

COMBINATIONS

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application No. 62/952,039, filed December 20, 2019.

Field

[0002] The present application relates to the fields of chemistry, biochemistry and medicine. More particularly, disclosed herein are combination therapies, and methods of treating diseases and/or conditions with a combination therapies described herein.

Description

[0003] Cancers are a family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. Cancer treatments today include surgery, hormone therapy, radiation, chemotherapy, immunotherapy, targeted therapy and combinations thereof. Survival rates vary by cancer type and by the stage at which the cancer is diagnosed. In 2019, roughly 1.8 million people will be diagnosed with cancer, and an estimated 606,880 people will die of cancer in the United States. Thus, there still exists a need for effective cancer treatments.

SUMMARY

[0004] Some embodiments described herein relate to a combination of compounds that can include an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments described herein relate to the use of a combination of compounds for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof. Other

embodiments described herein relate to the use of a combination of compounds in the manufacture of a medicament for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof.

[0006] In some embodiments, the disease or condition can be a cancer described herein.

DRAWINGS

[0007] Figure 1 provides examples of Compound (A).

[0008] Figure 2 provides examples of Compound (B).

[0009] Figure 3 shows inhibition of monotherapy and combination therapy against RS4;11, DMS053, MV4-11 and Toledo cell lines.

[0010] Figure 4 shows inhibition of monotherapy and combination therapy against the MCF-7 cell line.

[0011] Figure 5 shows tumor volume in response to monotherapy and combination therapy in an HL-60 (AML) mouse model.

DETAILED DESCRIPTION

Definitions for Compound (A), and pharmaceutically acceptable salts thereof

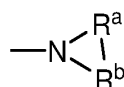
[0012] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety 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.

[0013] 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,

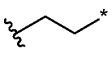
cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), cycloalkyl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, 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).

[0014] 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.

[0015] 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:



[0016] 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.

[0017] 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.*, ).

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

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

[0020] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic (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.

[0021] 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.

[0022] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic (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.

[0023] As used herein, “heteroaryl” refers to a monocyclic or polycyclic (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, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0024] As used herein, “heterocyclyl” or “heteroalicycyl” 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 heteroalicycyl” refers to compounds wherein the heterocyclyl or heteroalicycyl 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 heteroalicycyl 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 “heteroalicyclic” 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.

[0025] 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.

[0026] 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.

[0027] 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).

[0028] As used herein, the term “hydroxy” refers to a –OH group.

[0029] 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 alkoxy groups are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzyloxy. An alkoxy may be substituted or unsubstituted.

[0030] 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.

[0031] A “cyano” group refers to a “ $-CN$ ” group.

[0032] 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.

[0033] 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.

[0034] An “O-carbamyl” group refers to a “ $-OC(=O)N(R_A R_B)$ ” 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.

[0035] 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.

[0036] An “O-thiocarbamyl” group refers to a “ $-OC(=S)N(R_A R_B)$ ” 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.

[0037] 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.

[0038] 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.

[0039] An “N-amido” group refers to a “RC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0040] An “S-sulfonamido” group refers to a “-SO₂N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0041] An “N-sulfonamido” group refers to a “RSO₂N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0042] 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.

[0043] 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.

[0044] A “nitro” group refers to an “-NO₂” group.

[0045] 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.

[0046] 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.

[0047] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0048] 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.

[0049] 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.

[0050] The terms “amino” and “unsubstituted amino” as used herein refer to a –NH₂ group.

[0051] 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-C₁-C₆ alkylamine group, a mono-arylamine group, a mono-C₆-C₁₀ arylamine group and the like. Examples of mono-substituted amine groups include, but are not limited to, –NH(methyl), –NH(phenyl) and the like.

[0052] A “di-substituted amine” group refers to a “-NR_AR_B” group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. R_A and R_B can independently be substituted or unsubstituted. A di-substituted amine group can include, for example, a di-alkylamine group, a di-C₁-C₆ alkylamine group, a di-arylamine group, a di-C₆-C₁₀ arylamine group and the like. Examples of di-substituted amine groups include, but are not limited to, –N(methyl)₂, –N(phenyl)(methyl), –N(ethyl)(methyl) and the like.

[0053] 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-C₁-C₆ alkylamine(C₁-C₆ 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.

[0054] 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.

[0055] 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.

[0056] 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.”

[0057] 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. 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⁻).

[0058] 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.

[0059] 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).

[0060] 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.

[0061] 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.

[0062] 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.

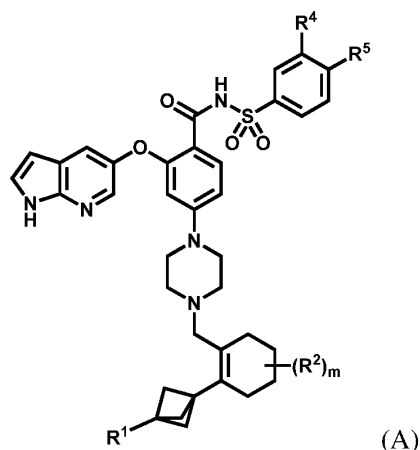
[0063] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term ‘including’ should be read to mean ‘including, without limitation,’ ‘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.

[0064] 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.

Compound (A)

[0065] Some embodiments disclosed herein relate to the use of a combination of compounds for treating a disease or condition, wherein the combination can include an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, wherein: the Compound (A) has 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 C_1 - C_6 alkoxy, an unsubstituted mono- C_1 - C_6 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; or when m is 2 or 3, 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, or two R² groups can be 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; R⁴ can be selected from NO₂, S(O)R⁶, SO₂R⁶, halogen, cyano and an unsubstituted C₁-C₆ haloalkyl; R⁵ can be -X¹-(Alk¹)_n-R⁷; Alk¹ can be 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, 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; m can be 0, 1, 2 or 3; n can be selected from 0 and 1; and X¹ can be selected from -O-, -S- and -NH-.

[0066] 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.

[0067] In some embodiments, R¹ can be a substituted or unsubstituted C₁-C₆ alkyl. For example, in some embodiments, R¹ can be a substituted C₁-C₆ alkyl. In other embodiments, R¹ can be an unsubstituted C₁-C₆ alkyl. Examples of suitable C₁-C₆ 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, R¹ can be an unsubstituted methyl or an unsubstituted ethyl.

[0068] In some embodiments, R¹ can be a substituted or unsubstituted C₁-C₆ haloalkyl, for example, a substituted or unsubstituted mono-halo C₁-C₆ alkyl, a substituted or unsubstituted di-halo C₁-C₆ alkyl, a substituted or unsubstituted tri-halo C₁-C₆ alkyl, a substituted

or unsubstituted tetra-halo C₁-C₆ alkyl or a substituted or unsubstituted penta-halo C₁-C₆ alkyl. In some embodiments, R¹ can be an unsubstituted -CHF₂, -CF₃, -CH₂CF₃ or -CF₂CH₃.

[0069] In some embodiments, R¹ can be a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl. For example, in some embodiments, R¹ can be a substituted monocyclic C₃-C₆ cycloalkyl. In other embodiments, R¹ can be an unsubstituted monocyclic C₃-C₆ cycloalkyl. Examples of suitable monocyclic or bicyclic C₃-C₆ cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, [1.1.1]bicyclopentyl and cyclohexyl.

[0070] In some embodiments, R¹ can be a substituted or unsubstituted C₁-C₆ alkoxy. For example, in some embodiments, R¹ can be a substituted C₁-C₆ alkoxy. In other embodiments, R¹ can be an unsubstituted C₁-C₆ alkoxy. Examples of suitable C₁-C₆ 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, R¹ can be an unsubstituted methoxy or an unsubstituted ethoxy.

[0071] In some embodiments, R¹ can be an unsubstituted mono-C₁-C₆ 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, R¹ can be methylamine or ethylamine.

[0072] In some embodiments, R¹ can be an unsubstituted di-C₁-C₆ alkylamine. In some embodiments, each C₁-C₆ alkyl in the di-C₁-C₆ alkylamine is the same. In other embodiments, each C₁-C₆ alkyl in the di-C₁-C₆ alkylamine is different. Examples of suitable di-C₁-C₆ alkylamine groups include, but are not limited to di-methylamine, di-ethylamine, (methyl)(ethyl)amine, (methyl)(isopropyl)amine and (ethyl)(isopropyl)amine.

[0073] In some embodiments, m can be 0. When m is 0, those skilled in the art understand that the ring to which R² 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.

[0074] In some embodiments, one R² can be an unsubstituted C₁-C₆ 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 R², if present, can be independently selected from halogen (for example, fluoro or chloro), a substituted or unsubstituted C₁-C₆ alkyl (such as those described herein), a substituted or unsubstituted C₁-C₆

haloalkyl (such as those described herein) and a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl (such as those described herein). In some embodiments, each R² can be independently selected from an unsubstituted C₁-C₆ alkyl, such as those described herein.

[0075] In some embodiments, m can be 2; and each R² can be geminal. In some embodiments, m can be 2; and each R² can be vicinal. In some embodiments, m can be 2; and each R² can be an unsubstituted methyl. In some embodiments, m can be 2; and each R² can be a geminal unsubstituted methyl.

[0076] In some embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted monocyclic C₃-C₆ cycloalkyl. For example, in some embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted monocyclic C₃-C₆ cycloalkyl, such as those described herein. In other embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form an unsubstituted monocyclic C₃-C₆ cycloalkyl, such as those described herein. In some embodiments, two R² groups can be taken together with the atom to which they are attached to form an unsubstituted cyclopropyl.

[0077] In some embodiments, two R² 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 R² 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 R² 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.

[0078] In some embodiments, R⁴ can be NO₂. In some embodiments, R⁴ can be cyano. In some embodiments, R⁴ can be halogen.

[0079] In some embodiments, R⁴ can be an unsubstituted C₁-C₆ haloalkyl, such as those described herein. In some embodiments, R⁴ can be -CF₃.

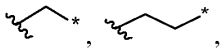
[0080] In some embodiments, R^4 can be $S(O)R^6$. In some embodiments, R^4 can be SO_2R^6 . In some embodiments, R^4 can be SO_2CF_3 .

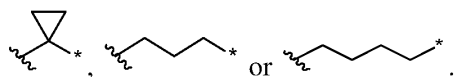
[0081] In some embodiments, R^6 can be a substituted or unsubstituted C_1 - C_6 alkyl. For example, in some embodiments, R^6 can be a substituted C_1 - C_6 alkyl, such as those described herein. In other embodiments, R^6 can be an unsubstituted C_1 - C_6 alkyl, such as those described herein.

[0082] In some embodiments, R^6 can be a substituted or unsubstituted monocyclic or bicyclic C_3 - C_6 cycloalkyl. For example, in some embodiments, R^6 can be a substituted monocyclic or bicyclic C_3 - C_6 cycloalkyl. In other embodiments, R^6 can be an unsubstituted monocyclic or bicyclic 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^6 can be a substituted or unsubstituted C_1 - C_6 haloalkyl, such as those described herein. In some embodiments, R^6 can be $-CF_3$.

[0084] In some embodiments, R^5 can be $-X^1-(Alk^1)_n-R^7$. In some embodiments, X^1 can be $-O-$. In some embodiments, X^1 can be $-S-$. In some embodiments, X^1 can be $-NH-$.

[0085] In some embodiments, Alk^1 can be unsubstituted $-(CH_2)_{1-4}-*$ for which "*" represents the point of attachment to R^7 . In some embodiments, Alk^1 can be ,



[0086] In some embodiments, Alk^1 can be a substituted $\xi-C_1-C_4$ alkylene* for which "*" represents the point of attachment to R^7 . For example, in some embodiments, Alk^1 can be a substituted methylene, a substituted ethylene, a substituted propylene or a substituted butylene. In some embodiments, Alk^1 can be mono-substituted, di-substituted or tri-substituted. In some embodiments, Alk^1 can be mono-substituted with a halogen (such as fluoro or chloro) or unsubstituted C_1 - C_3 alkyl, such as those described herein. In other embodiments, Alk^1 can be mono-substituted unsubstituted C_1 - C_3 haloalkyl, such as those described herein. In some embodiments, Alk^1 can be mono-substituted with fluoro or unsubstituted methyl. In some embodiments, Alk^1 can be di-substituted with one fluoro and one unsubstituted C_1 - C_3 alkyl, such as those described herein. In other embodiments, Alk^1 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.

[0087] In some embodiments, Alk¹ can be selected from:

The structures shown are: isopropyl, tert-butyl, 2-fluoropropyl, 1-chloroethyl, 1,1,1-trifluoroethyl, 2-chloropropyl, 2-fluoropropyl, 2,2,2-trifluoropropyl, 2,2,3-trifluorobutyl, 3-chlorobutyl, 3-fluorobutyl, 3,3,3-trifluorobutyl, 4-chloropentyl, 4-fluoropentyl, 4,4,4-trifluoropentyl, 4,4,5-trifluorohexyl, and 5-chlorohexyl.

[0088] 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.

[0089] In some embodiments, R⁷ can be a substituted or unsubstituted mono-substituted amine group. For example, R⁷ can be an amino group mono-substituted with 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). 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).

[0090] 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).

[0091] 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.

[0092] 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.

[0093] 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.

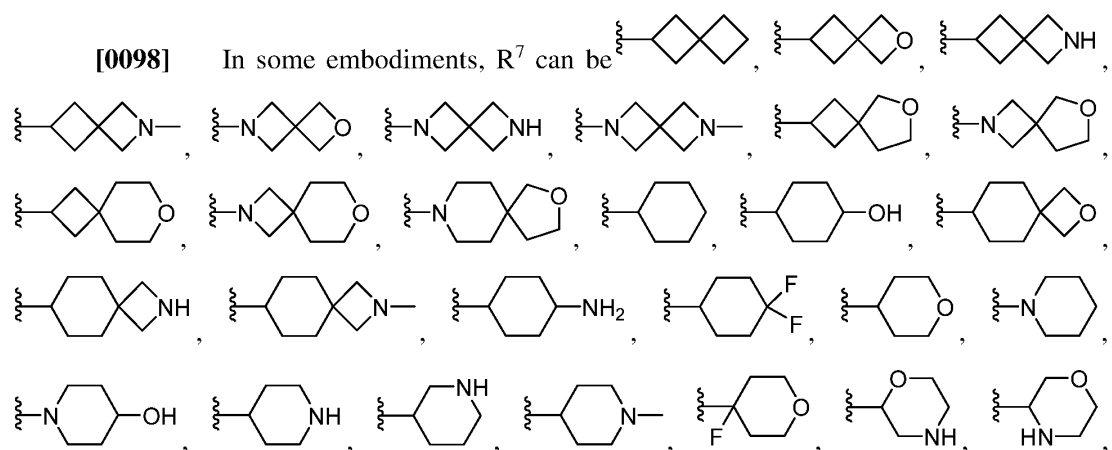
[0094] In some embodiments, R^7 can be a substituted or unsubstituted 3 to 10 membered heterocyclyl. In some embodiments, R^7 can be a substituted 3 to 10 membered heterocyclyl. In other embodiments, R^7 can be an unsubstituted 3 to 10 membered heterocyclyl. In some embodiments, R^7 can be a substituted or unsubstituted monocyclic 3 to 10 membered heterocyclyl. In other embodiments, R^7 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.

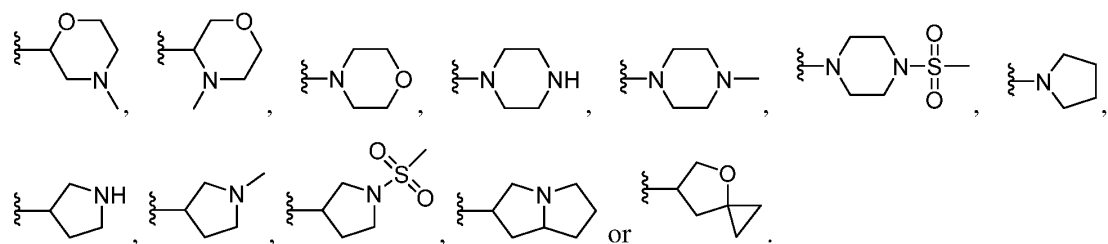
[0095] In some embodiments, R^7 can be a substituted or unsubstituted 6 to 10 membered spiro heterocyclyl. In some embodiments, R^7 can be a substituted 6 to 10 membered spiro heterocyclyl. In other embodiments, R^7 can be an unsubstituted 6 to 10 membered spiro heterocyclyl. In some embodiments, R^7 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.

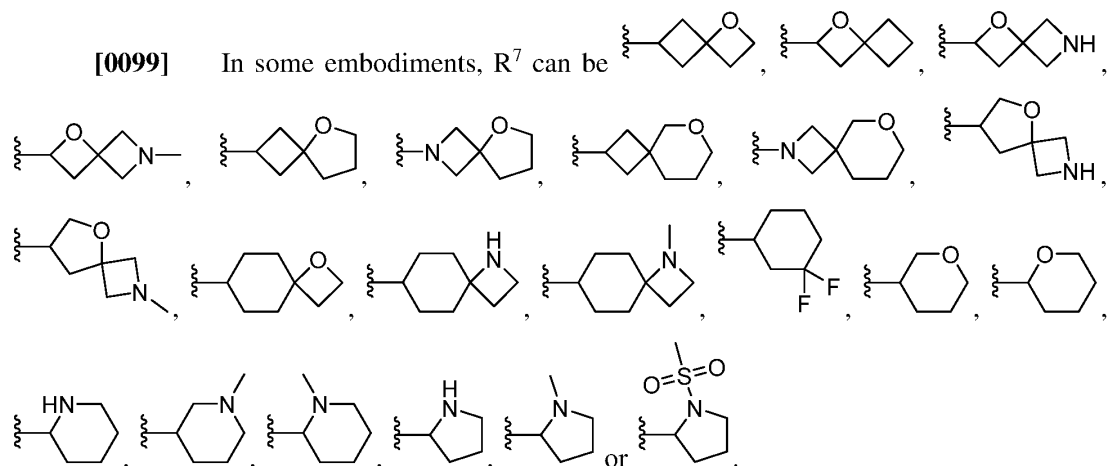
[0096] In some embodiments, R^7 can be hydroxy or amino.

[0097] 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.

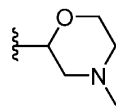




[0099] In some embodiments, R^7 can be



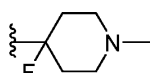
[0100] In some embodiments, R^7 can be



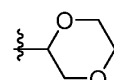
embodiments R^7 can be  or . In some embodiments R^7 can be



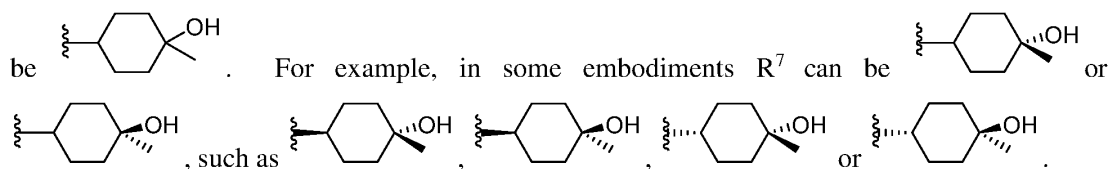
In some embodiments R^7 can be



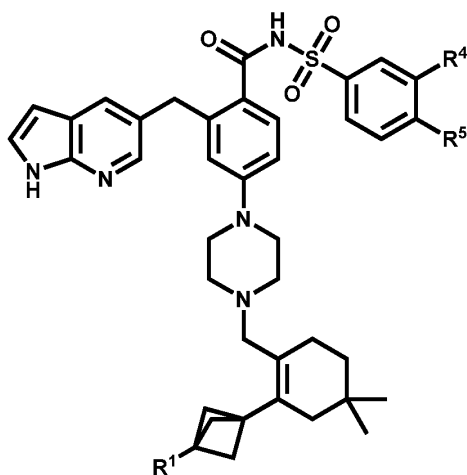
. In some embodiments R^7 can be



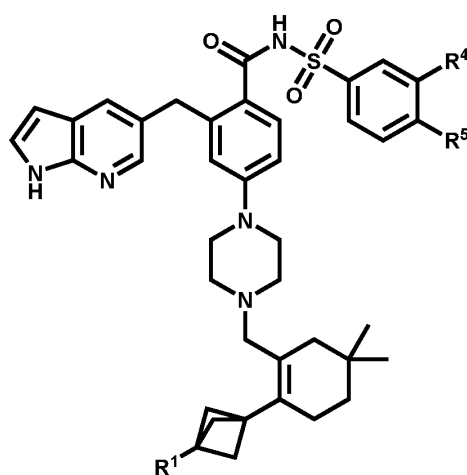
example, in some embodiments R^7 can be  or . In some embodiments R^7 can



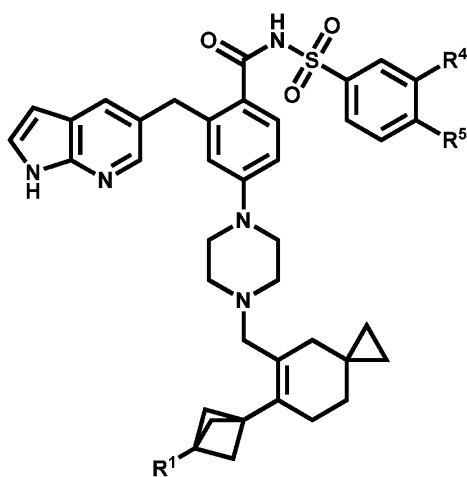
[0101] In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be selected from a compound of Formula (AA), Formula (BB), Formula (CC) and Formula (DD):



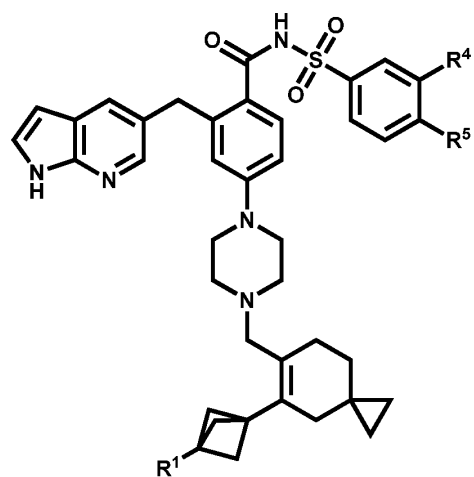
(AA)



(BB)



(CC)

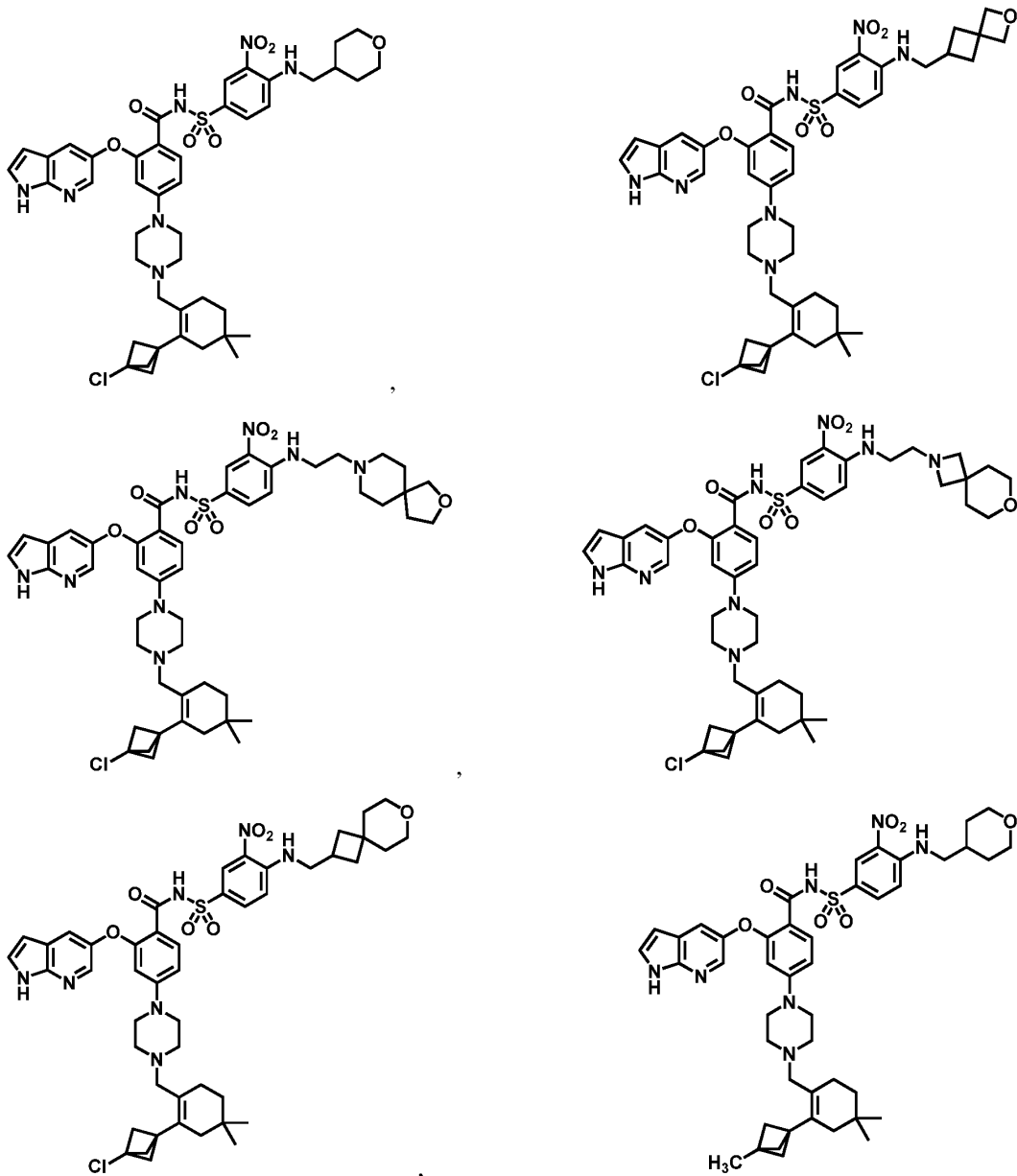


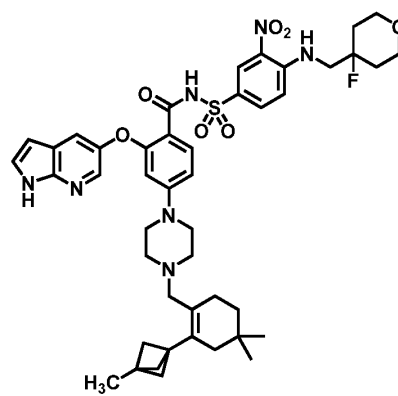
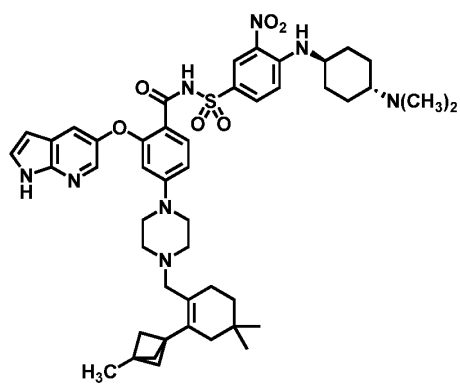
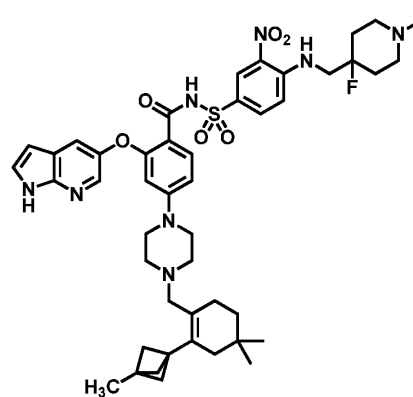
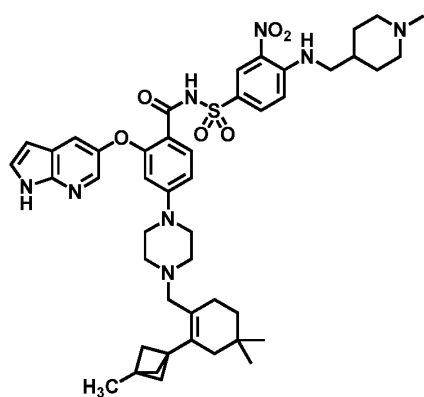
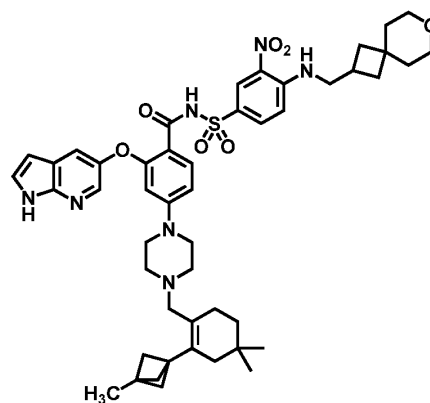
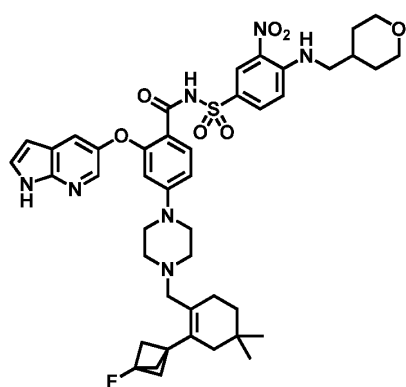
(DD),

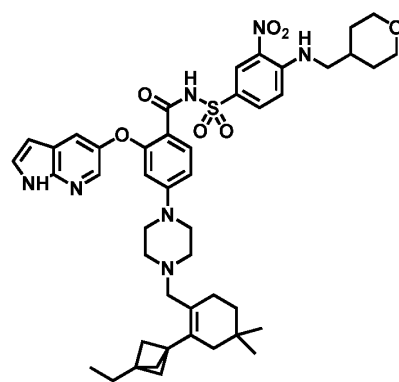
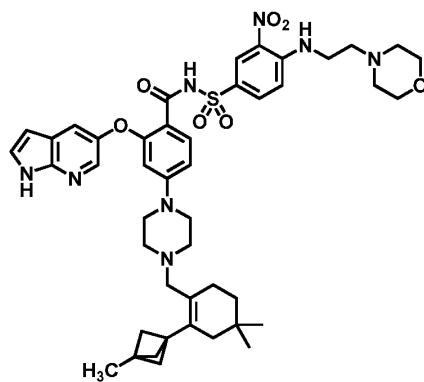
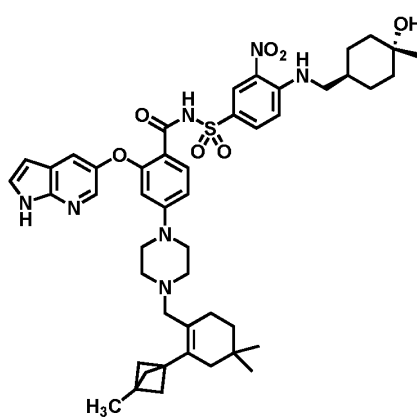
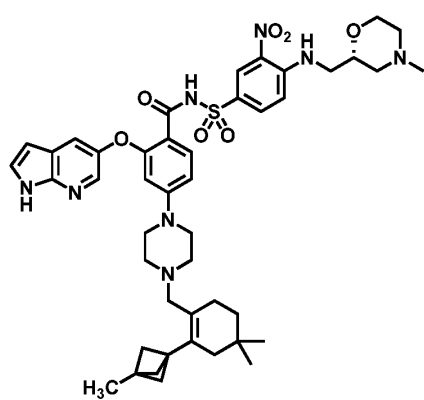
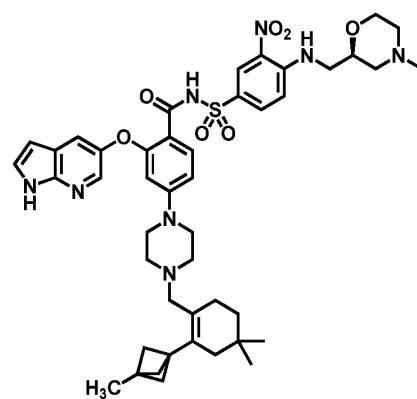
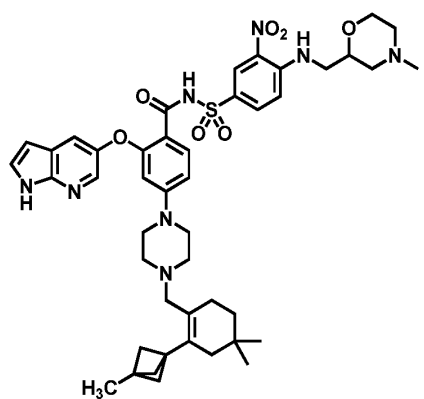
or pharmaceutically acceptable salts of any of the foregoing.

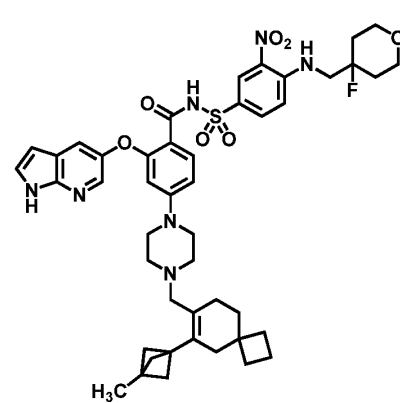
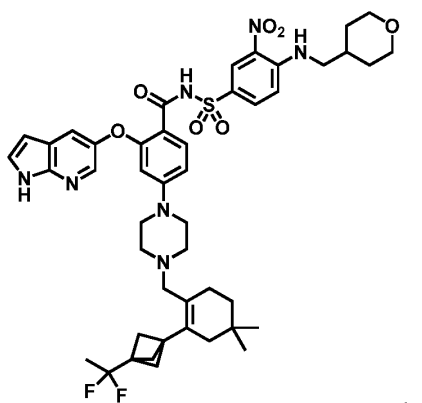
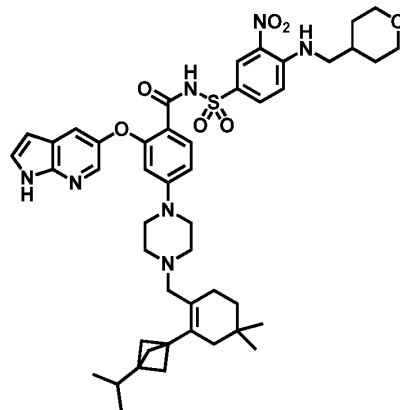
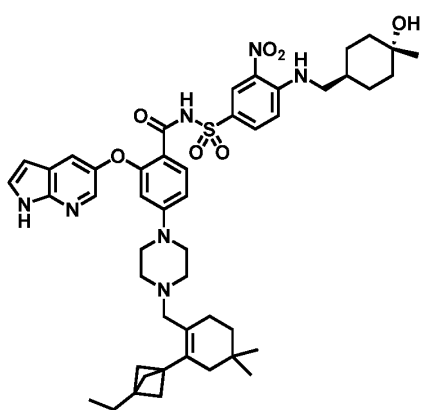
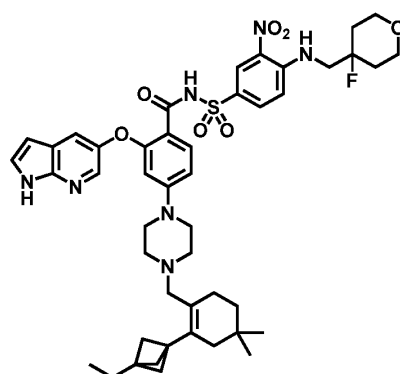
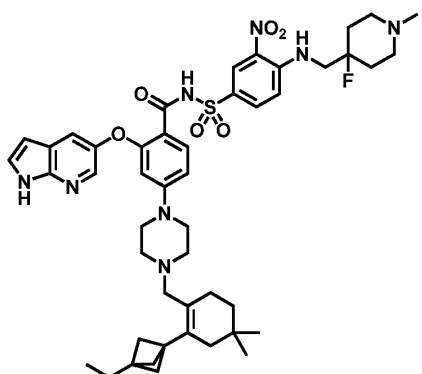
[0102] A non-limiting list of Bcl-2 inhibitors of Compound (A) are described herein, and include those provided in Figure 1.

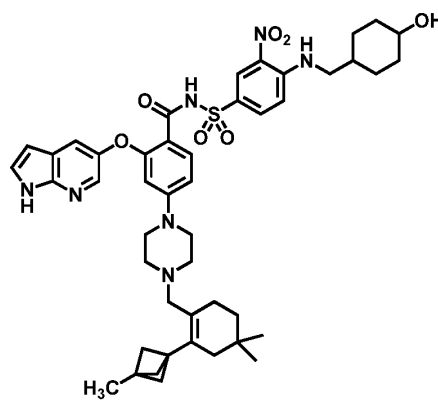
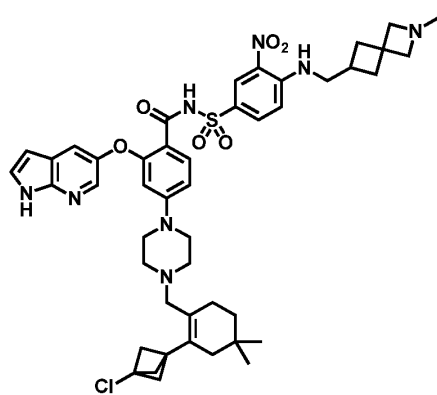
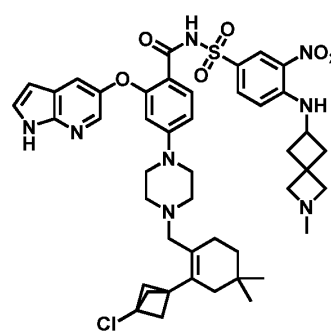
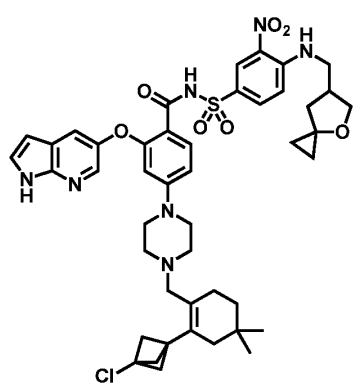
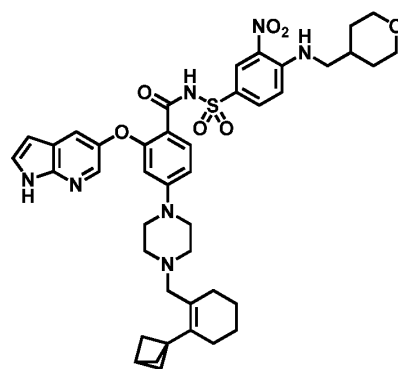
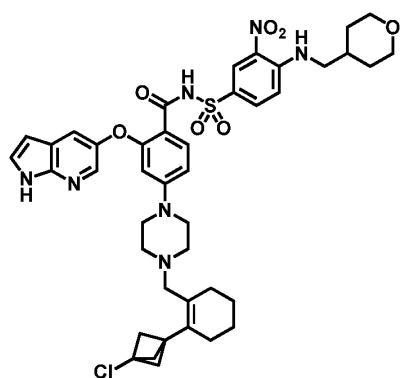
[0103] Examples of Compound (A) include the following:

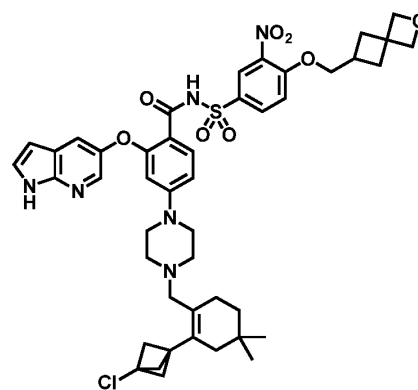
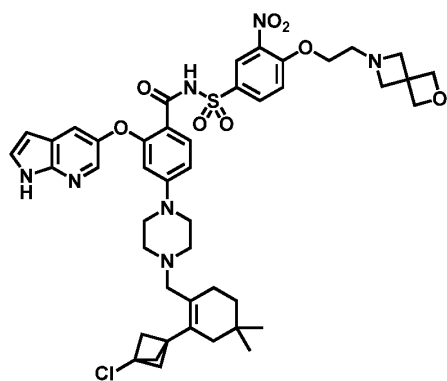
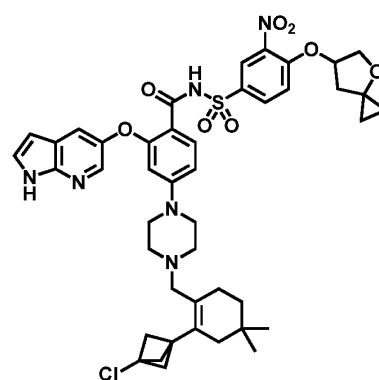
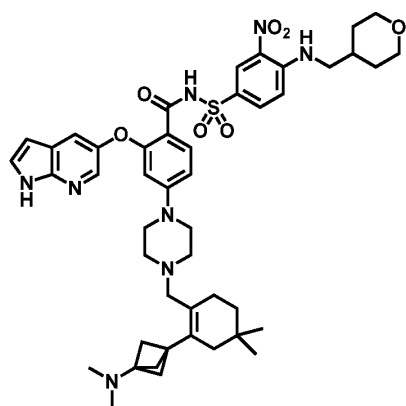
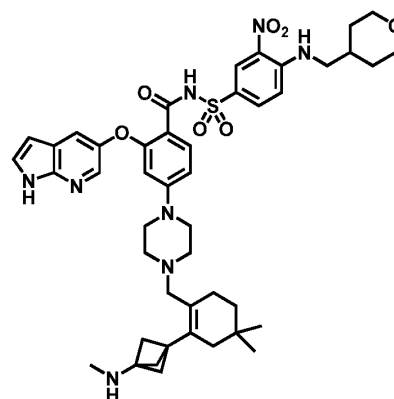
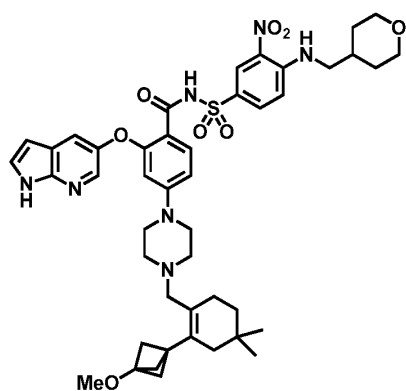


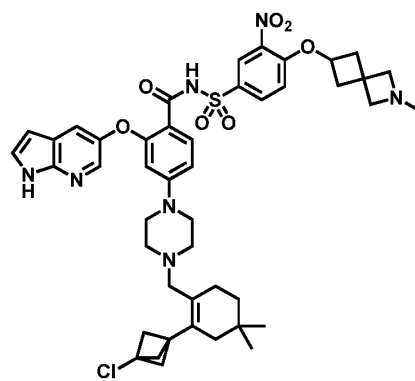
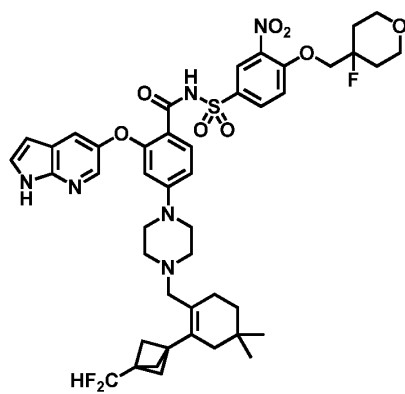
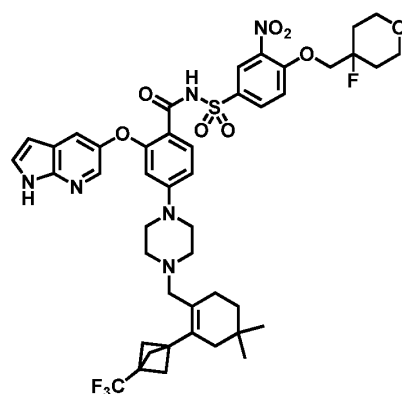
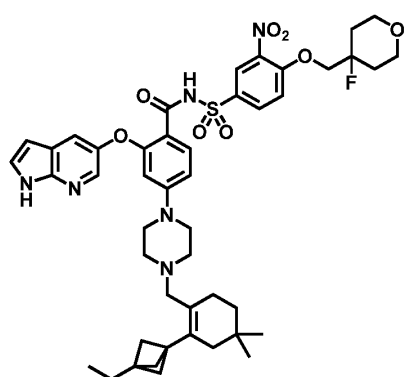
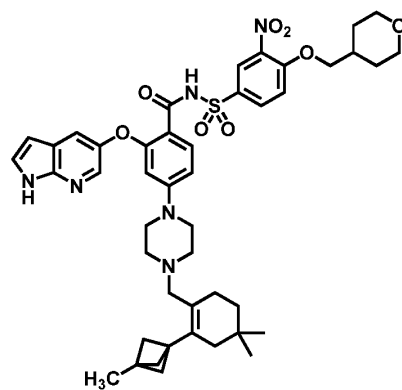
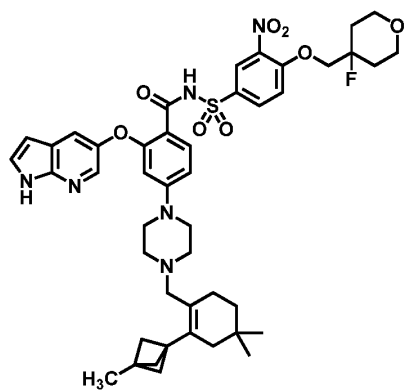


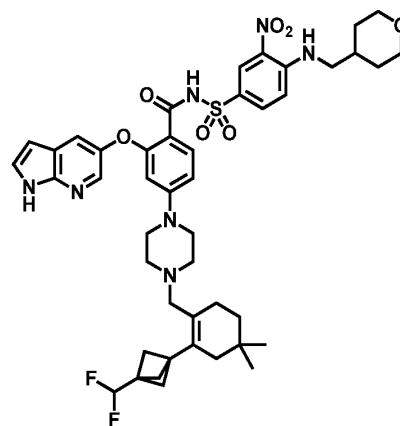
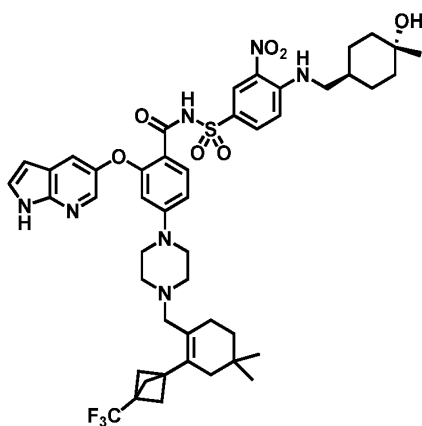
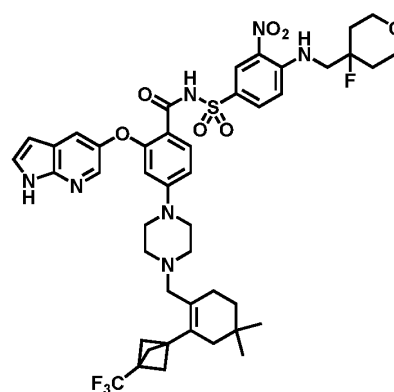
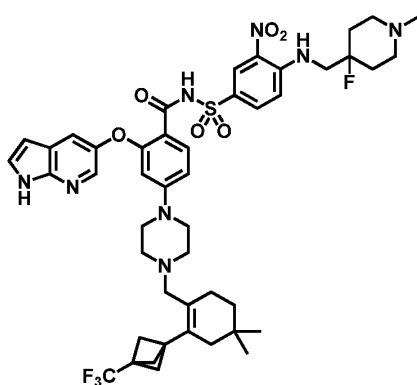
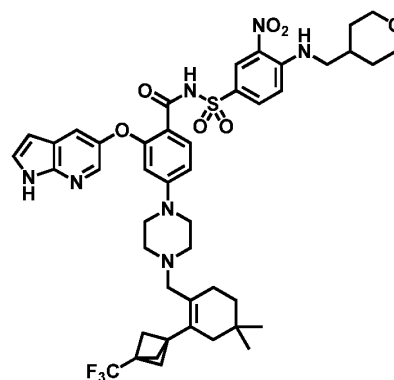
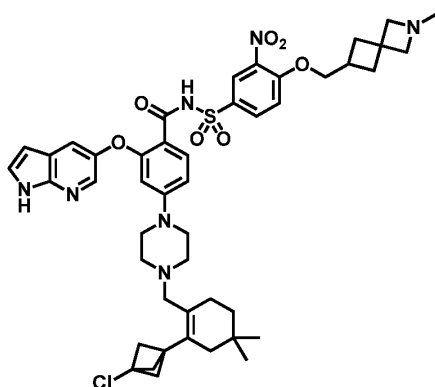


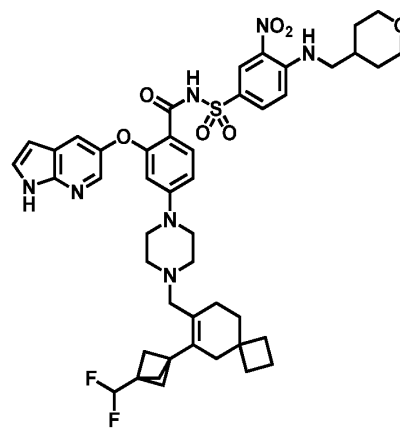
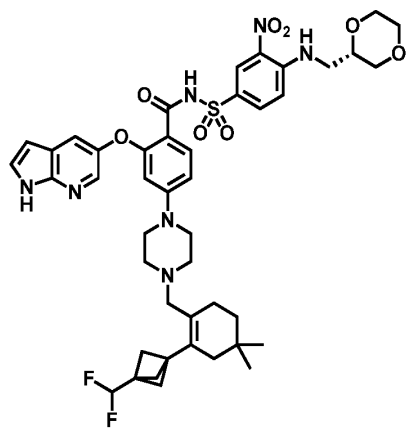
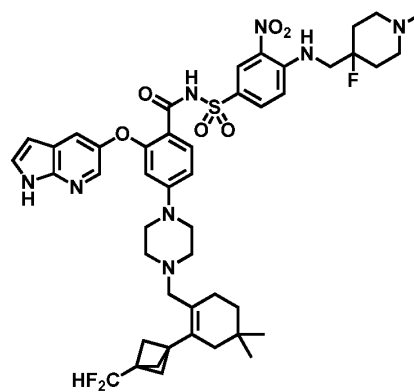
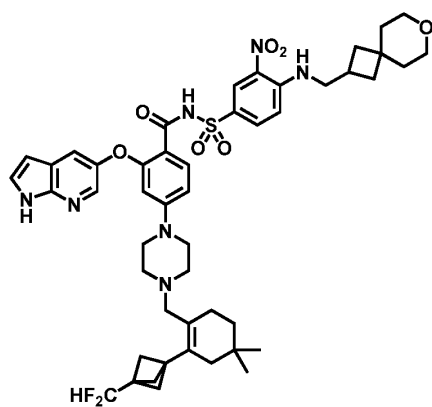
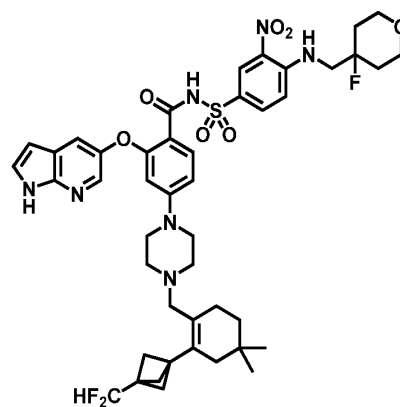
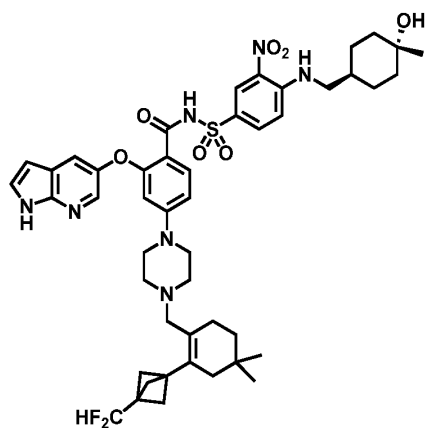


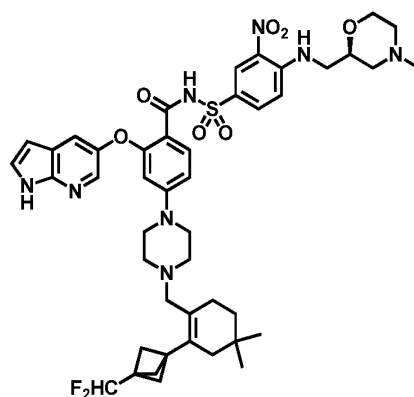
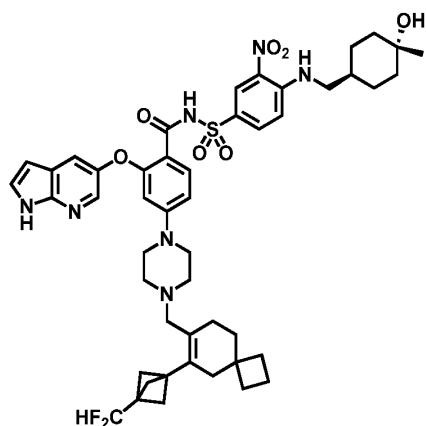












pharmaceutically acceptable salt of any of the foregoing.

[0104] Compound (A), along with pharmaceutically acceptable salts thereof, can be prepared as described herein and in WO 2019/139902, WO 2019/139900, WO 2019/139907 and WO 2019/139899, which are each hereby incorporated by reference in their entireties. As described in WO 2019/139902, WO 2019/139900, WO 2019/139907 and WO 2019/139899, Compound (A) is a Bcl-2 inhibitor.

Definitions for Compound (B), and pharmaceutically acceptable salts thereof

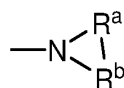
[0105] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety 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.

[0106] 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, hydroxyalkyl, haloalkoxy, an amino, a mono-substituted amine group, a di-substituted amine group and an amine(C₁-C₆ alkyl).

[0107] 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.

[0108] 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:



[0109] 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.

[0110] 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.

[0111] 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.

[0112] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term “fused” refers to two rings which have two atoms and one bond in common. As used herein, the term “bridged cycloalkyl” refers to compounds wherein the cycloalkyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term “spiro” refers to two rings which have one atom in common and the two rings are not linked by a bridge. Cycloalkyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Examples of mono-cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Examples of fused cycloalkyl groups are decahydronaphthalenyl, dodecahydro-1H-phenalenyl and tetradecahydroanthracenyl; examples of bridged cycloalkyl groups are bicyclo[1.1.1]pentyl, adamantanyl and norbornanyl; and examples of spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane.

[0113] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0114] As used herein, “carbocyclyl” refers to a non-aromatic a mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion, as described herein. Carbocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A carbocyclyl group may be unsubstituted

or substituted. Examples of carbocyclyl groups include, but are in no way limited to, cycloalkyl groups and cycloalkenyl groups, as defined herein, and the non-aromatic portions of 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1H-indene, 5,6,7,8-tetrahydroquinoline and 6,7-dihydro-5H-cyclopenta[b]pyridine.

[0115] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic 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.

[0116] As used herein, “heteroaryl” refers to a monocyclic or polycyclic 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.

[0117] 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, dihydrouacil, 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.

[0118] 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.

[0119] 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.

[0120] 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).

[0121] As used herein, “lower alkylene groups” are straight-chained $-\text{CH}_2-$ tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$) and butylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$). 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 cycloalkyl group (e.g., ).

[0122] As used herein, the term “hydroxy” refers to a $-\text{OH}$ group.

[0123] As used herein, “alkoxy” refers to the Formula $-\text{OR}$ wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (iso-propoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0124] 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.

[0125] A “cyano” group refers to a “-CN” group.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] A “nitro” group refers to an “ -NO_2 ” group.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] The term “amino” as used herein refers to a -NH_2 group.

[0145] A “mono-substituted amine” group refers to a “ -NHR_A ” group in which R_A can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. The R_A may be substituted or unsubstituted. Examples of mono-substituted amino groups include, but are not limited to, -NH(methyl) , -NH(phenyl) and the like.

[0146] 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. Examples of di-substituted amino groups include, but are not limited to, -N(methyl)_2 , $\text{-N(phenyl)(methyl)}$, -N(ethyl)(methyl) and the like.

[0147] As used herein, “amine(alkyl)” group refers to an $\text{-(alkylene)-NR'R''}$ radical where R' and R'' are independently hydrogen or alkyl as defined herein. An amine(alkyl) may be substituted or unsubstituted. Examples of amine(alkyl) groups include, but are not limited to, $\text{-CH}_2\text{NH(methyl)}$, $\text{-CH}_2\text{NH(phenyl)}$, $\text{-CH}_2\text{CH}_2\text{NH(methyl)}$, $\text{-CH}_2\text{CH}_2\text{NH(phenyl)}$, $\text{-CH}_2\text{N(methyl)}_2$, $\text{-CH}_2\text{N(phenyl)(methyl)}$, $\text{-NCH}_2\text{(ethyl)(methyl)}$, $\text{-CH}_2\text{CH}_2\text{N(methyl)}_2$, $\text{-CH}_2\text{CH}_2\text{N(phenyl)(methyl)}$, $\text{-NCH}_2\text{CH}_2\text{(ethyl)(methyl)}$ and the like.

[0148] 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, “ $\text{C}_1\text{-C}_3$ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0149] 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.”

[0150] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, trifluoroacetic, benzoic, salicylic, 2-oxopentanedioic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine and salts with amino acids such as arginine and lysine. 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⁻).

[0151] 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.

[0152] 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).

[0153] 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.

[0154] 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.

[0155] 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.

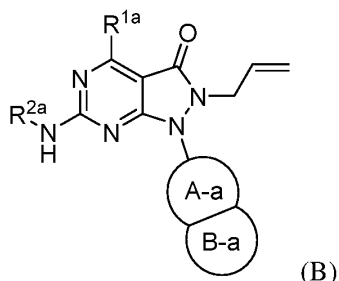
[0156] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term ‘including’ should be read to mean ‘including, without limitation,’ ‘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.

[0157] 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.

Compound (B)

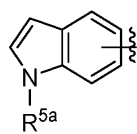
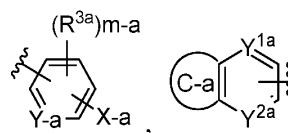
[0158] As described herein, some embodiments disclosed herein relate to the use of a combination of compounds for treating a disease or condition, wherein the combination can include an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof (as

described herein), and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, wherein: the Compound (B) has the structure:



wherein: R^{1a} can be selected from hydrogen, halogen and a substituted or unsubstituted C_1 - C_6 alkyl; Ring A-a can be selected from a substituted or unsubstituted phenyl and a substituted or unsubstituted 5-6 membered monocyclic heteroaryl; Ring B-a can be selected from a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl and a substituted or unsubstituted 5-7

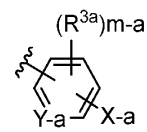
membered monocyclic heterocyclyl; R^{2a} can be selected from



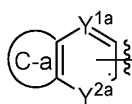
; m -a can be 0, 1, 2 or 3; R^{3a} can be selected from halogen and a substituted or unsubstituted C_1 - C_6 alkyl; X-a can be selected from hydrogen, halogen, hydroxy, cyano, a substituted or unsubstituted 4-6 membered monocyclic heterocyclyl, a substituted or unsubstituted amine(C_1 - C_6 alkyl), a substituted or unsubstituted $-NH-(CH_2)_{1-6}$ -amine, a mono-substituted amine, a di-substituted amine, an amino, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 alkoxy, a substituted or unsubstituted C_3 - C_6 cycloalkoxy, a substituted or unsubstituted (C_1 - C_6 alkyl)acyl, a substituted or unsubstituted C-amido, a substituted or unsubstituted N-amido, a substituted or unsubstituted C-carboxy, a substituted or unsubstituted O-carboxy, a substituted or unsubstituted O-carbamyl and a substituted or unsubstituted N-carbamyl; Y-a can be CH or N; Y^{1a} can be CR^{4A-a} or N; Y^{2a} can be CR^{4B-a} or N; Ring C-a can be selected from a substituted or unsubstituted C_6 - C_{10} aryl, a substituted or unsubstituted monocyclic 5-10 membered heteroaryl, a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl, a substituted or unsubstituted 5-7 membered monocyclic heterocyclyl and a substituted or unsubstituted 7-10 membered bicyclic heterocyclyl; R^{4A-a} and

R^{4B-a} can be independently selected from hydrogen, halogen and an unsubstituted C_{1-4} alkyl; and R^{5-a} can be a substituted or unsubstituted 5-7 membered monocyclic heterocyclyl.

[0159] In some embodiments, R^{1a} can be selected from hydrogen, halogen and a substituted or unsubstituted C_1-C_6 alkyl. In some embodiments, Ring A-a can be selected from a substituted or unsubstituted phenyl and a substituted or unsubstituted 5-6 membered monocyclic heteroaryl. In some embodiments, Ring B-a can be selected from a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl and a substituted or unsubstituted 5-7 membered



monocyclic heterocyclyl. In some embodiments, R^{2a} can be selected from



. In some embodiments, $m-a$ can be 0, 1, 2 or 3. In some embodiments, R^{3a} can be selected from halogen and a substituted or unsubstituted C_1-C_6 alkyl. In some embodiments, $X-a$ can be selected from hydrogen, halogen, hydroxy, cyano, a substituted or unsubstituted 4-6 membered monocyclic heterocyclyl, a substituted or unsubstituted amine(C_1-C_6 alkyl), a substituted or unsubstituted $-NH-(CH_2)_{1-6}$ -amine, a mono-substituted amine, a di-substituted amine, an amino, a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_1-C_6 alkoxy, a substituted or unsubstituted C_3-C_6 cycloalkoxy, a substituted or unsubstituted (C_1-C_6 alkyl)acyl, a substituted or unsubstituted C-amido, a substituted or unsubstituted N-amido, a substituted or unsubstituted C-carboxy, a substituted or unsubstituted O-carboxy, a substituted or unsubstituted O-carbamyl and a substituted or unsubstituted N-carbamyl. In some embodiments, $Y-a$ can be CH or N. In some embodiments, Y^{1-a} can be CR^{4A-a} or N. In some embodiments, Y^{2-a} can be CR^{4B-a} or N. In some embodiments, Ring C-a can be selected from a substituted or unsubstituted C_6-C_{10} aryl, a substituted or unsubstituted monocyclic 5-10 membered heteroaryl, a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl, a substituted or unsubstituted 5-7 membered monocyclic heterocyclyl and a substituted or unsubstituted 7-10 membered bicyclic heterocyclyl. In some embodiments, R^{4A-a} and R^{4B-a} are independently selected from hydrogen, halogen and an unsubstituted C_{1-4} alkyl.

[0160] In some embodiments, R^{1a} can be selected from hydrogen, halogen and C_1-C_6 alkyl. In some embodiments, R^{1a} can be hydrogen. In other embodiments, R^{1a} can be halogen.

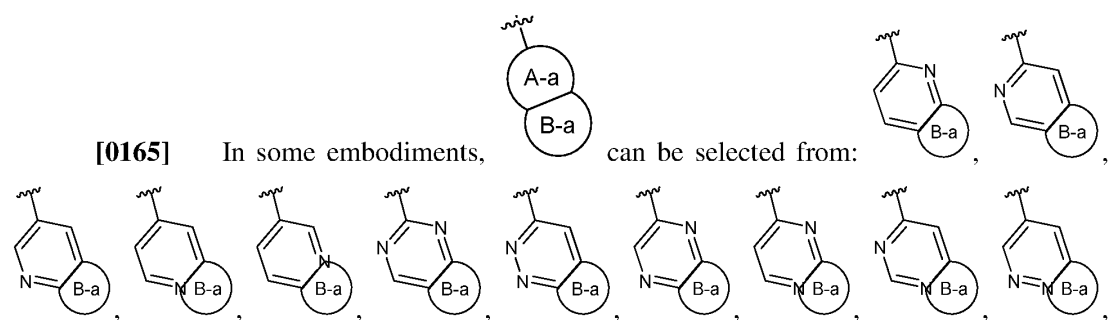
In some embodiments, R^{1a} can be fluoro. In still other embodiments, R^{1a} can be an unsubstituted C_1 - C_6 alkyl (such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl (straight chain or branched) or hexyl (straight chain or branched)). In some embodiments, R^{1a} can be an unsubstituted methyl. In some embodiments, R^{1a} can be a substituted C_1 - C_6 alkyl, such as those described herein. In some embodiments, R^{1a} can be an unsubstituted C_1 - C_6 haloalkyl (such as a C_1 - C_6 fluoroalkyl, a C_1 - C_6 chloroalkyl or a C_1 - C_6 chlorofluoroalkyl). In some embodiments, R^{1a} can be $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$ or $-\text{CH}_2\text{CF}_3$.

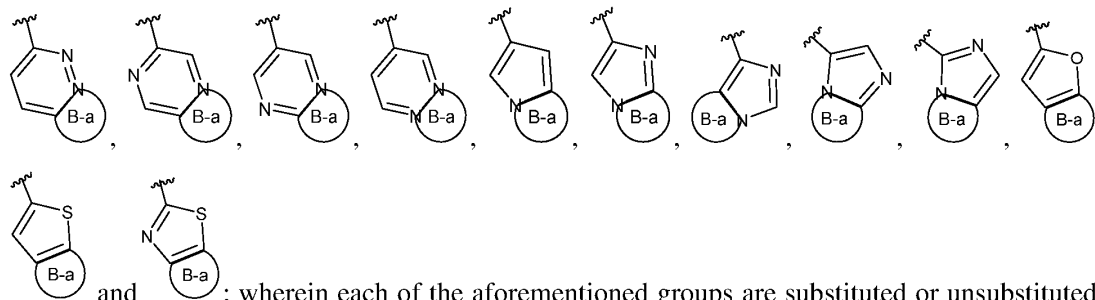
[0161] In some embodiments, Ring A-a can be selected from a substituted or unsubstituted phenyl and a substituted or unsubstituted 5-6 membered monocyclic heteroaryl.

[0162] In some embodiments, Ring A-a can be a substituted phenyl. In other embodiments, Ring A can be an unsubstituted phenyl.

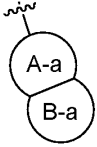
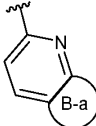
[0163] In some embodiments, Ring A-a can be a substituted 5-6 membered monocyclic heteroaryl. In some embodiments, Ring A-a can be an unsubstituted 5-6 membered monocyclic heteroaryl. In some embodiments, Ring A-a can be selected from a substituted or unsubstituted pyrrole, a substituted or unsubstituted furan, a substituted or unsubstituted thiophene, a substituted or unsubstituted imidazole, a substituted or unsubstituted pyrazole, a substituted or unsubstituted oxazole, a substituted or unsubstituted thiazole, a substituted or unsubstituted pyridine, a substituted or unsubstituted pyrazine, a substituted or unsubstituted pyrimidine and a substituted or unsubstituted pyridazine.

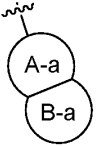
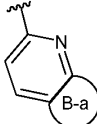
[0164] When substituted, Ring A-a can be substituted with one or more substituents selected from halogen, an unsubstituted C_1 - C_4 haloalkyl and an unsubstituted C_1 - C_4 alkyl. In some embodiments, Ring A-a is mono-substituted with a halogen (for example, fluoro).

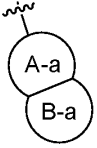


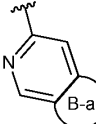
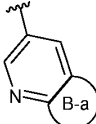


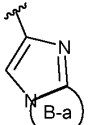
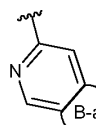
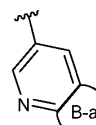
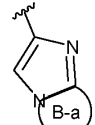
; wherein each of the aforementioned groups are substituted or unsubstituted.

In some embodiments,  can be a substituted or unsubstituted . In some

embodiments,  can be a substituted or unsubstituted , wherein the Ring A-a is

unsubstituted. In other embodiments,  can be selected from a substituted or

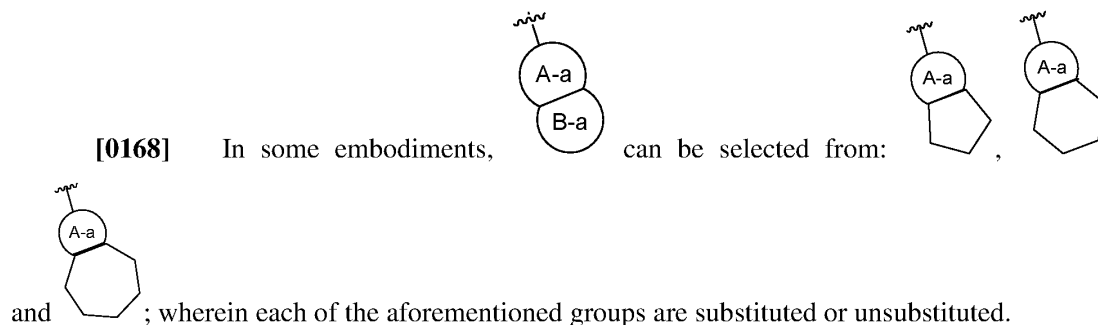
unsubstituted , a substituted or unsubstituted  and a substituted or unsubstituted

. As described herein, the Ring A-a portion of , a  and  can be unsubstituted.

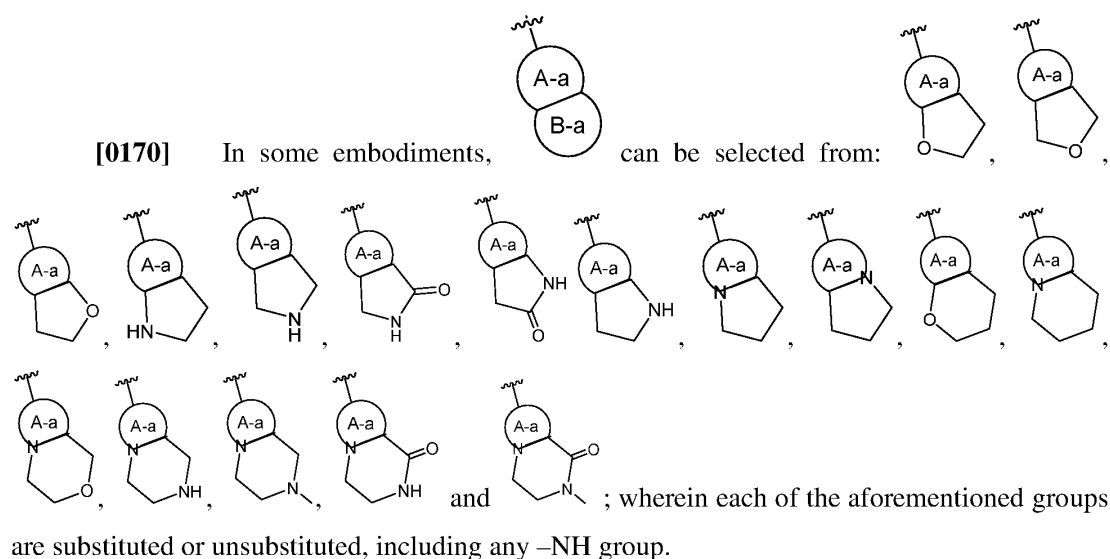
[0166] In some embodiments, Ring B-a can be selected from a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl and a substituted or unsubstituted 5-7 membered monocyclic heterocyclyl.

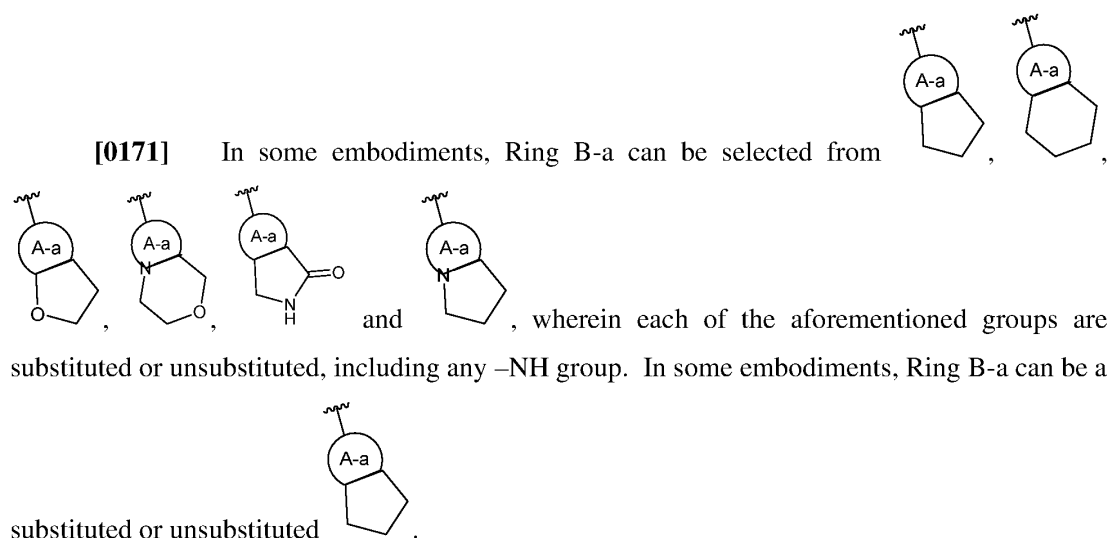
[0167] In some embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl. In some embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 5 membered carbocyclyl. In other embodiments, Ring B-a can be a

substituted or unsubstituted monocyclic 6 membered carbocyclyl. In still other embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 7 membered carbocyclyl.

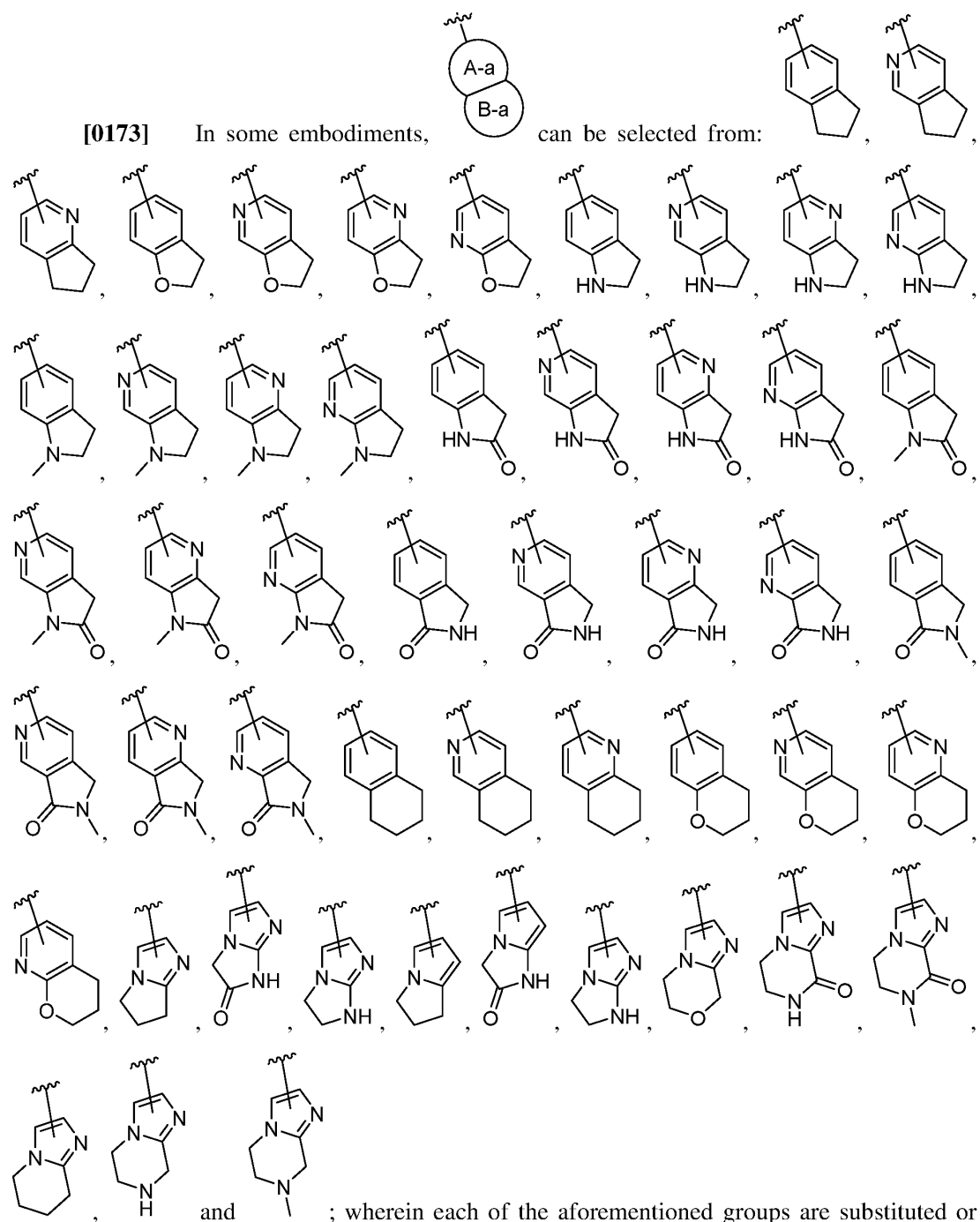


[0169] In some embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 5-7 membered heterocyclyl. In some embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 5 membered heterocyclyl. In other embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 6 membered heterocyclyl. In still other embodiments, Ring B-a can be a substituted or unsubstituted monocyclic 7 membered heterocyclyl.

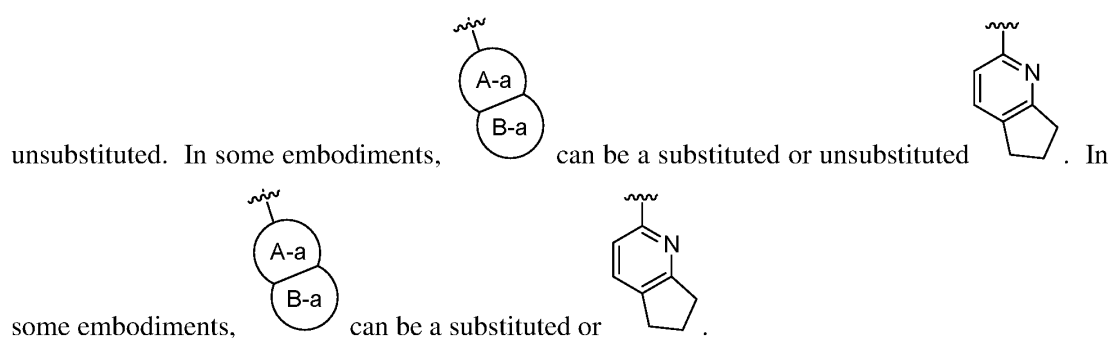
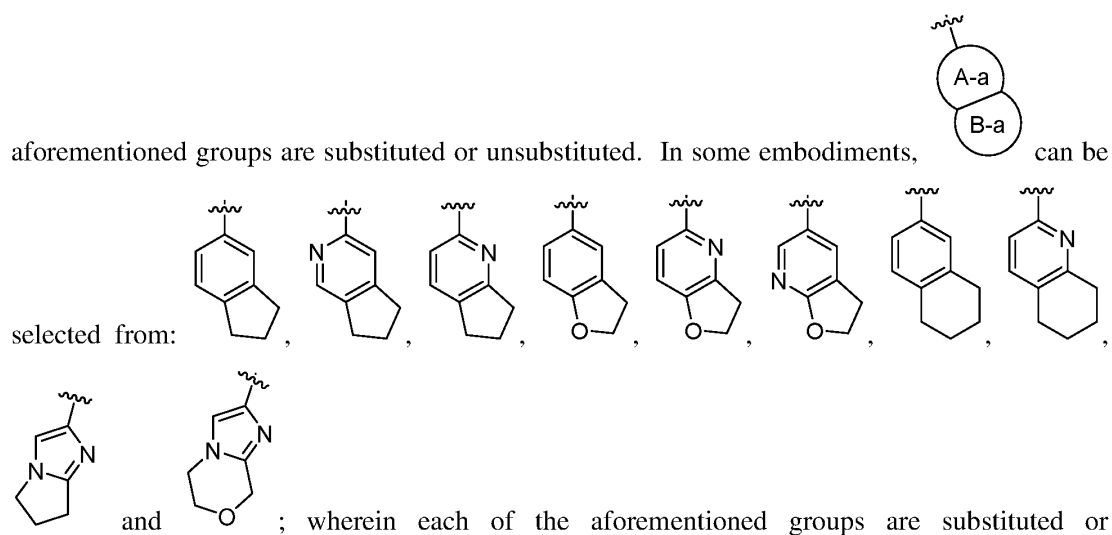
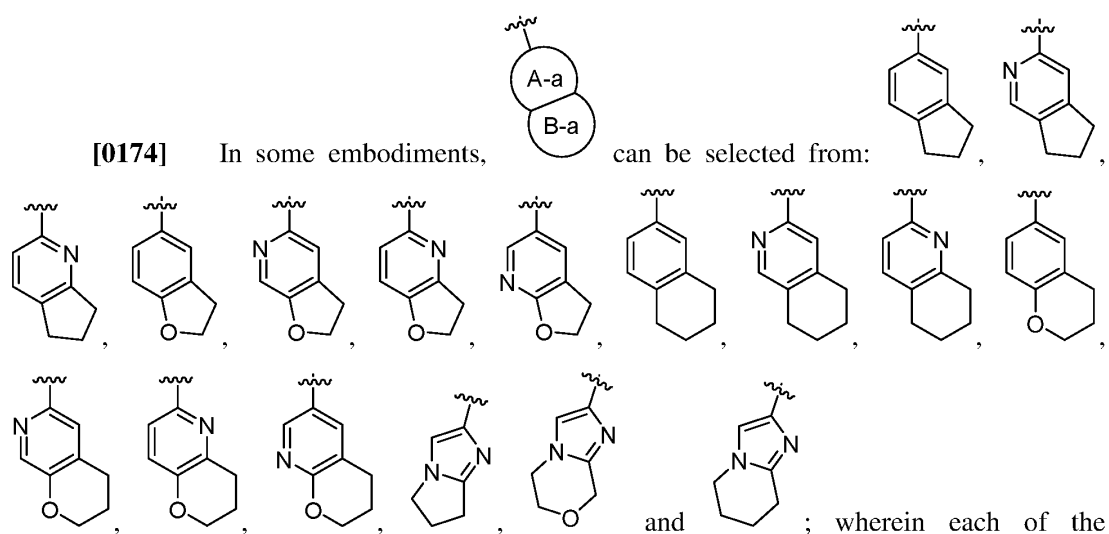




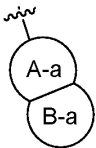
[0172] In some embodiments, when Ring B-a is substituted, Ring B-a can be substituted with 1, 2 or 3 substituents independently selected from halogen, hydroxy, amino, an unsubstituted N-linked amido (for example, –NHC(O)C₁-C₆ alkyl), an unsubstituted C₁-C₆ haloalkyl (such as those described herein) and a substituted or unsubstituted C₁-C₆ alkyl (such as those described herein). In some embodiments, when Ring B-a is substituted, Ring B-a can be substituted with 1, 2 or 3 substituents independently selected from halogen, hydroxy, amino, an unsubstituted N-linked amido (for example, –NHC(O)C₁-C₆ alkyl) and a substituted or unsubstituted C₁-C₆ alkyl (such as those described herein). In some embodiments, Ring B-a can be substituted with 1, 2 or 3 substituents independently selected from fluoro, hydroxy, amino, an unsubstituted –NHC(O)C₁-C₆ alkyl, an unsubstituted C₁-C₆ haloalkyl (such as those described herein) and an unsubstituted C₁-C₆ alkyl (such as those described herein). In some embodiments, Ring B-a can be substituted with 1 or 2 substituents independently selected from fluoro, hydroxy, –CF₃, –CHF₂, –CF₂CH₃, an unsubstituted methyl, an unsubstituted ethyl and –NHC(O)CH₃.

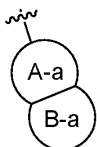


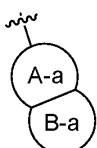
; wherein each of the aforementioned groups are substituted or unsubstituted, including any -NH group.

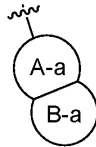


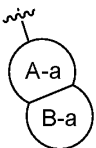
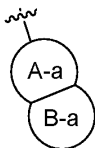
[0175] Both Ring A-a and Ring B-a can be substituted or unsubstituted. In some

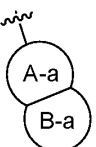
embodiments, Ring A-a and Ring B-a of  can be independently substituted or

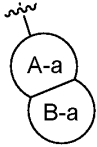
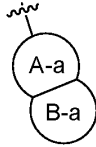
unsubstituted. In some embodiments, Ring A-a and Ring B-a of  can be both

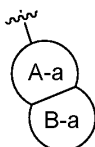
unsubstituted. In some embodiments, Ring A-a and Ring B-a of  can be both

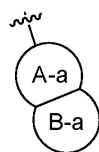
independently substituted. In some embodiments, Ring A-a of  can be substituted and

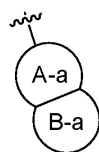
Ring B of  can be unsubstituted. In some embodiments, Ring A-a of  can be

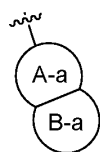
unsubstituted and Ring B-a of  can be substituted. In some embodiments, Ring A of

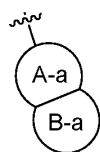
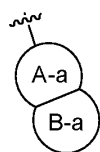
 can be unsubstituted and Ring B-a of  can be substituted with 1, 2 or 3 substituents independently selected from halogen, hydroxy and a substituted or unsubstituted C₁-

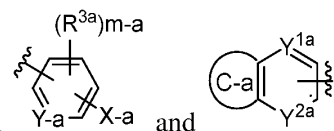
C₆ alkyl (such as those described herein). In some embodiments, Ring A-a of  can be

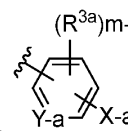
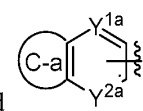


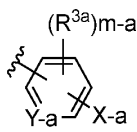
unsubstituted and Ring B-a of  can be substituted with 1, 2 or 3 substituents independently selected from fluoro, hydroxy, amino, an unsubstituted N-linked amido (for example, $-\text{NHC(O)C}_1\text{-C}_6$ alkyl), an unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl (such as those described herein) and an unsubstituted $\text{C}_1\text{-C}_6$ alkyl (such as those described herein). In some embodiments,

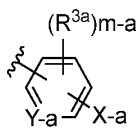
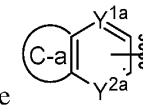


Ring A-a of  can be unsubstituted and Ring B-a of  can be substituted with 1 or 2 substituents independently selected from fluoro, hydroxy, amino, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CF}_2\text{CH}_3$, an unsubstituted methyl, an unsubstituted ethyl and $-\text{NHC(O)CH}_3$.



[0176] In some embodiments, R^{2a} can be selected from  and .



In some embodiments, R^{2a} can be . In some embodiments, R^{2a} can be .

[0177] In some embodiments, Y-a can be CH or N (nitrogen). In some embodiments, Y-a can be CH. In some embodiments, Y-a can be N (nitrogen).

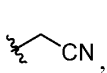
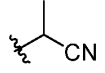
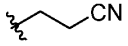
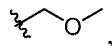
[0178] In some embodiments, R^{3a} can be selected from halogen and a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl (such as those described herein). In some embodiments, R^{3a} can be halogen. In some embodiments, R^{3a} can be a substituted $\text{C}_1\text{-C}_6$ alkyl (such as those described herein). In some embodiments, R^{3a} can be an unsubstituted $\text{C}_1\text{-C}_6$ alkyl (such as those described herein).

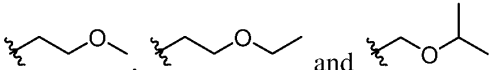
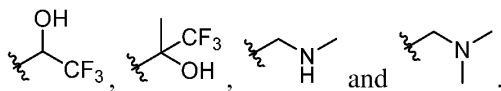
[0179] In some embodiments, m-a can be 0, 1, 2 or 3. In some embodiments, m-a can be 0. In some embodiments, m-a can be 1. In some embodiments, m-a can be 2. In some embodiments, m-a can be 3. When m-a is 2 or 3, the R^{3a} groups can be the same or different from each other.

[0180] In some embodiments, X-a can be selected from hydrogen, halogen, hydroxy, cyano, a substituted or unsubstituted 4-6 membered monocyclic heterocyclyl, a substituted or unsubstituted amine(C₁-C₆ alkyl), a substituted or unsubstituted –NH-(CH₂)₁₋₆-amine, a mono-substituted amine, a di-substituted amine, an amino, a substituted or unsubstituted C₁-C₆ alkyl (such as those described herein), a substituted or unsubstituted C₁-C₆ alkoxy (such as methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy, pentoxy (straight chain or branched) or hexoxy (straight chain or branched)), a substituted or unsubstituted C₃-C₆ cycloalkoxy (such as cyclopropoxy, cyclobutoxy, cyclopentoxo or cyclohexoxy), a substituted or unsubstituted (C₁-C₆ alkyl)acyl, a substituted or unsubstituted C-amido, a substituted or unsubstituted N-amido, a substituted or unsubstituted C-carboxy, a substituted or unsubstituted O-carboxy, a substituted or unsubstituted O-carbamyl and a substituted or unsubstituted N-carbamyl.

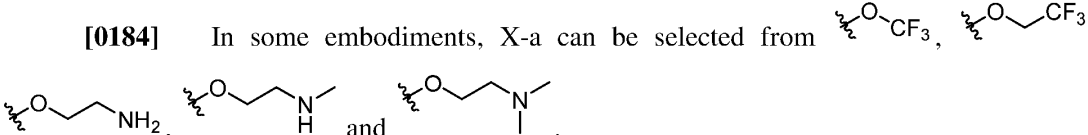
[0181] In some embodiments, X-a can be hydrogen. In other embodiments, X-a can be halogen. In some embodiments, X-a can be fluoro. In some embodiments, X-a can be chloro. In still other embodiments, X-a can be hydroxy. In yet still other embodiments, X-a can be cyano. In some embodiments, X-a can be an amino.

[0182] In some embodiments, X-a can be an unsubstituted C₁-C₆ alkyl (such as those described herein). In some embodiments, X-a can be an unsubstituted methyl, an unsubstituted ethyl or an unsubstituted iso-propyl. In some embodiments, X-a can be a substituted C₁-C₆ alkyl (such as those described herein). In some embodiments, X-a can be an unsubstituted C₁-C₆ haloalkyl (such as a C₁-C₆ fluoroalkyl, a C₁-C₆ chloroalkyl or a C₁-C₆ chlorofluoroalkyl). In some embodiments, X-a can be selected from –CHF₂, –CF₃, –CF₂CH₃ and –CH₂CF₃. In some embodiments, X-a can be an unsubstituted C₁-C₆ hydroxyalkyl (such as a C₁-C₆ mono-hydroxyalkyl or a C₁-C₆ di-hydroxyalkyl). In some embodiments, X-a can be selected from –CH₂OH, –CH₂CH₂OH, –CH(OH)CH₃ and –C(OH)(CH₃)₂. In some embodiments, X-a can be an unsubstituted C₁-C₆ cyanoalkyl (such as a C₁-C₆ mono-cyanoalkyl or a C₁-C₆ di-cyanoalkyl). In

some embodiments, X-a can be selected from ,  and . In some embodiments, X-a can be an unsubstituted C₁-C₆ alkoxyalkyl (such as a C₁-C₆ mono-alkoxyalkyl or a C₁-C₆ di-alkoxyalkyl). In some embodiments, X-a can be selected from .

. In some embodiments, X-a can be a substituted C₁-C₆ alkyl selected from .

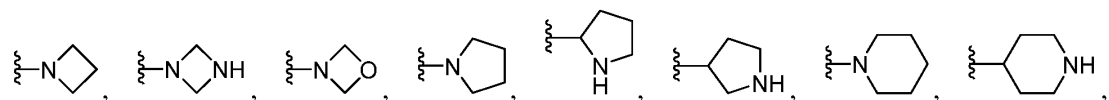
[0183] In some embodiments, X-a can be an unsubstituted C₁-C₆ alkoxy (such as those described herein). In some embodiments, X-a can be an unsubstituted methoxy, an unsubstituted ethoxy or an unsubstituted iso-propoxy. In some embodiments, X-a can be a substituted C₁-C₆ alkoxy (such as those described herein). In some embodiments, X-a can be a C₁-C₆ alkoxy substituted with 1, 2 or 3 substituents independently selected from halogen, an amino, a mono-substituted amine (such as those described herein) and a di-substituted amine (such as those described herein). In some embodiments, X-a can be a C₁-C₆ alkoxy substituted with 1 substituent selected from halogen, an amino, a mono-substituted amine (such as those described herein) and a di-substituted amine (such as those described herein).

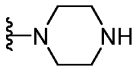
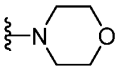
[0184] In some embodiments, X-a can be selected from .

[0185] In some embodiments, X-a can be a substituted C₃-C₆ cycloalkoxy (such as those described herein). In some embodiments, X-a can be an unsubstituted C₃-C₆ cycloalkoxy (such as those described herein).

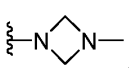
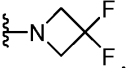
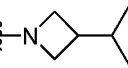
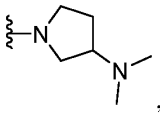
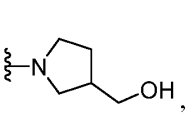
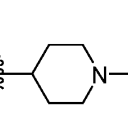
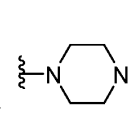
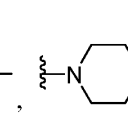
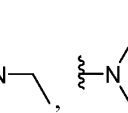
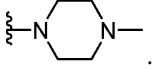
[0186] In some embodiments, X-a can be a substituted (C₁-C₆ alkyl)acyl, such as a substituted -(CO)-CH₃. In some embodiments, X-a can be an unsubstituted (C₁-C₆ alkyl)acyl, such as an unsubstituted -(CO)-CH₃.

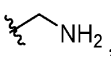
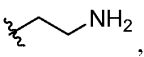
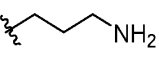
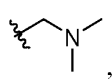
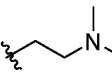
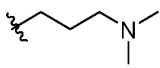
[0187] In some embodiments, X-a can be a substituted 4-6 membered monocyclic heterocyclyl. In some embodiments, X-a can be an unsubstituted 4-6 membered monocyclic heterocyclyl. In some embodiments, X-a can be selected from azetidine, oxetane, diazetidine, azaoxetane, pyrrolidine, tetrahydrofuran, imidazoline, pyrazolidine, piperidine, tetrahydropyran, piperazine, morpholine and dioxane; wherein each of the aforementioned groups are substituted or unsubstituted, including any -NH group. . In some embodiments, X-a can be selected from

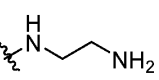
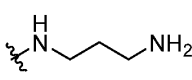
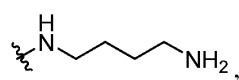
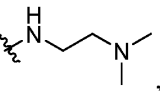
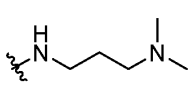
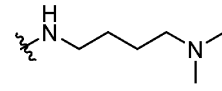


 and ; wherein each of the aforementioned groups are substituted or unsubstituted, including any –NH group.

[0188] In some embodiments, X-a can be a 4-6 membered monocyclic heterocyclyl (such as those described herein) substituted with 1 or 2 substituents independently selected from halogen, a substituted or unsubstituted C₁-C₆ alkyl (such as those described herein), a mono-substituted amine (such as those described herein), a di-substituted amine (such as those described herein), an amino, substituted or unsubstituted amine(C₁-C₆ alkyl) and a substituted or unsubstituted (C₁-C₆ alkyl)acyl. In some embodiments, X-a can be a 4-6 membered monocyclic heterocyclyl substituted with 1 or 2 substituents independently selected from fluoro, an unsubstituted methyl, an unsubstituted ethyl, an unsubstituted iso-propyl, –CH₂OH and –

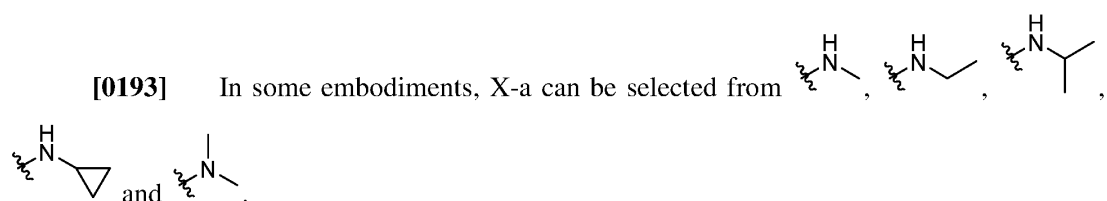
N(CH₃)₂. In some embodiments, X-a can be selected from , , , , , , , ,  and .

[0189] In some embodiments, X-a can be a substituted amine(C₁-C₆ alkyl). In some embodiments, X-a can be an unsubstituted amine(C₁-C₆ alkyl). In some embodiments, X-a can be selected from , , , ,  and ; wherein each of the aforementioned groups are substituted or unsubstituted, including any –NH group. .

[0190] In some embodiments, X-a can be a substituted –NH-(CH₂)₁₋₆-amine. In some embodiments, X-a can be an unsubstituted –NH-(CH₂)₁₋₆-amine. In some embodiments, X-a can be selected from , , , ,  and ; wherein each of the aforementioned groups are substituted or unsubstituted, including any –NH group.

[0191] In some embodiments, X-a can be a mono-substituted amine. In some embodiments, the substituent of the mono-substituted amine is an unsubstituted C₁-C₆ alkyl (such as those as described herein) or an unsubstituted C₃-C₆ cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl).

[0192] In some embodiments, X-a can be a di-substituted amine. In some embodiments, the two substituents of the di-substituted amine are independently selected from an unsubstituted C₁-C₆ alkyl (such as those as described herein) and an unsubstituted C₃-C₆ cycloalkyl (such as those as described herein).



[0194] In some embodiments, X-a can be a substituted or unsubstituted C-amido. In some embodiments, X-a can be a substituted or unsubstituted N-amido. In some embodiments, X-a can be a substituted or unsubstituted C-carboxy. In some embodiments, X-a can be a substituted or unsubstituted O-carboxy. In some embodiments, X-a can be a substituted or unsubstituted O-carbamyl. In some embodiments, X-a can be a substituted or unsubstituted N-carbamyl. In some embodiments, X-a can be mono-substituted with an unsubstituted C₁-C₆ hydroxyalkyl (such as those described herein).

[0195] In some embodiments, Y^{1-a} can be CR^{4A-a} or N (nitrogen). In some embodiments, Y^{1-a} can be CR^{4A-a}. In some embodiments, Y^{1-a} can be N (nitrogen).

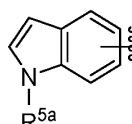
[0196] In some embodiments, Y^{2-a} can be CR^{4B-a} or N (nitrogen). In some embodiments, Y^{2-a} can be CR^{4B-a}. In some embodiments, Y^{2-a} can be N (nitrogen).

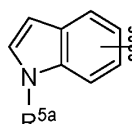
[0197] In some embodiments, Y^{1-a} and Y^{2-a} can each be N (nitrogen). In some embodiments, Y^{1-a} can be CR^{4A-a} and Y^{2-a} can be CR^{4B-a}. In some embodiments, Y^{1-a} can be CR^{4A-a} and Y^{2-a} can be N (nitrogen). In some embodiments, Y^{1-a} can be N (nitrogen) and Y^{2-a} can be CR^{4B-a}.

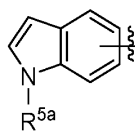
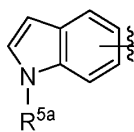
[0198] In some embodiments, R^{4A-a} can be hydrogen. In some embodiments, R^{4A-a} can be halogen. In some embodiments, R^{4A-a} can be an unsubstituted C₁₋₄ alkyl (such as those described herein).

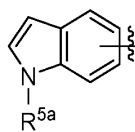
[0199] In some embodiments, R^{4B-a} can be hydrogen. In some embodiments, R^{4B-a} can be halogen. In some embodiments, R^{4B-a} can be an unsubstituted C_{1-4} alkyl (such as those described herein).

[0200] In some embodiments, R^{4A-a} and R^{4B-a} can each be hydrogen. In some embodiments, R^{4A-a} and R^{4B-a} can each be halogen (wherein the halogens can be the same or different from each other). In some embodiments, R^{4A-a} and R^{4B-a} can each be an unsubstituted C_{1-4} alkyl (such as those described herein, and wherein the C_{1-4} alkyls can be the same or different from each other). In some embodiments, one of R^{4A-a} and R^{4B-a} can be hydrogen and the other of R^{4A-a} and R^{4B-a} can be halogen. In some embodiments, one of R^{4A-a} and R^{4B-a} can be hydrogen and the other of R^{4A-a} and R^{4B-a} can be an unsubstituted C_{1-4} alkyl (such as those described herein). In some embodiments, one of R^{4A-a} and R^{4B-a} can be halogen and the other of R^{4A-a} and R^{4B-a} can be an unsubstituted C_{1-4} alkyl (such as those described herein).



[0201] In some embodiments, R^{2a} can be . For example, R^{2a} can be



. When R^{2a} is , in some embodiments, R^{5-a} can be a substituted 5-7 membered monocyclic heterocyclyl. In other embodiments, R^{5-a} can be an unsubstituted 5-7 membered monocyclic heterocyclyl. Examples of R^{5-a} groups include a substituted or unsubstituted piperidinyl, a substituted or unsubstituted pyrrolidinyl and a substituted or unsubstituted azepanyl. When substituted the R^{5-a} group, possible substituents include an unsubstituted C_{1-4} alkyl, halogen, hydroxy and unsubstituted C_{1-4} haloalkyl.

[0202] In some embodiments, Ring C-a can be selected from a substituted or unsubstituted C_6-C_{10} aryl, a substituted or unsubstituted monocyclic 5-10 membered heteroaryl, a substituted or unsubstituted monocyclic 5-7 membered carbocyclyl, a substituted or unsubstituted 5-7 membered monocyclic heterocyclyl and a substituted or unsubstituted 7-10 membered bicyclic heterocyclyl.

[0203] In some embodiments, Ring C-a can be a substituted C_6-C_{10} aryl. In some embodiments, Ring C-a can be an unsubstituted C_6-C_{10} aryl. In some embodiments, Ring C-a can be a substituted C_6 aryl. In some embodiments, Ring C-a can be an unsubstituted C_6 aryl.

[0204] In some embodiments, Ring C-a can be a substituted 5-10 membered heteroaryl. In some embodiments, Ring C-a can be an unsubstituted 5-10 membered heteroaryl. In some embodiments, Ring C-a can be a substituted 5-6 membered heteroaryl. In some embodiments, Ring C-a can be an unsubstituted 5-6 membered heteroaryl. In some embodiments, Ring C-a can be selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, benzimidazole, indole, pyrazole, isoxazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, quinoline, isoquinoline, quinazoline and quinoxaline; wherein each of the aforementioned groups are substituted or unsubstituted, including any –NH group.

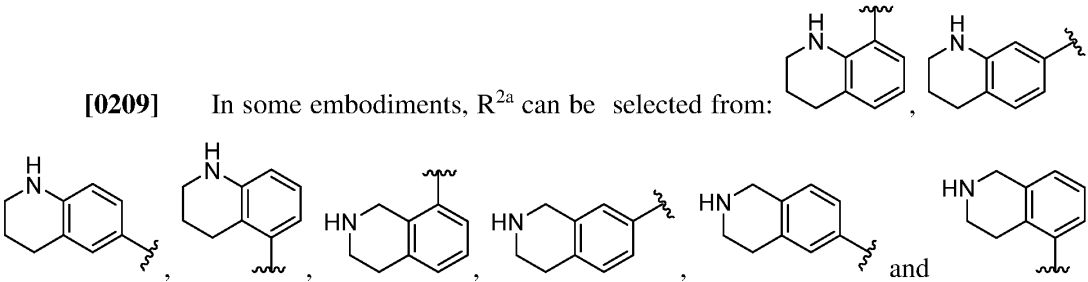
[0205] In some embodiments, Ring C-a can be a substituted or unsubstituted monocyclic 5 membered carbocyclyl. In some embodiments, Ring C-a can be a substituted or unsubstituted monocyclic 6 membered carbocyclyl. In some embodiments, Ring C-a can be a substituted or unsubstituted monocyclic 7 membered carbocyclyl.

[0206] In some embodiments, Ring C-a can be a substituted or unsubstituted 5 membered monocyclic heterocyclyl. In some embodiments, Ring C-a can be a substituted or unsubstituted 6 membered monocyclic heterocyclyl. In some embodiments, Ring C-a can be a substituted or unsubstituted 7 membered monocyclic heterocyclyl. In some embodiments, Ring C can be selected from imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, piperidine, piperazine, pyrrolidine, pyrrolidone, 4-piperidone, pyrazoline, pyrazolidine, tetrahydropyran, azepine, oxepine and diazepine; wherein each of the aforementioned groups are substituted or unsubstituted, including any –NH group.

[0207] In some embodiments, Ring C-a can be a substituted or unsubstituted 7 membered bicyclic heterocyclyl (for example, a fused, a bridged or a spiro heterocyclyl). In some embodiments, Ring C-a can be a substituted or unsubstituted 8 membered bicyclic heterocyclyl, such as, a fused, a bridged or a spiro heterocyclyl. In some embodiments, Ring C-a can be a substituted or unsubstituted 9 membered bicyclic heterocyclyl (for example, a fused, a bridged or a spiro heterocyclyl). In some embodiments, Ring C-a can be a substituted or unsubstituted 10 membered bicyclic heterocyclyl, such as, a fused, a bridged or a spiro heterocyclyl. In some embodiments, Ring C-a can be selected from pyrrolizidine, indoline, 1,2,3,4 tetrahydroquinoline, 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-

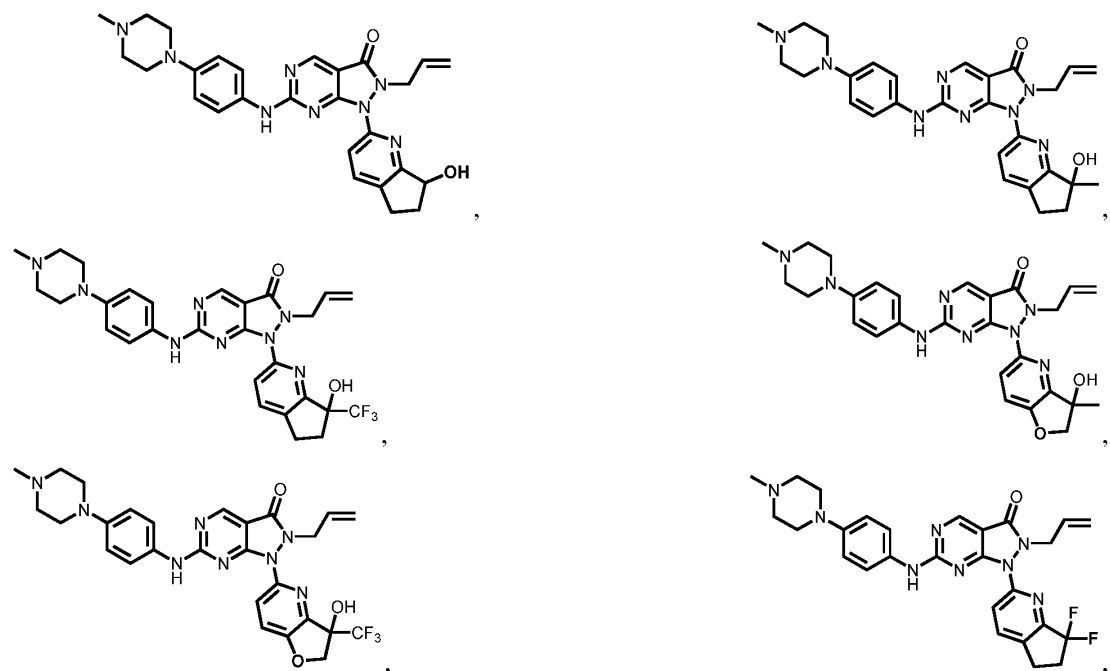
azaspiro[3.4]octane; wherein each of the aforementioned groups are substituted or unsubstituted, including any –NH group.

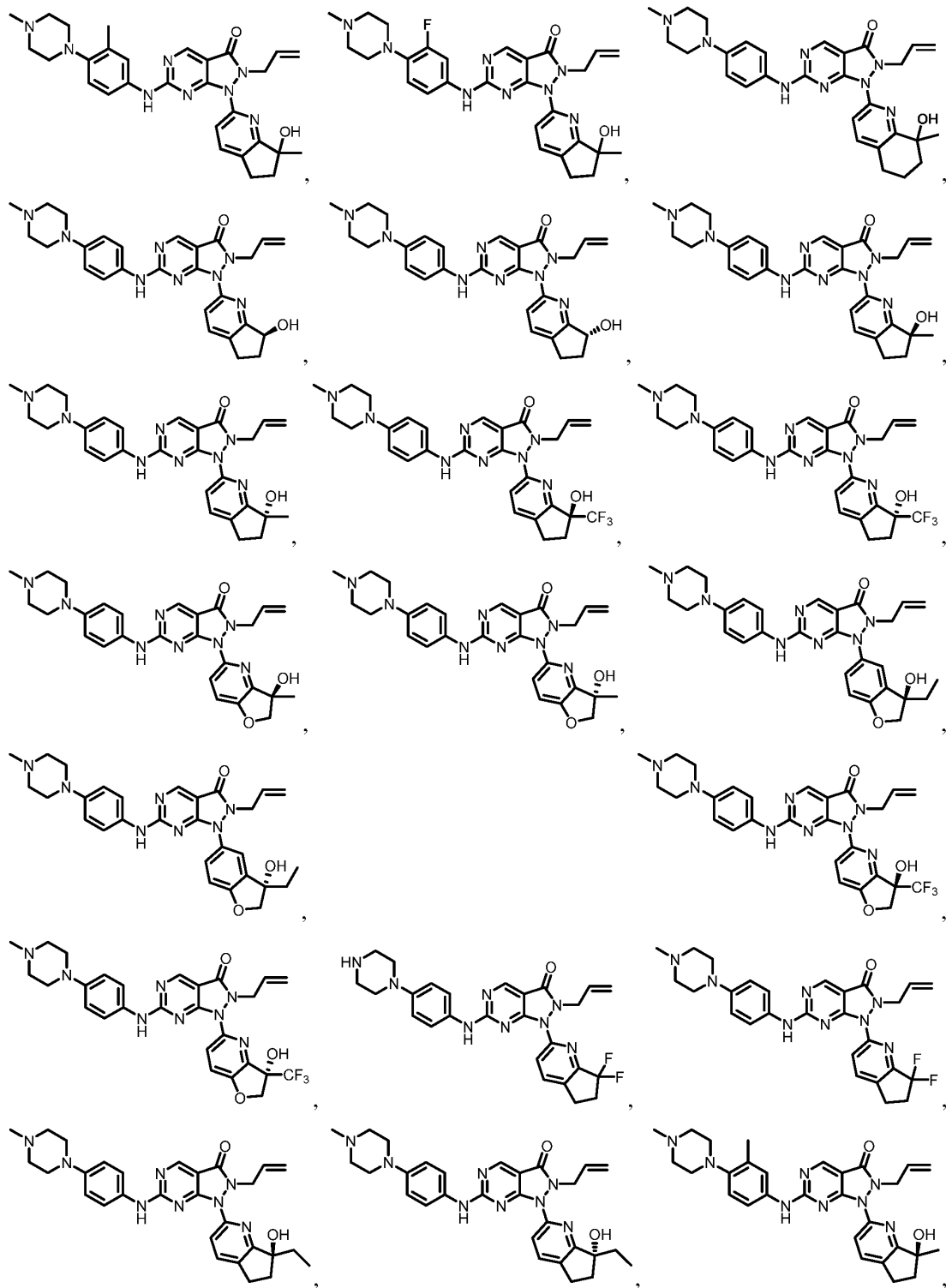
[0208] In some embodiments, Ring C-a can be substituted with one or more substituents independently selected from an unsubstituted C₁-C₆ alkyl (as described herein) and an unsubstituted (C₁-C₆ alkyl)acyl. In some embodiments, Ring C-a can be substituted with one substituent selected from an unsubstituted C₁-C₆ alkyl (as described herein) and an unsubstituted (C₁-C₆ alkyl)acyl.

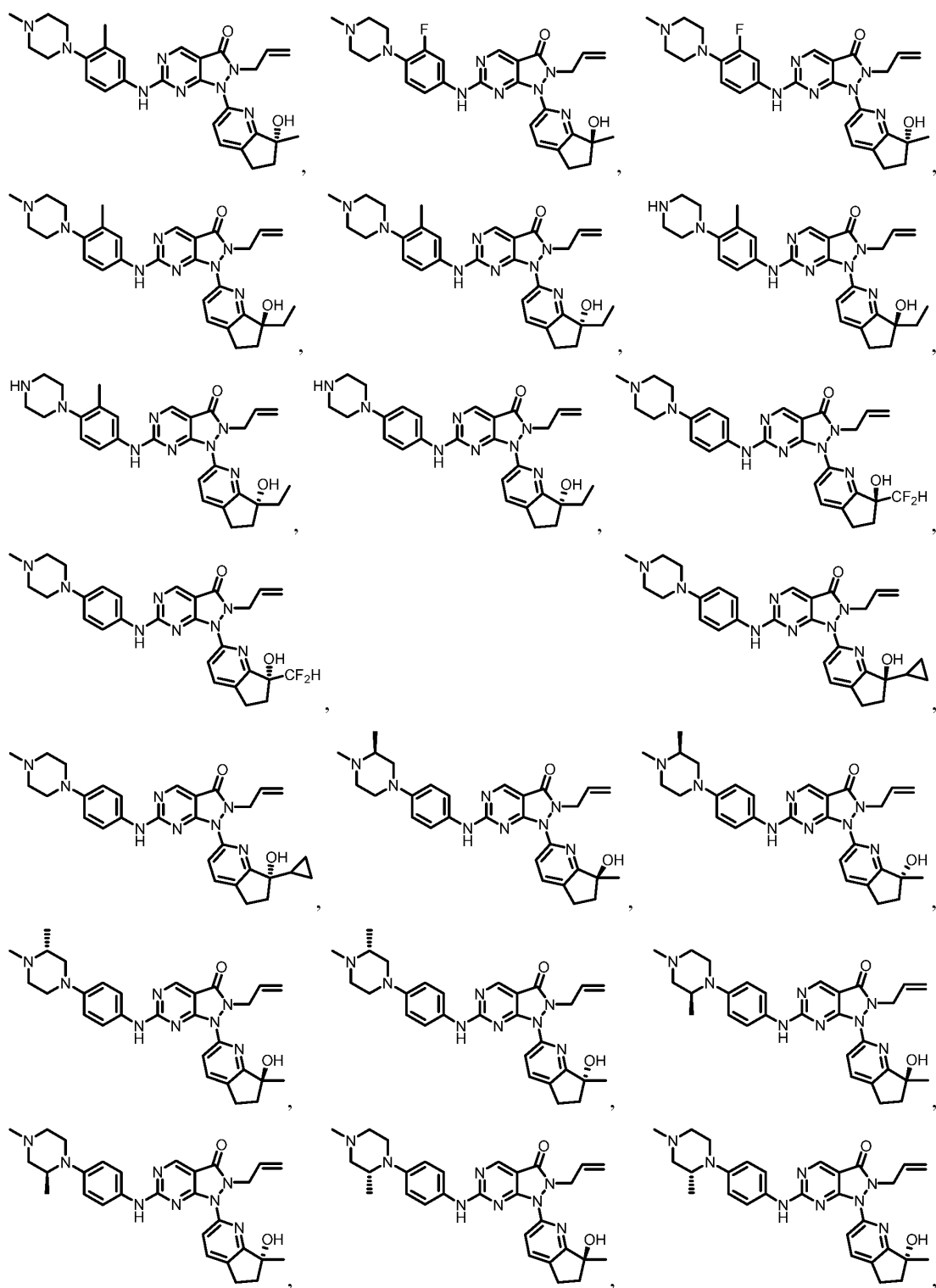
[0209] In some embodiments, R^{2a} can be selected from:  ,
wherein each of the aforementioned groups can be substituted or unsubstituted.

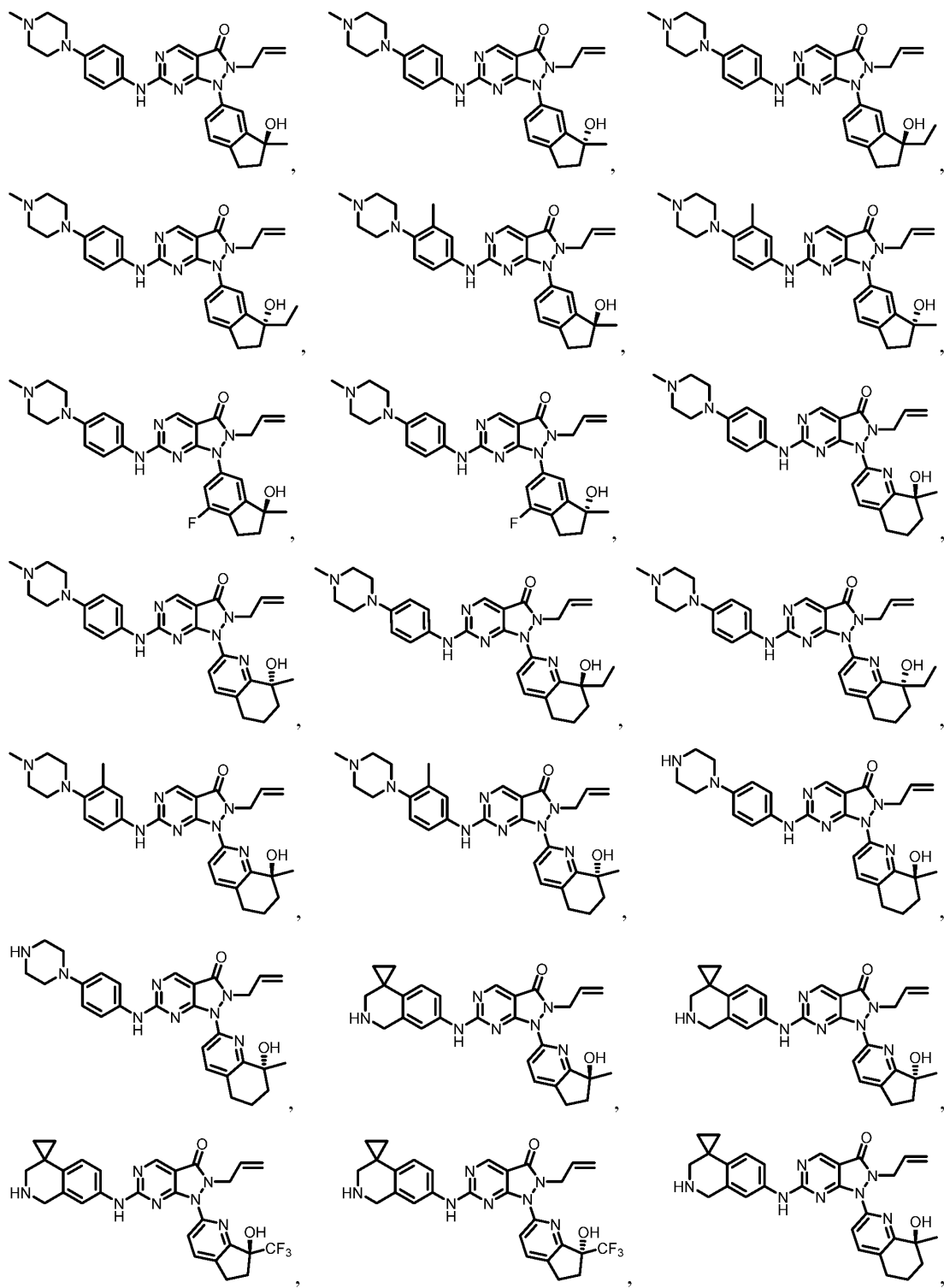
[0210] A non-limiting list of WEE1 inhibitors of Compound (B) are described herein, and include those provided in Figure 2.

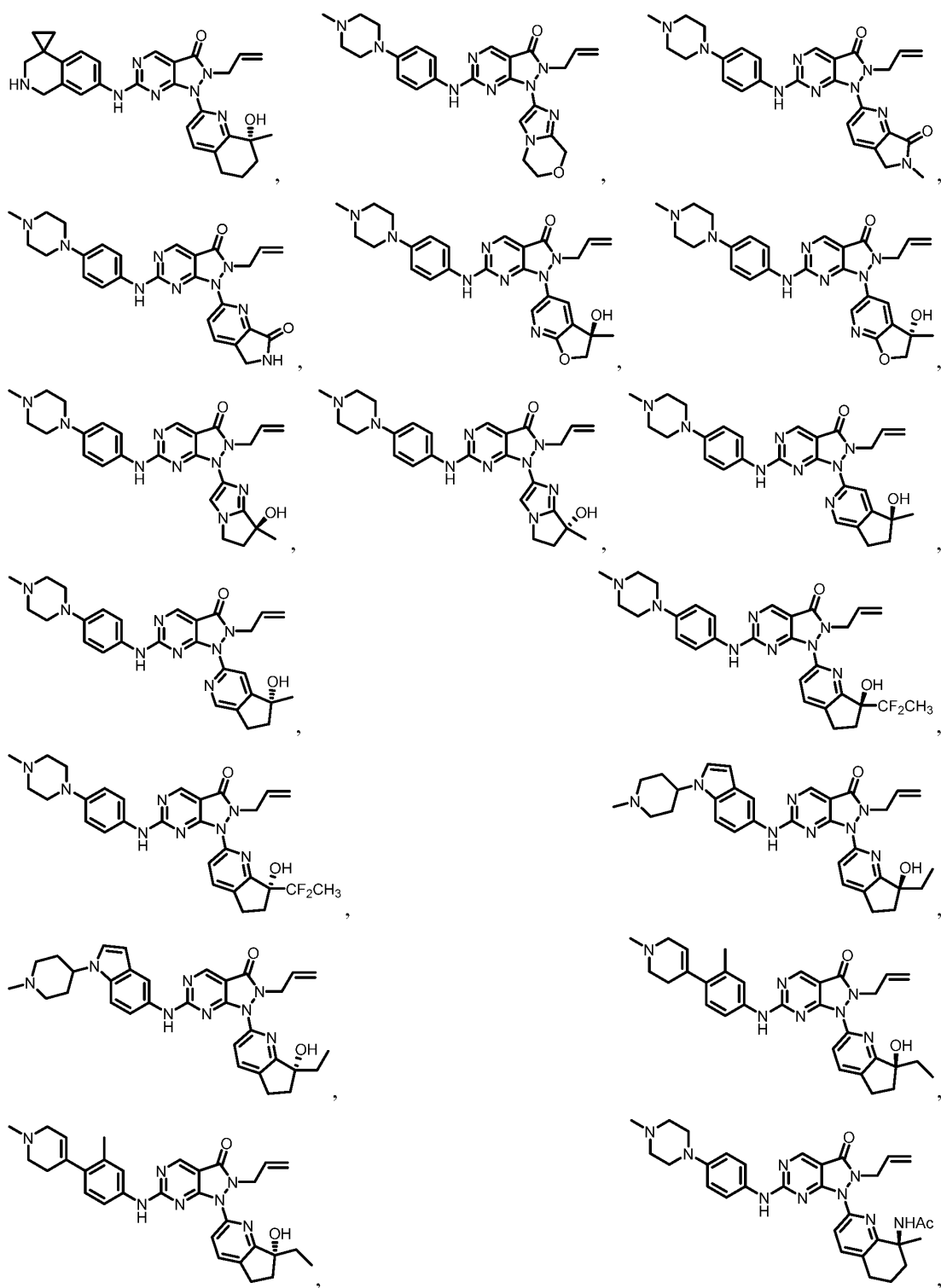
[0211] Examples of Compound (B) include the following:

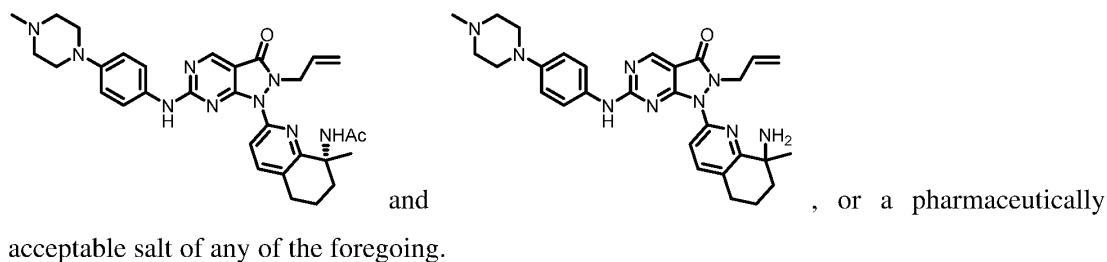












[0212] Compound (B), along with pharmaceutically acceptable salts thereof, can be prepared as described herein and in WO 2019/173082, which is hereby incorporated by reference in its entirety. As described in WO 2019/173082, Compound (B) is a WEE1 inhibitor.

[0213] Embodiments of combinations of Compound (A) and Compound (B), including pharmaceutically acceptable salts of any of the foregoing, are provided in Table 1. The numbers in Table 1 represent a compound as provided in Figures 1 and 2. For example, in Table 1, a combination represented by 1:4A corresponds to a combination of

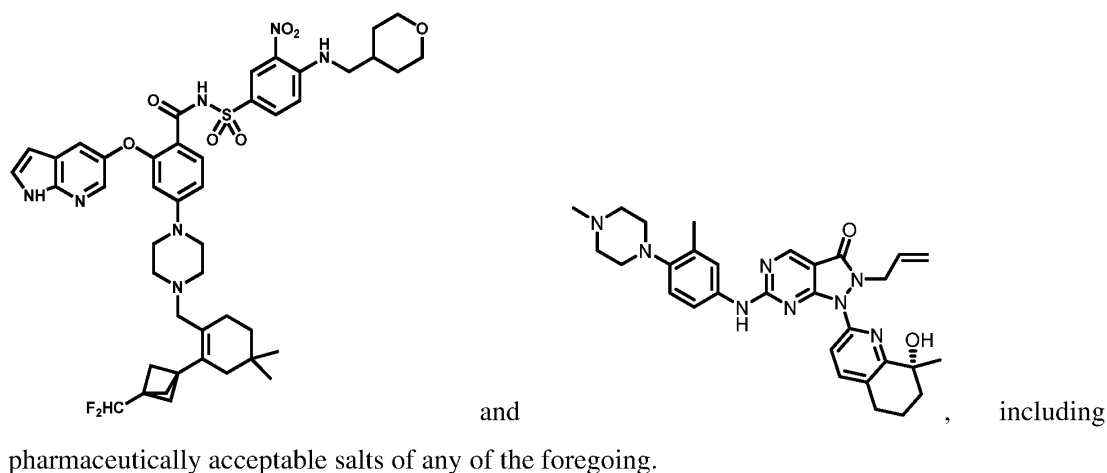


Table 1

Cmpd:Cmpd	Cmpd:Cmpd	Cmpd:Cmpd	Cmpd:Cmpd
1:1A	1:10A	2:7A	3:4A
1:2A	1:11A	2:8A	3:5A
1:3A	1:12A	2:9A	3:6A
1:4A	2:1A	2:10A	3:7A
1:5A	2:2A	2:11A	3:8A
1:6A	2:3A	2:12A	3:9A
1:7A	2:4A	3:1A	3:10A
1:8A	2:5A	3:2A	3:11A
1:9A	2:6A	3:3A	3:12A

Cmpd:Cmpd	Cmpd:Cmpd	Cmpd:Cmpd	Cmpd:Cmpd
4:1A	5:10A	7:7A	9:4A
4:2A	5:11A	7:8A	9:5A
4:3A	5:12A	7:9A	9:6A
4:4A	6:1A	7:10A	9:7A
4:5A	6:2A	7:11A	9:8A
4:6A	6:3A	7:12A	9:9A
4:7A	6:4A	8:1A	9:10A
4:8A	6:5A	8:2A	9:11A
4:9A	6:6A	8:3A	9:12A
4:10A	6:7A	8:4A	10:1A
4:11A	6:8A	8:5A	10:2A
4:12A	6:9A	8:6A	10:3A
5:1A	6:10A	8:7A	10:4A
5:2A	6:11A	8:8A	10:5A
5:3A	6:12A	8:9A	10:6A
5:4A	7:1A	8:10A	10:7A
5:5A	7:2A	8:11A	10:8A
5:6A	7:3A	8:12A	10:9A
5:7A	7:4A	9:1A	10:10A
5:8A	5:5A	9:2A	10:11A
5:9A	5:6A	9:3A	10:12A

[0214] The order of administration of compounds in a combination described herein can vary. In some embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered prior to all of Compound (B), or a pharmaceutically acceptable salt thereof. In other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered prior to at least one Compound (B), or a pharmaceutically acceptable salt thereof. In still other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered concomitantly with Compound (B), or a pharmaceutically acceptable salt thereof. In yet still other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered subsequent to the administration of at least one Compound (B), or a pharmaceutically acceptable salt thereof. In some embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered subsequent to the administration of all Compound (B), or a pharmaceutically acceptable salt thereof.

[0215] There may be several advantages for using a combination of compounds described herein. For example, combining compounds that attack multiple pathways at the same

time, can be more effective in treating a cancer, such as those described herein, compared to when the compounds of combination are used as monotherapy.

[0216] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can decrease the number and/or severity of side effects that can be attributed to a compound described herein, such as Compound (B), or a pharmaceutically acceptable salt thereof.

[0217] Using a combination of compounds described herein can result in additive, synergistic or strongly synergistic effect. A combination of compounds described herein can result in an effect that is not antagonistic.

[0218] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in an additive effect. In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in a synergistic effect. In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in a strongly synergistic effect. In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, is not antagonistic.

[0219] As used herein, the term “antagonistic” means that the activity of the combination of compounds is less compared to the sum of the activities of the compounds in combination when the activity of each compound is determined individually (i.e., as a single compound). As used herein, the term “synergistic effect” means that the activity of the combination of compounds is greater than the sum of the individual activities of the compounds in the combination when the activity of each compound is determined individually. As used herein, the term “additive effect” means that the activity of the combination of compounds is about equal to the sum of the individual activities of the compounds in the combination when the activity of each compound is determined individually.

[0220] A potential advantage of utilizing a combination as described herein may be a reduction in the required amount(s) of the compound(s) that is effective in treating a disease condition disclosed herein compared to when each compound is administered as a monotherapy. For example, the amount of Compound (B), or a pharmaceutically acceptable salt thereof, used in a combination described herein can be less compared to the amount of Compound (B), or a pharmaceutically acceptable salt thereof, needed to achieve the same reduction in a disease marker (for example, tumor size) when administered as a monotherapy. Another potential advantage of utilizing a combination as described herein is that the use of two or more compounds having different mechanisms of action can create a higher barrier to the development of resistance compared to when a compound is administered as monotherapy. Additional advantages of utilizing a combination as described herein may include little to no cross resistance between the compounds of a combination described herein; different routes for elimination of the compounds of a combination described herein; and/or little to no overlapping toxicities between the compounds of a combination described herein.

Pharmaceutical Compositions

[0221] Compound (A), including pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition. Likewise, Compound (B), including pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition.

[0222] 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, carriers and/or excipients. 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.

[0223] 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.

[0224] 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.

[0225] 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.

[0226] In some embodiments, Compound (B), along with pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition that includes Compound (A), including pharmaceutically acceptable salts thereof. In other embodiments, Compound (B), along with pharmaceutically acceptable salts thereof, can be administered in a pharmaceutical composition that is separate from a pharmaceutical composition that includes Compound (A), including pharmaceutically acceptable salts thereof.

[0227] 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.

[0228] 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.

[0229] 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, Compound (A), including pharmaceutically acceptable salts thereof, can be administered orally. In some embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be provided to a subject by the same route of administration as Compound (B), along with pharmaceutically acceptable salts thereof. In other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be provided to a subject by a different route of administration as Compound (B), along with pharmaceutically acceptable salts thereof.

[0230] 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.

[0231] 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

[0232] As provided herein, in some embodiments, a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, can be used to treat a disease or condition.

[0233] Examples of diseases or conditions that can be treated by a combination of compounds, along with pharmaceutically acceptable salts thereof, include malignancies, cancers and syndromes such as those described herein. In some embodiments, the disease or condition can be a hematological malignancy. Exemplary hematological malignancies include is a leukemia, a lymphoma, or a myeloma. In some embodiments, the hematological malignancy can be refractory. In some embodiments, the disease or condition can be a leukemia including, but not limited to: acute myeloid leukemia (AML) (including its subtypes, such as, subtypes TP53 wildtype AML, TP53 mutant AML, refractory AML, acute promyelocytic leukemia, acute basophilic leukemia, and therapy-related AML), chronic lymphocytic leukemia (CLL) (including, but not limited to hairy cell leukemia and small lymphocytic lymphoma), acute lymphoblastic leukemia (ALL) (including, but not limited to specification for B-cell, T-cell, and ETP) and chronic myeloid leukemia (CML) (chronic myelogenous leukemia).

[0234] In some embodiments, the disease or condition can be a Myelodysplastic syndrome. In some embodiments, the disease or condition can be a myeloproliferative neoplasm (MPN), such as polycythemia vera (PV), myelofibrosis (MF) and essential thrombocythemia (ET).

[0235] As described herein, a combination of compounds described herein can be used to treat and/or ameliorate a lymphoma. Exemplary lymphomas include, but are not limited to, a non-Hodgkin's lymphoma (NHL) (including, but not limited to mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), peripheral T-cell lymphoma, cutaneous T-cell lymphoma, NK lymphoma, Burkitt lymphoma and Waldenstrom's macroglobulinemia). A combination of compounds, including pharmaceutically acceptable salts thereof, can also be used to treat a myeloma. Examples of myelomas that can be treated include, but are not limited to, multiple myeloma (MM) (including but not limited to translocation(11;14) and non-translocation(11;14)). As

described herein, a combination of compounds described herein can be used to treat and/or ameliorate a systemic mastocytosis, and blastic plasmacytoid dendritic cell neoplasm.

[0236] A disease or condition described herein can be in an adult or pediatric subject. In some embodiments, the subject that suffers from the disease or condition, such as those described herein, can be a pediatric subject. In some embodiments, the disease or condition can be a pediatric hematological malignancy, for example, pediatric AML and/or pediatric ALL.

[0237] A combination of compounds described herein can be used to treat and/or ameliorate a solid tumor. For example, in some embodiments, the solid tumor can be selected from an Ewing's tumor and a Wilms' cancer. Additional examples of a solid tumor that can be treated by a combination of compounds described herein, including pharmaceutically acceptable salts thereof, are a bladder cancer, a brain cancer, a breast cancer (including but not limited to ER+ breast cancer and triple negative breast cancer), a cervical cancer, a choriocarcinoma, a cervicocerebral cancer, a colon cancer, an endometrial cancer, an esophageal cancer, a gallbladder/bile duct cancer, a head and neck cancer (including oral cancer), a hepatocellular cancer, a lung cancer (including a non-small cell cancer and small-cell lung cancer), a mesothelioma, an ovarian cancer, an osteosarcoma, a pancreatic cancer, a penis cancer, an anal cancer, a prostate cancer, a small cell cancer, a stomach cancer, a rectal cancer, a renal pelvis/ureter cancer, a skin cancer, a soft tissue sarcoma, a stomach cancer, a testicular cancer, a thyroid cancer, an uterus body cancer, and an uterocervical cancer. In some embodiments, the disease or condition can be a cancer that expresses BCL-2 protein.

[0238] 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.

[0239] 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.

[0240] The term "effective amount" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an 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 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.

[0241] For example, an effective amount of a compound, or radiation, is the amount that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor.

[0242] The amount of compound, salt and/or composition 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.

[0243] Various dosages of Compound (A) and Compound (B), along with pharmaceutically acceptable salts thereof, can be used in a combination described herein. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be dosed

in an amount in the range of 20-500 mg/day. In some embodiments, Compound (B), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 20-500 mg/day. For example, Compound (A) and/or Compound (B), including pharmaceutically acceptable salts thereof, can be dosage at about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 110 mg/day, about 120 mg/day, about 130 mg/day, about 140 mg/day, about 150 mg/day, about 160 mg/day, about 170 mg/day, about 180 mg/day, about 190 mg/day, about 200 mg/day, about 210 mg/day, about 220 mg/day, about 230 mg/day, about 240 mg/day, about 250 mg/day, about 260 mg/day, about 270 mg/day, about 280 mg/day, about 290 mg/day, about 300 mg/day, about 310 mg/day, about 320 mg/day, about 330 mg/day, about 340 mg/day, about 350 mg/day, about 360 mg/day, about 370 mg/day, about 380 mg/day, about 390 mg/day, about 400 mg/day, about 410 mg/day, about 420 mg/day, about 430 mg/day, about 440 mg/day, about 450 mg/day, about 460 mg/day, about 470 mg/day, about 480 mg/day, about 490 mg/day, or about 500 mg/day. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 200-400 mg/day. In some embodiments, Compound (B), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 200-400 mg/day.

[0244] Various dosages of Compound (A) and Compound (B), along with pharmaceutically acceptable salts thereof, can be used in a combination described herein. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 20-500 mg. In some embodiments, Compound (B), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 20-500 mg. For example, Compound (A) and/or Compound (B), including pharmaceutically acceptable salts thereof, can be dosage at about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 200-400 mg.

In some embodiments, Compound (B), or a pharmaceutically acceptable salt thereof, can be dosed in an amount in the range of 200-400 mg.

[0245] 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 compounds (A) and/or (B), or pharmaceutically acceptable salts of any of the foregoing, 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)

[0246] 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.

[0247] 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.

[0248] 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

[0249] 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.

CTG assay

[0250] 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. MV4-11 (ATCC, CRL-9591), Toledo (ATCC, CRL-2631), MCF-7 (ATCC, HTB-22) and DMS-53 (ATCC, CRL-2062) cells were cultured according to ATCC recommendations and were seeded at 20,000 cells per well.

[0251] Compound 5 (free base) and Compound 1a (free base) were prepared as a DMSO stock solution (10 mM). For RS4;11, MV4-11, Toledo, and DMS-53 cell lines, compounds were tested in triplicate using the respective IC₅₀ concentrations indicated in Table 1. The MCF-7 combination assay was performed in duplicate with a 10-point serial dilution curve (1:3 dilution) for Compounds 5 and 1a, and a 10-point serial dilution curve (1:5 dilution) when

treated in combination. The highest compound concentration was 10 μ M with a 0.1% final DMSO concentration. Plates were incubated at 37 °C, 5% CO₂ for 72 h and then equilibrated at room temperature for approximately 30 min. An equal-volume amount of CellTiter-Glo® Reagent (100 μ L) was added to each well. Plates were mixed for 2 min on an orbital shaker to induce cell lysis and then incubated at room temperature for 10 min to stabilize the luminescent signal. Luminescence (RLU (relative light unit)) was recorded using a SpectraMAX, M5e plate reader according to CellTiter-Glo protocol. Percent inhibition was calculated using the following formula: % inhibition = (RLU * 100 / (RLU of the cell background)). IC₅₀ of each compound was calculated using GraphPad Prism by nonlinear regression analysis.

[0252] Figures 3 and 4 along with Tables 2 and 3 demonstrate that the addition of Compound 5 to Compound 1a (alternatively referred to as “Compound 1A” throughout the specification and figures) resulted in combination efficacy.

Table 2

	RS4;11		MV4-11	
	Concentration (nM)	Inhibition (%)	Concentration (nM)	Inhibition (%)
Compound 5	4	32.5	18	37.3
Compound 1a	400	26.8	500	47.6
Compounds 5 +1a	4 + 400	87.3	18 + 500	94.2
	Toledo		DMS-53	
	Concentration (nM)	Inhibition (%)	Concentration (nM)	Inhibition (%)
Compound 5	20	14.7	370	51
Compound 1a	300	34.5	650	33
Compounds 5 +1a	20 + 300	73.4	370 + 650	77

Table 3

	IC ₅₀ Based on % Inhibition		
MCF7	Compound 5	Compound 1a	Compound 5 + 1a
Relative IC ₅₀ (nM)	5023	193	17
Absolute IC ₅₀ (nM)	3569	252	43

Xenograft Tumor Model

[0253] Mice were inoculated with HL-60 cells subcutaneously on the right flank with the single cell suspension of 95% viable tumor cells (1×10^7) in 100 μ L IMDM Matrigel mixture (1:1 ratio) without serum for the tumor development. The treatment was started when the mean tumor size reached approximately 215 mm³, with individual tumor size ranging from 185-245 mm³. Animals were randomly distributed into treatment groups of 10 animals each and dosed with vehicle and indicated compounds at indicated dosage and frequency shown in Figure 5 and Table 4. Compound 5 was dosed as a free base and Compound 1a was dosed as a free base. In Figure 5, the bottom line (indicated with diamonds) represents data for Compound 5 (50 mg/kg) + Compound 1a (80 mg/kg), the second line from the bottom (indicated with triangles) represents data for Compound 5 (50 mg/kg) + Compound 1a (60 mg/kg) and the third line from the bottom (indicated with diamonds) represents data for Compound 5 (50 mg/kg). Tumor volumes were evaluated twice per week to calculate tumor volume over time, and mice were weighed twice per week as a surrogate for signs of toxicity. Tumor growth inhibition (TGI) was calculated using the following equation $TGI = (1 - (T_d - T_0) / (C_d - C_0)) \times 100\%$. T_d and C_d are the mean tumor volumes of the treated and control animals, and T_0 and C_0 are the mean tumor volumes of the treated and control animals at the start of the experiment. The tumor regression was defined as individual tumor volume (TV) decrease (terminal TV compared to initial TV). The percent tumor regression was calculated using the formula: $(1 - (T_d / T_0)) \times 100\%$. Figure 5 and Table 4 illustrate that single agent treatment of Compound 1a at 60 or 80 mg/kg did not result in tumor growth inhibition and single agent treatment with Compound 5 resulted in minor efficacy (30%). The combination of Compound 5 (50 mg/kg) and Compound 1a (60 mg/kg) exhibited significant TGI and resulted in the complete regression of 8 out of 10 tumors on day 18. The combination of Compound 5 (50 mg/kg) and Compound 1a (80 mg/kg) exhibited significant TGI and resulted in the complete regression of 9 out of 10 tumors on day 18. The data provided herein demonstrates that a combination of a Bcl-2 inhibitor and a WEE1 inhibitor described herein can be used to treat a disease or condition described herein.

Table 4

COMPOUND	TGI % (DAY 18)	TUMOR REGRESSION % (DAY 18)	COMPLETE REGRESSION (DAY 18)
Compound 5 (50 mg/kg)	31	0	0/10
Compound 1a (60 mg/kg)	0	0	0/10
Compound 1a (80 mg/kg)	0	0	0/10
Compound 5 (50 mg/kg) + Compound 1a (60 mg/kg)	109	94	8/10
Compound 5 (50 mg/kg) + Compound 1a (80 mg/kg)	110	98	9/10

[0254] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the disclosure.