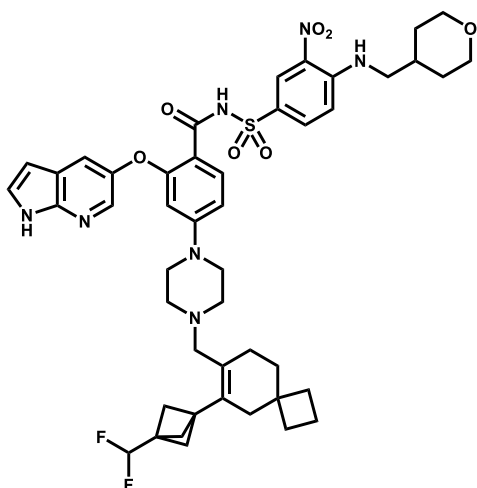




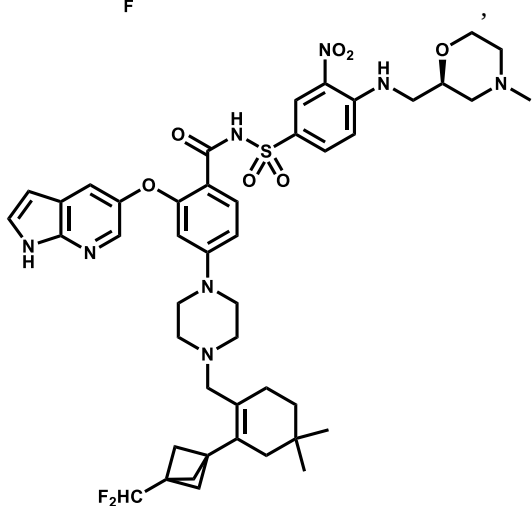




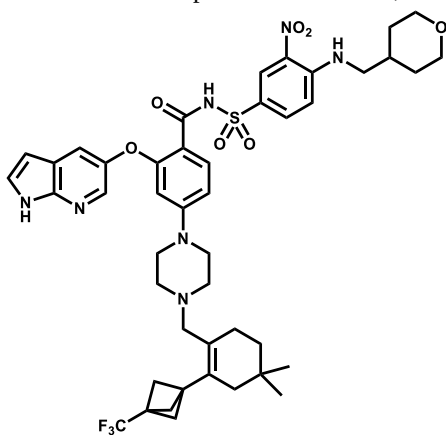




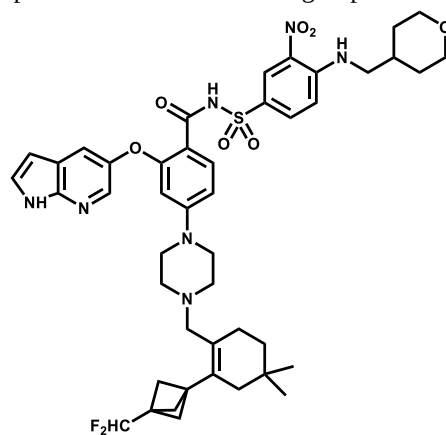
, and



52. The compound of Claim 51, wherein the compound is selected from the group consisting of:

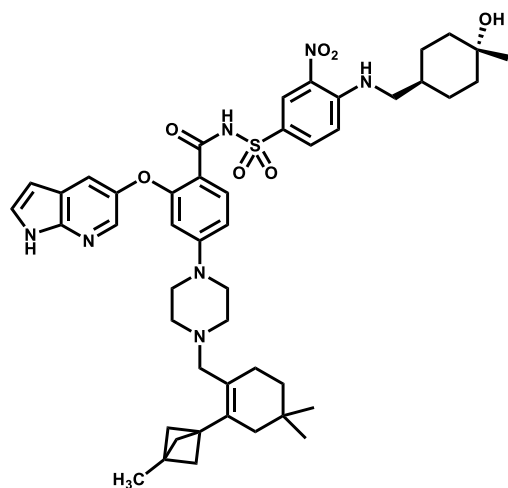


and

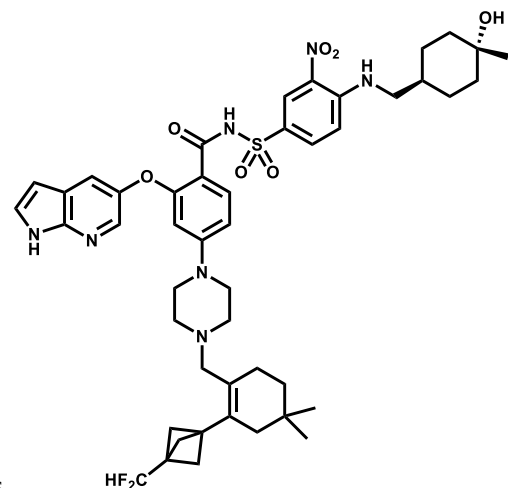


, or a

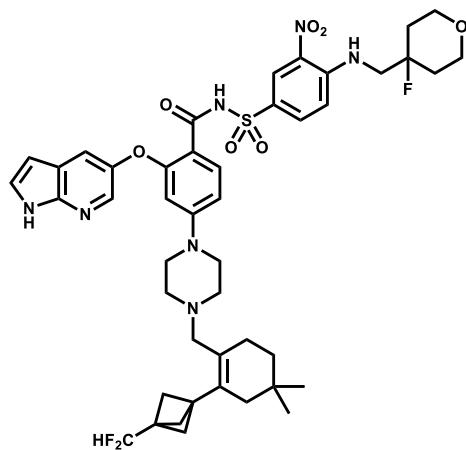
pharmaceutically acceptable salt of any of the foregoing.



53. The compound of Claim 51, wherein the compound is or a pharmaceutically acceptable salt thereof.

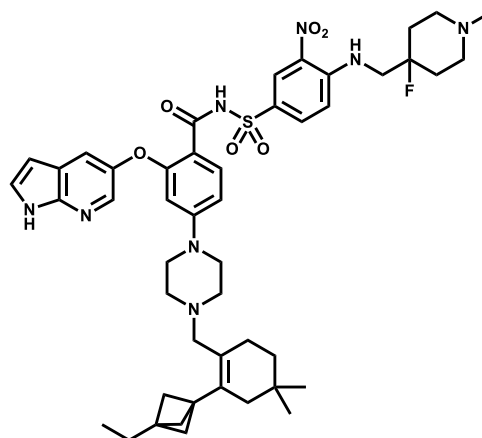


54. The compound of Claim 51, wherein the compound is or a pharmaceutically acceptable salt thereof.

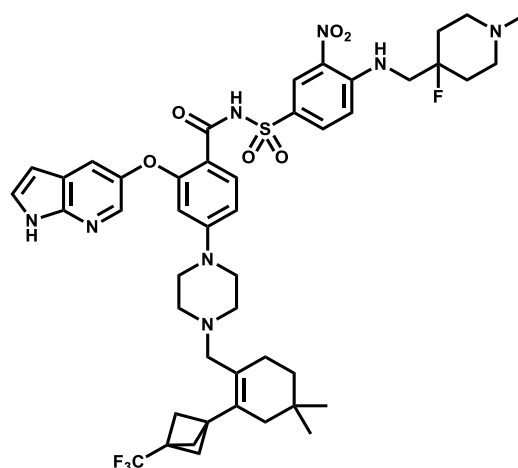


55. The compound of Claim 51, wherein the compound is or a pharmaceutically acceptable salt thereof.

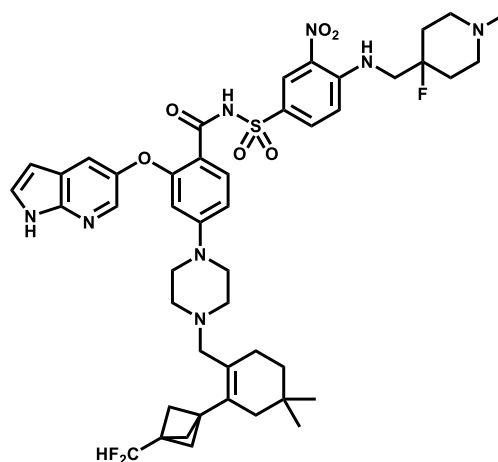
or a



56. The compound of Claim 51, wherein the compound is a pharmaceutically acceptable salt thereof.



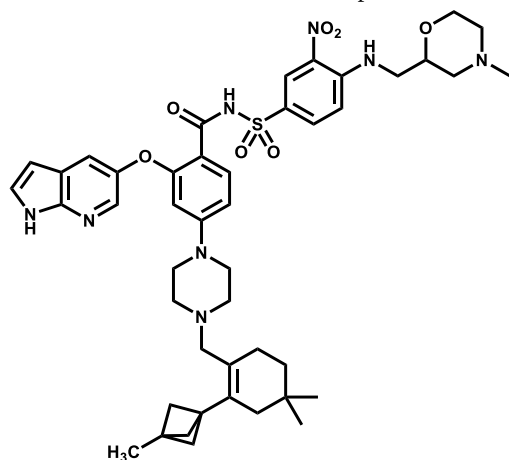
57. The compound of Claim 51, wherein the compound is , or a pharmaceutically acceptable salt thereof.



58. The compound of Claim 51, wherein the compound is or a pharmaceutically acceptable salt thereof.

CN1CC2(C)C(C1)C3(C)C(C2)C(F3)C(F)(F)F

60. The compound of Claim 51, wherein the compound is

C[C@H]1C=C[C@H]2[C@@H]1C=C(C)[C@H]2C[C@H]3C=C(C)C=C(C)[C@H]3CN4CCN(CC4)Cc5ccc(OC6=NC7=CC=CC=C7N6)cc5C(=O)NS(=O)(=O)c8ccc(cc8[N+](=O)[O-])NCC(F)C9=CC=CC=C9

62. A pharmaceutical composition comprising an effective amount of the compound of any one of any claims 1-61, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or combination thereof.

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a cancer or a tumor, wherein the cancer or the tumor is selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

64. Use of an effective amount of a compound of any one of Claims 1-61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or the tumor is due to a cancer selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

65. Use of an effective amount of a compound of any one of Claims 1-61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 in the manufacture of a medicament for treating a malignant growth or a tumor, wherein the malignant growth or the tumor is due to a cancer selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

66. Use of a compound of any one of Claims 1-61, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of Claim 62, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for preparing a medicament for treating a HIV infection.

67. Use of a compound of any one of Claims 1-61, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of Claim 62, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for preparing a medicament for reducing the reoccurrence of a HIV infection.

68. Use of a compound of any one of Claims 1-61, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of Claim 62, and an effective amount of a HIV latency reversing agent, or a pharmaceutically acceptable salt thereof, for preparing a medicament suitable for use in reducing the population of HIV infected cells.

69. The use of Claim 68, wherein the cells are CD4+T cells.

70. The use of any one of Claims 66-68, wherein the HIV latency reversing agent is selected from: a protein kinase C agonist, a PD-1 inhibitor, a PD-L1 inhibitor, an HDAC inhibitor, a phorbol ester and a bromodomain inhibitor.

71. The use of Claim 70, wherein the HIV latency reversing agent is selected from: ingenol, rostatin, nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, REGN2810, MEDI0680, Durvalumab, Atezolizumab, Avelumab, BMS-936559, BGB-A317, vorinostat, panobinostat, valproic acid, romidepsin, prostratin, phorbol 12-myristate-13-acetate, bryostatin-1, (S)-tert-butyl 2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate, JQ1, I-BET762, OTX015, I-BET151, CPI203, PFI-1, MS436, CPI-0610, RVX2135, FT-1101, BAY1238097, INCB054329, TEN-010, GSK2820151, ZEN003694, BAY-299, BMS-986158, ABBV-075 and GS-5829.

72. The use of any one of Claims 66-71, further comprising the use of one or more agents selected from the group consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI), a nucleoside reverse transcriptase inhibitor (NRTI), a protease inhibitor (PI), a fusion/entry inhibitor, an integrase strand transfer inhibitor (INSTI), a HIV vaccine, a HIV other antiretroviral therapy compound and combinations thereof, or a pharmaceutically acceptable salt of any of the aforementioned.