

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 Nos. 62/952,056, filed December 20, 2019, 63/004,978, filed April 3, 2020, and 63/009,916, filed April 14, 2020.

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] Other embodiments described herein relate to a combination of compounds that can include an effective amount of Compound (C), or a pharmaceutically acceptable salt

thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof.

[0006] 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.

[0007] 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 (C), 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 (C), or a pharmaceutically acceptable salt thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof.

[0008] In some embodiments, the disease or condition can be a cancer described herein.

DRAWINGS

[0009] Figure 1 provides examples of Compound (B).

[0010] Figure 2 shows the tumor volume in response to monotherapy and combination therapy with Compound (A) and Compound 5 in an MCF-7 mouse model.

[0011] Figure 3 shows the tumor volume in response to monotherapy and combination therapy with Compound (A) and Compound 5 in an MCF-7 mouse model.

[0012] Figure 4 shows the tumor volume in response to monotherapy and combination therapy with Compound (A) and Compound 6 in an MCF-7 mouse model.

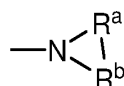
Definitions for Compound (A), and pharmaceutically acceptable salts thereof

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

[0014] Whenever a group is described as being “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, cycloalkynyl, 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 amino group and a di-substituted amino group.

[0015] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in a group. The indicated group can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “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.

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



[0017] As used herein, the term “alkyl” refers to a fully saturated aliphatic hydrocarbon group. The alkyl moiety may be branched or straight chain. Examples of branched alkyl groups include, but are not limited to, iso-propyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and the like. The alkyl group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as “1 to 30” refers to each integer in the given range; *e.g.*, “1 to 30 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. An alkyl group may be substituted or unsubstituted.

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

[0019] The term “alkynyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond(s) including, but not limited to, 1-propynyl, 1-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 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. Typical mono-cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Examples of fused cycloalkyl groups are decahydronaphthalenyl, dodecahydro-1H-phenalenyl and tetradecahydroanthracenyl; examples of bridged cycloalkyl groups are bicyclo[1.1.1]pentyl, adamantanyl, and norbornanyl; and examples of spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane.

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

[0023] 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.

[0024] 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). Furthermore, the term “heteroaryl” includes fused ring systems where two rings, such as at least one aryl ring and at

least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0025] As used herein, “heterocyclyl” 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). Additionally, any nitrogens in a heteroalicyclic may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such “heterocyclyl” or “heteroalicyclyl” groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine,

isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, azepane, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and/or 3,4-methylenedioxyphenyl). Examples of spiro heterocyclyl groups include 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxaspiro[3.4]octane and 2-azaspiro[3.4]octane.

[0026] 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.

[0027] 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.

[0028] 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).

[0029] As used herein, “lower alkylene groups” are straight-chained -CH₂- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-) and butylene (-CH₂CH₂CH₂CH₂-). 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., ).

[0030] As used herein, the term “hydroxy” refers to a -OH group.

[0031] 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.

[0032] 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.

[0033] A “cyano” group refers to a “ $-CN$ ” group.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] A “nitro” group refers to an “-NO₂” group.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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 and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0051] 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.

[0052] The term “amino” as used herein refers to a –NH₂ group.

[0053] A “mono-substituted amino” group refers to a “-NHR” group in which R 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. A mono-substituted amino may be substituted or unsubstituted. Examples of mono-substituted amino groups include, but are not limited to, –NH(methyl), –NH(phenyl) and the like.

[0054] A “di-substituted amino” 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. A di-substituted amino may be substituted or unsubstituted. Examples of di-substituted amino groups include, but are not limited to, –N(methyl)₂, –N(phenyl)(methyl), –N(ethyl)(methyl) and the like.

[0055] Where the numbers 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] As used herein, when a chemical group or unit includes an asterisk (*), that asterisk indicates a point of attachment of the group or unit to another structure.

[0058] As used herein, “linking groups” are chemical groups that are indicated as having multiple open valencies for connecting to two or more other groups. For example, lower alkylene groups of the general formula $-(CH_2)_n-$ where n is in the range of 1 to 10, are examples of linking groups that are described elsewhere herein as connecting molecular fragments via their terminal carbon atoms. Other examples of linking groups include $-(CH_2)_nO-$, $-(CH_2)_nNH-$, $-(CH_2)_nN(C_1-C_6alkyl)-$, and $-(CH_2)_nS-$, wherein each n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. Those skilled in the art will recognize that n can be zero for some linking groups such as $-(CH_2)_nO-$, in which case the linking group is simply $-O-$. Those skilled in the art will also recognize that reference herein to an asymmetrical linking group will be understood as a reference to all orientations of that group (unless stated otherwise). For example, reference herein to $-(CH_2)_nO-$ will be understood as a reference to both $-(CH_2)_nO-$ and $-O-(CH_2)_n-$.

[0059] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, trifluoroacetic, benzoic, salicylic, 2-oxopentanedioic, or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine. For compounds of

Formulae (A) and/or (B), those skilled in the art understand that when a salt is formed by protonation of a nitrogen-based group (for example, NH_2), the nitrogen-based group can be associated with a positive charge (for example, NH_2 can become NH_3^+) and the positive charge can be balanced by a negatively charged counterion (such as Cl^-).

[0060] 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.

[0061] 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).

[0062] 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.

[0063] 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.

[0064] 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.

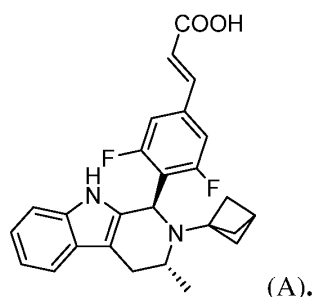
[0065] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' '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 process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. 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.

[0066] 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)

[0067] 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:

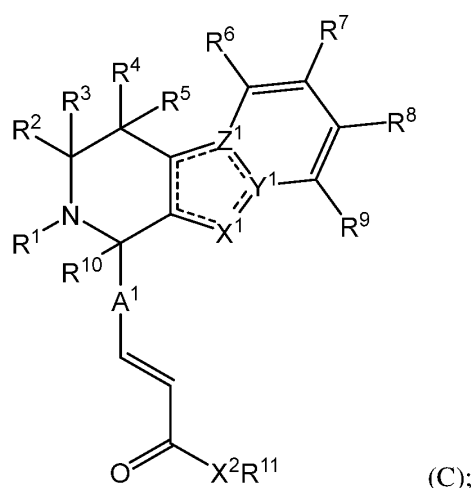


[0068] Compound (A) can be a salt. For example, in some embodiments, Compound (A) can be a hydrogen sulfate salt. Those skilled in the art understand that the hydrosulfate salt of Compound (A) has a single molecule of Compound (A) for a single molecule of hydrogen sulfate. In other embodiments, Compound (A) can be a sulfate salt. Those skilled in the art understand that the sulfate salt of Compound (A) has two molecules of Compound (A) for a single molecule of sulfate. Further, those skilled in the art understand that hydrogen sulfate and sulfate salts of Compound (A) are where the nitrogen of Compound (A) can be protonated.

[0069] In some embodiments, Compound (A) can be a pharmaceutically acceptable salt form of Compound (A) that can include the hydrosulfate salt of Compound A and the sulfate salt of Compound (A). As an example, a pharmaceutically acceptable salt form of Compound (A) can be a pharmaceutically acceptable salt form of Compound (A) that consists essentially of the hydrosulfate salt of Compound (A) and the sulfate salt of Compound (A). Exemplary salt

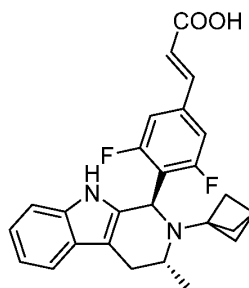
forms of Compound (A) include Form A and Form C. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be Form A. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can be Form C. In some embodiments, Compound (A), or a pharmaceutically acceptable salt thereof, can include Form A and Form C. Additional details regarding Form A and Form C of Compound (A) are provided in International Application No. PCT/US2020/058526, filed November 2, 2020, which is hereby incorporated by reference in its entirety.

[0070] Other 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 (C), 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 (C) has the structure:



wherein: X¹, Y¹ and Z¹ can be each independently C or N; with the first proviso that at least one of X¹, Y¹ and Z¹ is N; with the second proviso that each of X¹, Y¹ and Z¹ is uncharged; with third proviso that two of the dotted lines indicate double bonds; with the fourth proviso that the valencies of X¹, Y¹ and Z¹ can be each independently satisfied by attachment to a substituent selected from H and R¹²; X² can be O; A¹ can be selected from an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; R¹ can be selected from an optionally substituted C₁₋₆ alkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an

optionally substituted cycloalkyl(C₁₋₆ alkyl), an optionally substituted cycloalkenyl(C₁₋₆ alkyl), an optionally substituted aryl(C₁₋₆ alkyl), an optionally substituted heteroaryl(C₁₋₆ alkyl) and an optionally substituted heterocyclyl(C₁₋₆ alkyl); R² and R³ can be each independently selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl and an optionally substituted C₁₋₆ haloalkyl; or R² and R³ together with the carbon to which R² and R³ are attached can form an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted heterocyclyl; R⁴ and R⁵ can be each independently selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl and an optionally substituted C₁₋₆ haloalkyl; or R⁴ and R⁵ together with the carbon to which R⁴ and R⁵ are attached can form an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted heterocyclyl; R⁶, R⁷, R⁸ and R⁹ can be each independently selected from hydrogen, halogen, hydroxy, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted haloalkyl, an optionally substituted mono-substituted amine, and an optionally substituted di-substituted amine; R¹⁰ can be hydrogen, halogen, an optionally substituted alkyl, or an optionally substituted cycloalkyl; R¹¹ can be hydrogen; R¹² can be hydrogen, halogen, an optionally substituted C₁₋₃ alkyl, an optionally substituted C₁₋₃ haloalkyl or an optionally substituted C₁₋₃ alkoxy; and



provided that the Compound (C) cannot be , or a pharmaceutically acceptable salt thereof.

[0071] In some embodiments, for Compound (C), or a pharmaceutically acceptable salt thereof, when X¹ is NH; Y¹ and Z¹ are each C; A¹ is a phenyl, 2-fluorophenyl or 2,6-difluorophenyl; R² and R³ are each methyl or one of R² and R³ is hydrogen and the other of R² and R³ is methyl; and R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen; then R¹ cannot be 2-hydroxyethyl, 2-methylpropyl, 2-fluoro-2-methylpropyl, 3-fluoro-2-methylpropyl, 3-hydroxy-2-methylpropyl or 2-fluoro-3-hydroxy-2-methylpropyl. In other embodiments, for Compound (C), or a pharmaceutically acceptable salt thereof, when R¹⁰ is hydrogen, R¹¹ is hydrogen, X¹ is NH, Y¹ and Z¹ are each C, A¹ is an optionally substituted phenyl, one of R² and R³ is hydrogen

or an optionally substituted C₁₋₆ alkyl and the other of R² and R³ is an optionally substituted C₁₋₆ alkyl, then R¹ cannot be a substituted C₁₋₆ alkyl substituted with one or more substituents selected from the group consisting of halogen and hydroxy.

[0072] In some embodiments, A¹ can be an optionally substituted aryl. For example, A¹ can be an optionally substituted phenyl. Thus, A¹ can be a substituted phenyl or an unsubstituted phenyl. In other embodiments, A¹ can be an optionally substituted cycloalkyl, such as an optionally substituted bicyclopentyl.

[0073] In some embodiments, R¹ can be selected from an optionally substituted C₁₋₆ alkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C₁₋₆ alkyl), an optionally substituted heterocyclyl and an optionally substituted heterocyclyl(C₁₋₆ alkyl).

[0074] In some embodiments, R¹ can be a substituted cycloalkyl. In some embodiments, R¹ is substituted cycloalkyl that can be substituted with one or more substituents selected from halogen, hydroxy, haloalkyl, an optionally substituted alkyl, an optionally substituted cycloalkyl, a substituted alkoxy, a substituted mono-substituted amine and a substituted di-substituted amine. In some embodiments, R¹ can be an optionally substituted cycloalkyl selected from unsubstituted cyclobutyl, unsubstituted difluorocyclobutyl, unsubstituted cyclopentyl and unsubstituted bicyclopentyl. In other embodiments, R¹ can be an optionally substituted cycloalkyl(C₁₋₆ alkyl) selected from unsubstituted cyclopropylmethyl, unsubstituted bicyclopentylmethyl, unsubstituted fluorocyclopropylmethyl, unsubstituted fluorocyclobutylmethyl, unsubstituted methoxycyclopropylmethyl and unsubstituted trifluoromethylcyclopropylmethyl. In still other embodiments, R¹ can be an optionally substituted heterocyclyl selected from unsubstituted tetrahydropyranyl, unsubstituted tetrahydrofuranyl, and unsubstituted oxetanyl. In yet still other embodiments, R¹ is an optionally substituted heterocyclyl(C₁₋₆ alkyl) can be selected from unsubstituted oxetanylmethyl and unsubstituted fluorooxetanylmethyl

[0075] In some embodiments, R¹ can be a substituted alkyl. In some embodiments, R¹ can be a substituted alkyl that is substituted with one or more substituents selected from halogen, hydroxy, haloalkyl, an optionally substituted cycloalkyl, a substituted alkoxy, a substituted mono-substituted amine and a substituted di-substituted amine. For example, R¹ can be a substituted alkyl that is a haloalkyl. In some embodiments, R¹ can be an optionally substituted C₁₋₆ alkyl selected from C₄ alkyl, fluoro(C₄ alkyl), and trifluoro(C₂ alkyl).

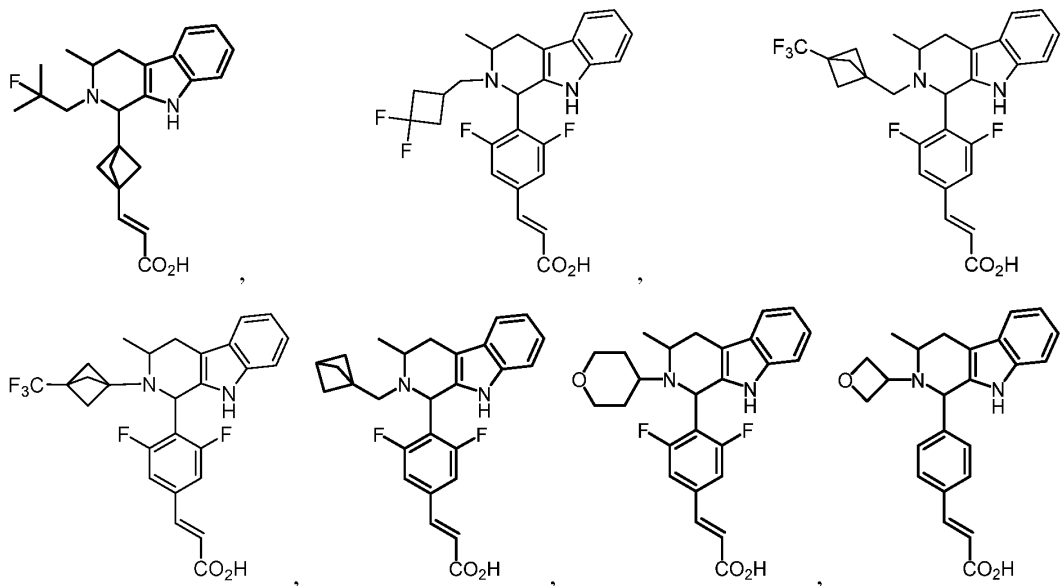
[0076] In some embodiments, R^2 and R^3 can be each independently selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl and an optionally substituted C_{1-6} haloalkyl. In other embodiments, R^2 and R^3 together with the carbon to which R^2 and R^3 are attached can form an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted heterocyclyl. In some embodiments, R^2 can be selected from hydrogen, methyl, fluoromethyl and difluoromethyl.

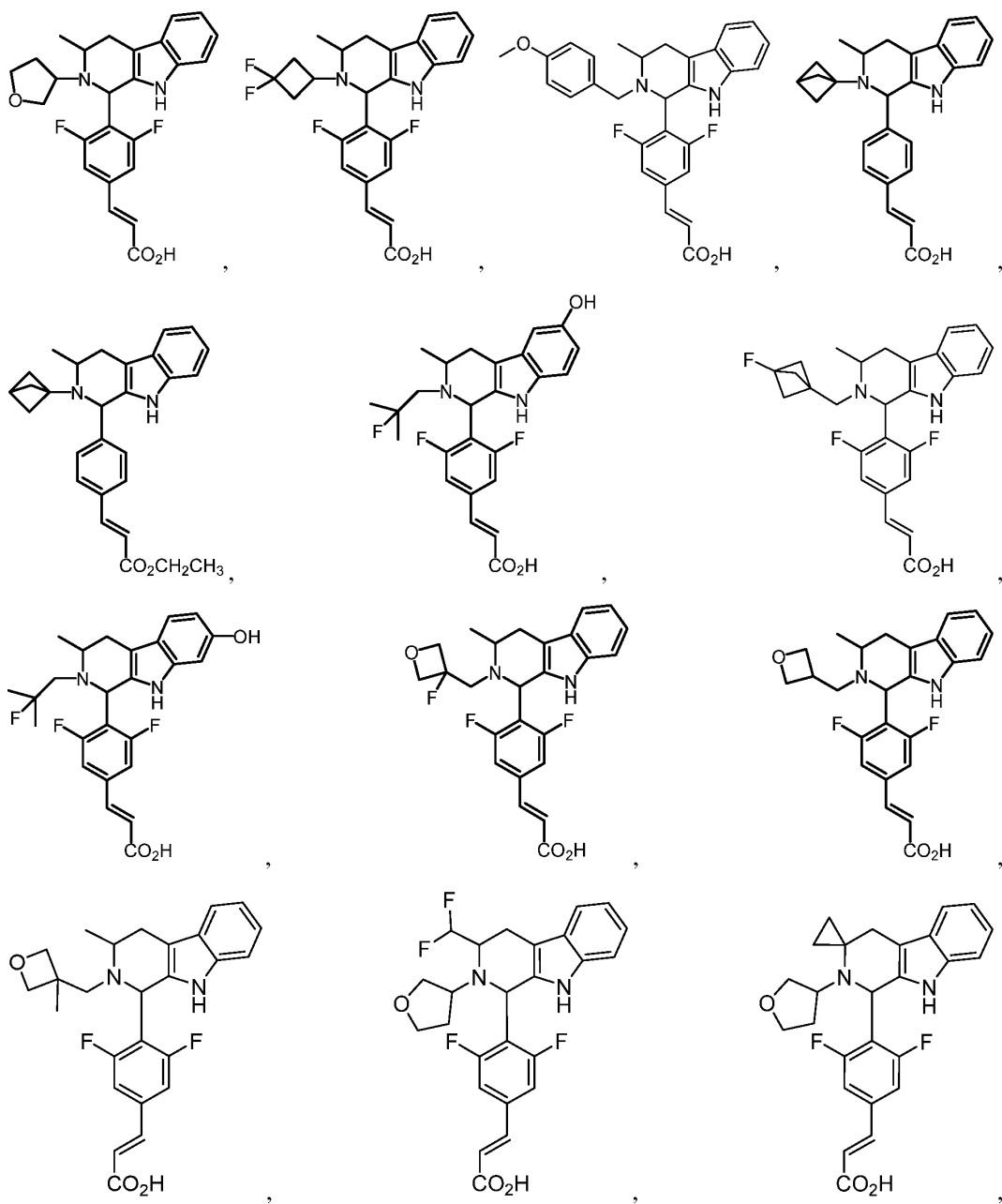
[0077] In some embodiments R^4 and R^5 can be each independently selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl and an optionally substituted C_{1-6} haloalkyl. In other embodiments, R^4 and R^5 together with the carbon to which R^4 and R^5 are attached can form an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted heterocyclyl.

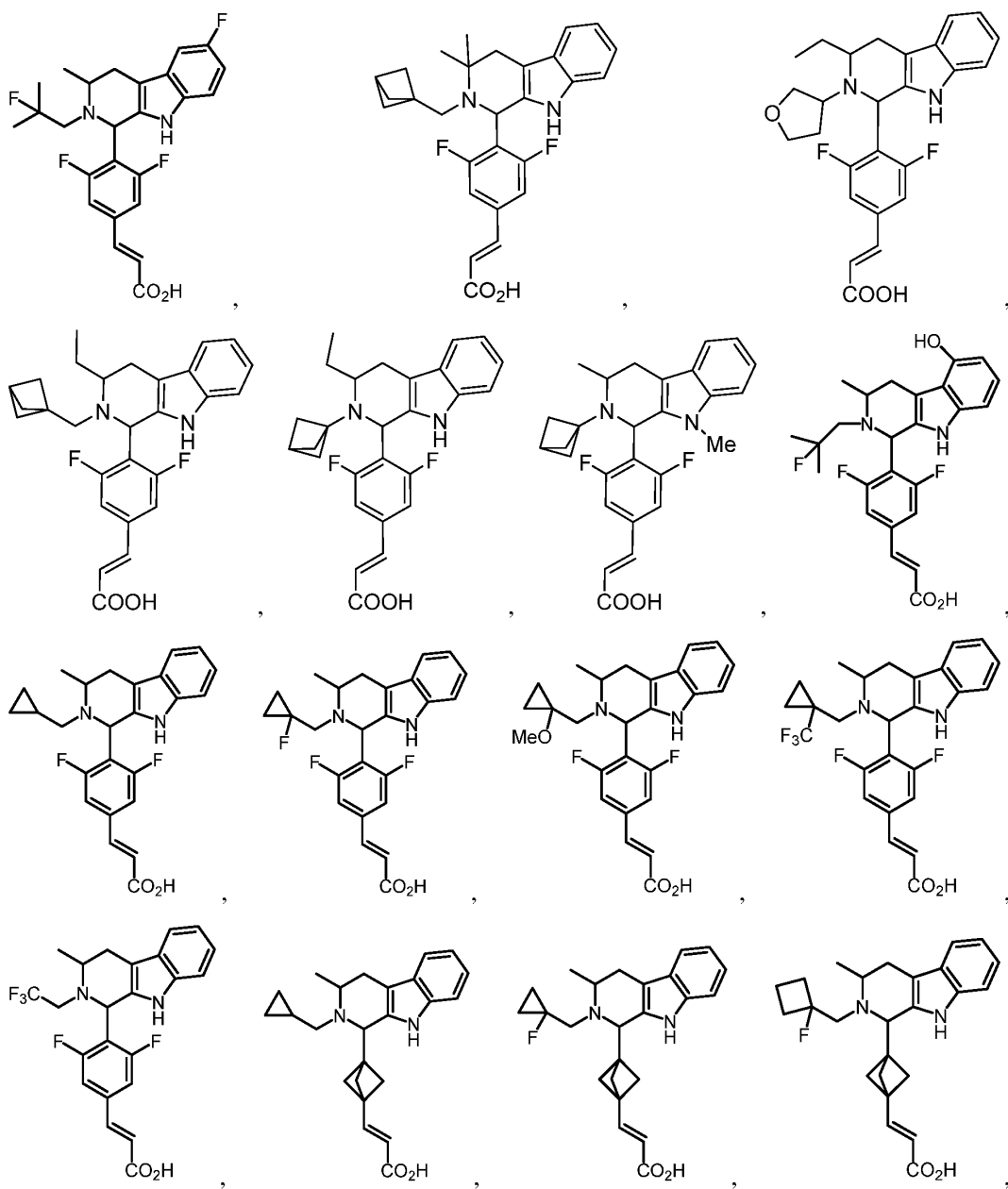
[0078] In some embodiments, R^7 can be selected from halogen, hydroxy and unsubstituted alkoxy. For example, in some embodiments, R^7 can be selected from fluoro and methoxy.

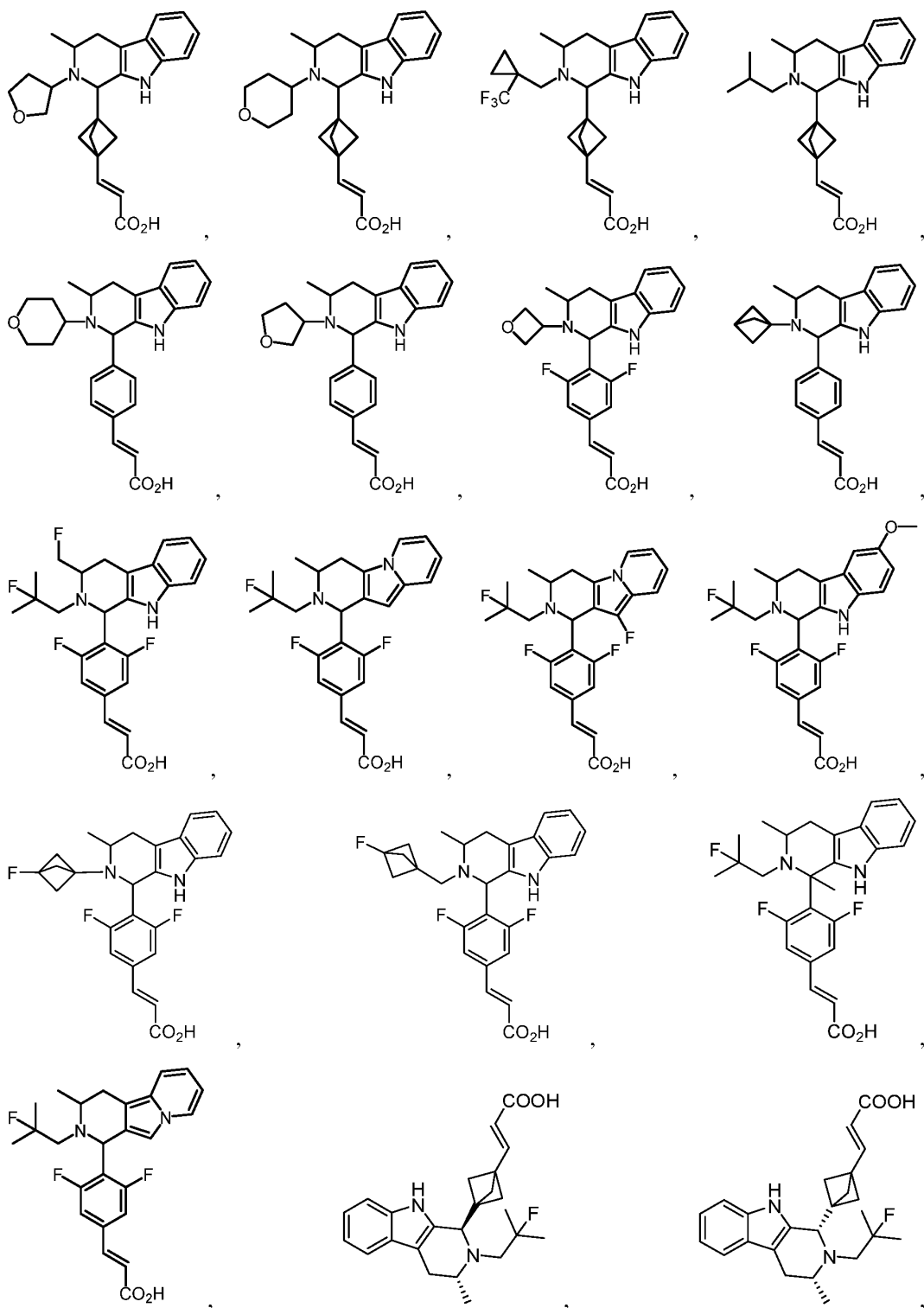
[0079] In some embodiments, R^{12} can be hydrogen. In other embodiments, R^{12} can be not hydrogen.

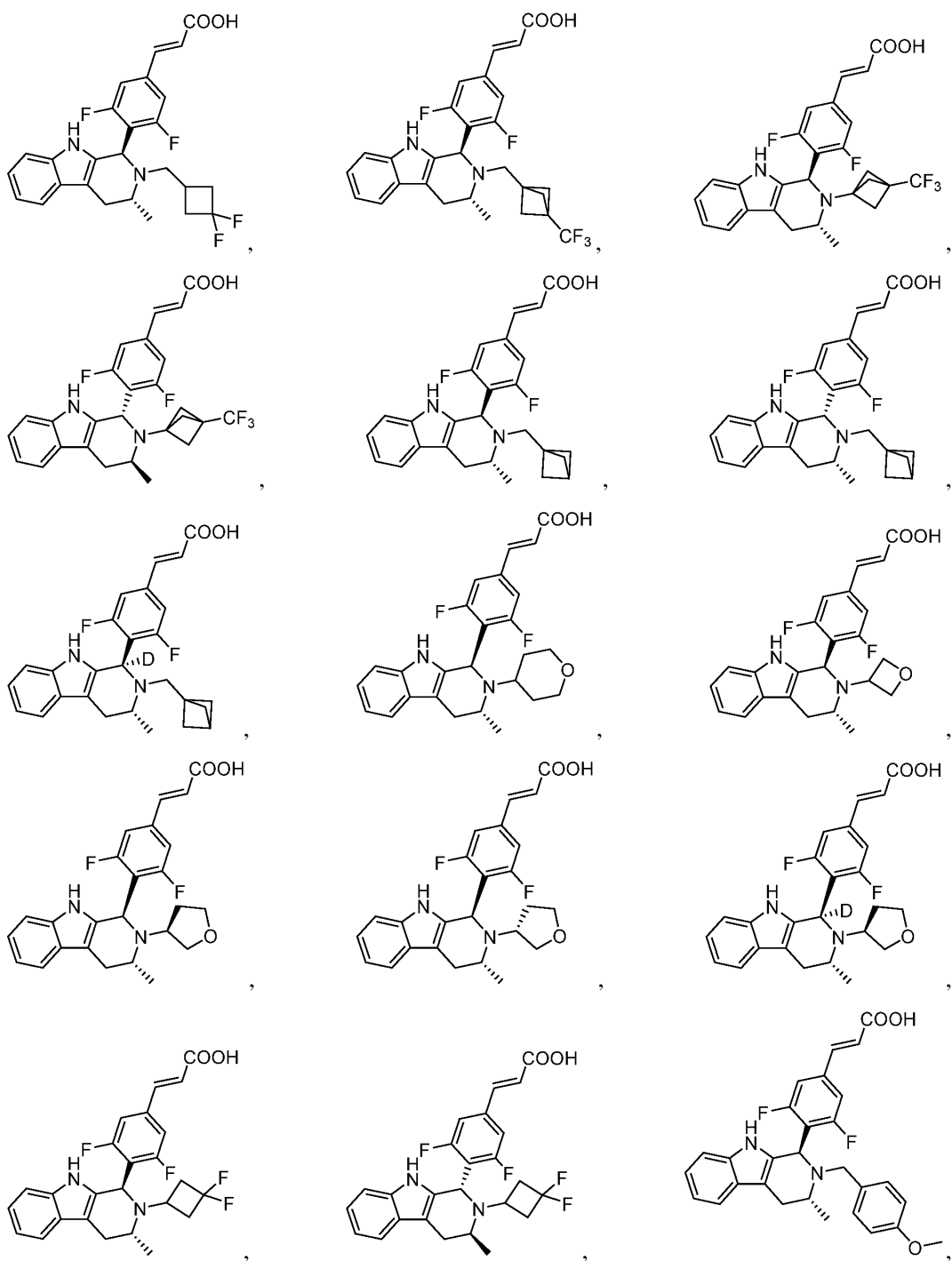
[0080] Examples of Compound (C) include the following:

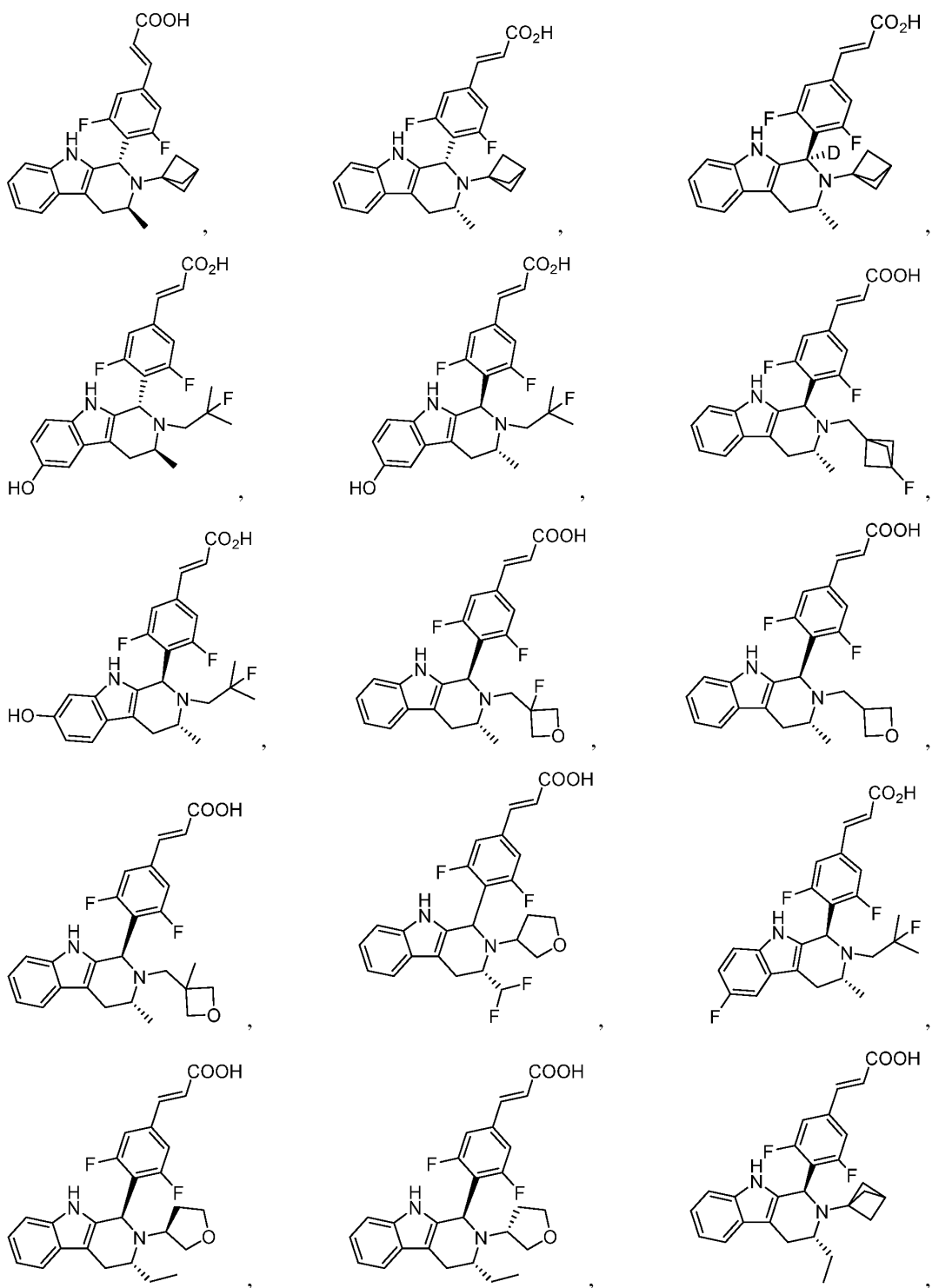


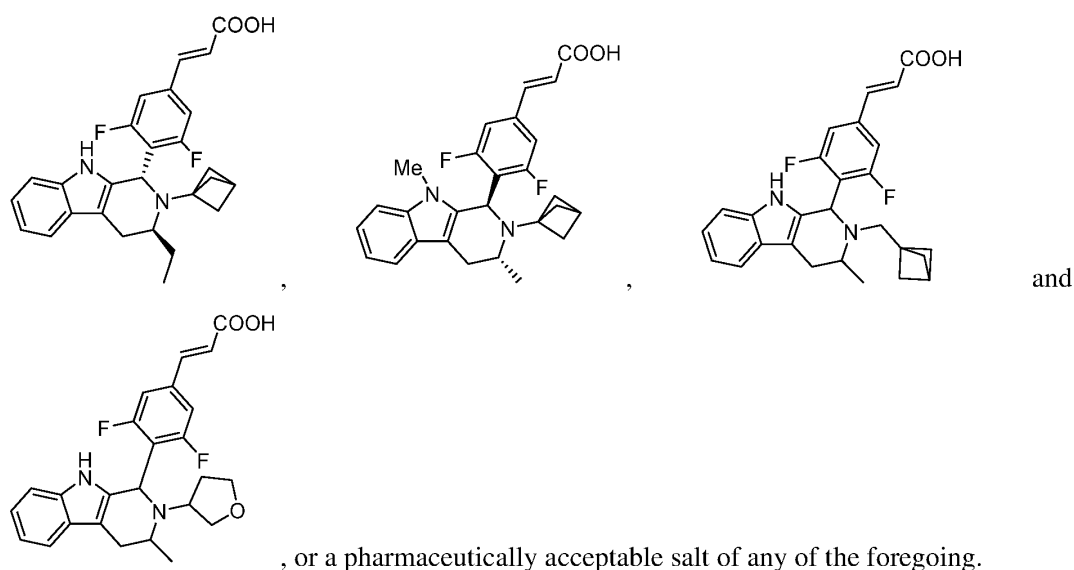












[0081] Compound (A) and Compound (C), along with pharmaceutically acceptable salts of any of the foregoing, can be prepared as described herein and in WO 2017/172957, which is hereby incorporated by reference in its entirety. As described in WO 2017/172957, Compound (A) is an estrogen receptor alpha (ER α) inhibitor.

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

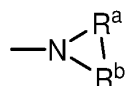
[0082] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety 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.

[0083] 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).

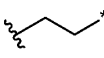
[0084] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in a group. The indicated group can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, 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.

[0085] 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:



[0086] 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.

[0087] 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.*, ).

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0094] 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 heteroalicyclyl may be quaternized. Heterocyclyl or heteroalicyclyl groups may be unsubstituted or substituted. Examples of such “heterocyclyl” or “heteroalicyclyl” groups include but are not limited to, 1,3-

dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, azepane, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and/or 3,4-methylenedioxyphenyl). Examples of spiro heterocyclyl groups include 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxaspiro[3.4]octane and 2-azaspiro[3.4]octane.

[0095] 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.

[0096] 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.

[0097] A “heteroalicycyl(alkyl)” and “heterocycyl(alkyl)” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocycyl 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).

[0098] As used herein, the term “hydroxy” refers to a –OH group.

[0099] As used herein, “alkoxy” refers to the Formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocycyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocycyl(alkyl) is defined herein. A non-limiting list of

alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0100] 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.

[0101] A “cyano” group refers to a “-CN” group.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] A “nitro” group refers to an “-NO₂” group.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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.

[0120] The terms “amino” and “unsubstituted amino” as used herein refer to a -NH_2 group.

[0121] A “mono-substituted amine” group refers to a “ -NHR_A ” group in which R_A can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. The R_A may be substituted or unsubstituted. A mono-substituted amine group can include, for example, a mono-alkylamine group, a mono- $\text{C}_1\text{-C}_6$ alkylamine group, a mono-arylamine group, a mono- $\text{C}_6\text{-C}_{10}$ arylamine group and the like. Examples of mono-substituted amine groups include, but are not limited to, -NH(methyl) , -NH(phenyl) and the like.

[0122] A “di-substituted amine” group refers to a “ $\text{-NR}_A\text{R}_B$ ” group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. R_A and R_B can independently be substituted or unsubstituted. A di-substituted amine group can include, for example, a di-alkylamine group, a di- $\text{C}_1\text{-C}_6$ alkylamine group, a di-arylamine group, a di- $\text{C}_6\text{-C}_{10}$ arylamine group and the like. Examples of di-substituted amine groups include, but are not limited to, -N(methyl)_2 , $\text{-N(phenyl)(methyl)}$, -N(ethyl)(methyl) and the like.

[0123] As used herein, “mono-substituted amine(alkyl)” group refers to a mono-substituted amine as provided herein connected, as a substituent, via a lower alkylene group. A mono-substituted amine(alkyl) may be substituted or unsubstituted. A mono-substituted amine(alkyl) group can include, for example, a mono-alkylamine(alkyl) group, a mono- $\text{C}_1\text{-C}_6$

alkylamine(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.

[0124] 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.

[0125] 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.

[0126] 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.”

[0127] 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⁻).

[0128] 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.

[0129] 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).

[0130] 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.

[0131] 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.

[0132] 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.

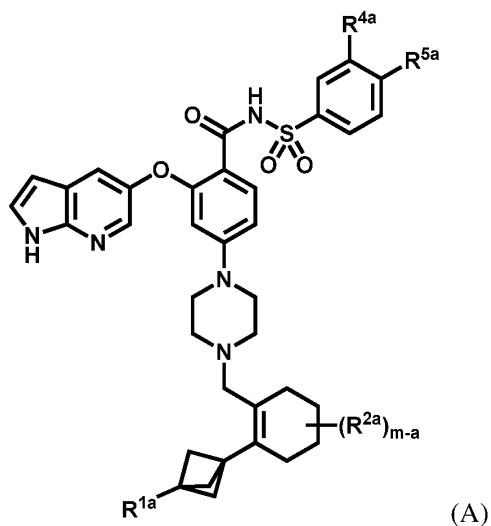
[0133] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' '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.

[0134] 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)

[0135] 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, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6 cycloalkyl, a

substituted or unsubstituted C₁-C₆ alkoxy, an unsubstituted mono-C₁-C₆ alkylamine and an unsubstituted di-C₁-C₆ alkylamine; each R^{2a} 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-a is 2 or 3, each R^{2a} 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 R^{2a} 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; R^{4a} can be selected from NO₂, S(O)R^{6a}, SO₂R^{6a}, halogen, cyano and an unsubstituted C₁-C₆ haloalkyl; R^{5a} can be -X^{1a}-(Alk^{1a})_{n-a}-R^{7a}; Alk^{1a} 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; R^{6a} 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; R^{7a} 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-a can be 0, 1, 2 or 3; n-a can be selected from 0 and 1; and X^{1a} can be selected from -O-, -S- and -NH-.

[0136] In some embodiments, R^{1a} can be halogen, for example, fluoro, chloro, bromo or iodo. In some embodiments, R^{1a} can be fluoro. In some embodiments, R^{1a} can be chloro. In some embodiments, R^{1a} can be hydrogen.

[0137] In some embodiments, R^{1a} can be a substituted or unsubstituted C₁-C₆ alkyl. For example, in some embodiments, R^{1a} can be a substituted C₁-C₆ alkyl. In other embodiments, R^{1a} 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, R^{1a} can be an unsubstituted methyl or an unsubstituted ethyl.

[0138] In some embodiments, R^{1a} 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, R^{1a} can be an unsubstituted -CHF₂, -CF₃, -CH₂CF₃ or -CF₂CH₃.

[0139] In some embodiments, R^{1a} can be a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl. For example, in some embodiments, R^{1a} can be a substituted monocyclic C₃-C₆ cycloalkyl. In other embodiments, R^{1a} 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.

[0140] In some embodiments, R^{1a} can be a substituted or unsubstituted C₁-C₆ alkoxy. For example, in some embodiments, R^{1a} can be a substituted C₁-C₆ alkoxy. In other embodiments, R^{1a} 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, R^{1a} can be an unsubstituted methoxy or an unsubstituted ethoxy.

[0141] In some embodiments, R^{1a} 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, R^{1a} can be methylamine or ethylamine.

[0142] In some embodiments, R^{1a} 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.

[0143] In some embodiments, m-a can be 0. When m-a is 0, those skilled in the art understand that the ring to which R^{2a} is attached is unsubstituted. In some embodiments, m-a can be 1. In some embodiments, m-a can be 2. In some embodiments, m-a can be 3.

[0144] In some embodiments, one R^{2a} 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 R^{2a}, 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 R^{2a} can be independently selected from an unsubstituted C₁-C₆ alkyl, such as those described herein.

[0145] In some embodiments, m-a can be 2; and each R^{2a} can be geminal. In some embodiments, m-a can be 2; and each R^{2a} can be vicinal. In some embodiments, m-a can be 2; and each R^{2a} can be an unsubstituted methyl. In some embodiments, m-a can be 2; and each R^{2a} can be a geminal unsubstituted methyl.

[0146] In some embodiments, two R^{2a} 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 R^{2a} 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 R^{2a} 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 R^{2a} groups can be taken together with the atom to which they are attached to form an unsubstituted cyclopropyl.

[0147] In some embodiments, two R^{2a} groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted monocyclic 3 to 6 membered heterocyclyl. For example, in some embodiments, two R^{2a} groups can be taken together with the atom(s) to which they are attached to form a substituted monocyclic 3 to 6 membered heterocyclyl. In other embodiments, two R^{2a} 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.

[0148] In some embodiments, R^{4a} can be NO₂. In some embodiments, R^{4a} can be cyano. In some embodiments, R^{4a} can be halogen.

[0149] In some embodiments, R^{4a} can be an unsubstituted C_1 - C_6 haloalkyl, such as those described herein. In some embodiments, R^{4a} can be $-CF_3$.

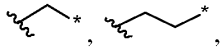
[0150] In some embodiments, R^{4a} can be $S(O)R^6$. In some embodiments, R^{4a} can be SO_2R^{6a} . In some embodiments, R^{4a} can be SO_2CF_3 .

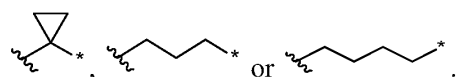
[0151] In some embodiments, R^{6a} can be a substituted or unsubstituted C_1 - C_6 alkyl. For example, in some embodiments, R^{6a} can be a substituted C_1 - C_6 alkyl, such as those described herein. In other embodiments, R^{6a} can be an unsubstituted C_1 - C_6 alkyl, such as those described herein.

[0152] In some embodiments, R^{6a} can be a substituted or unsubstituted monocyclic or bicyclic C_3 - C_6 cycloalkyl. For example, in some embodiments, R^{6a} can be a substituted monocyclic or bicyclic C_3 - C_6 cycloalkyl. In other embodiments, R^{6a} 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.

[0153] In some embodiments, R^{6a} can be a substituted or unsubstituted C_1 - C_6 haloalkyl, such as those described herein. In some embodiments, R^{6a} can be $-CF_3$.

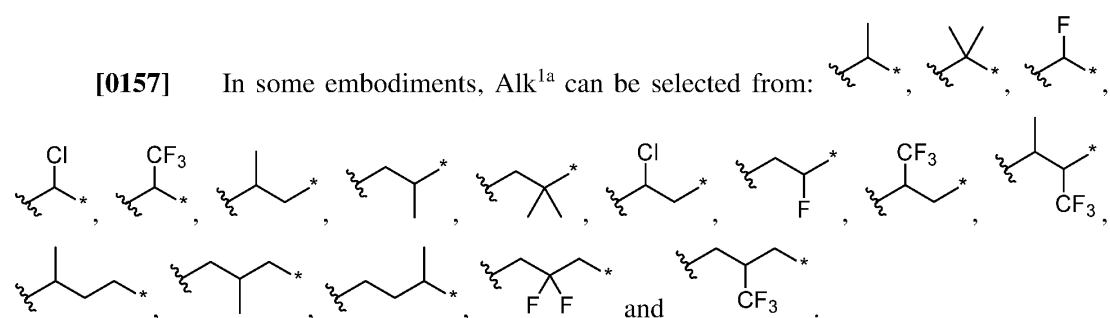
[0154] In some embodiments, R^{5a} can be $-X^{1a}-(Alk^{1a})_{n-a}-R^{7a}$. In some embodiments, X^{1a} can be $-O-$. In some embodiments, X^{1a} can be $-S-$. In some embodiments, X^{1a} can be $-NH-$.

[0155] In some embodiments, Alk^{1a} can be unsubstituted $-(CH_2)_{1-4}-*$ for which “*” represents the point of attachment to R^{7a} . In some embodiments, Alk^{1a} can be .



[0156] In some embodiments, Alk^{1a} can be a substituted $\text{---}C_1-C_4\text{---}*$ for which “*” represents the point of attachment to R^{7a} . For example, in some embodiments, Alk^{1a} can be a substituted methylene, a substituted ethylene, a substituted propylene or a substituted butylene. In some embodiments, Alk^{1a} can be mono-substituted, di-substituted or tri-substituted. In some embodiments, Alk^{1a} 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^{1a} can be mono-substituted unsubstituted C_1 - C_3 haloalkyl, such as those described herein. In some embodiments, Alk^{1a} can be mono-substituted with fluoro or unsubstituted methyl. In some embodiments, Alk^{1a} can be di-substituted with one fluoro and one unsubstituted C_1 - C_3 alkyl,

such as those described herein. In other embodiments, Alk^{1a} can be di-substituted with one unsubstituted $\text{C}_1\text{-C}_3$ haloalkyl, such as those described herein, and one unsubstituted $\text{C}_1\text{-C}_3$ alkyl, such as those described herein. In some embodiments, Alk^{1a} can be di-substituted with one fluoro and one unsubstituted methyl. In some embodiments, Alk^{1a} can be di-substituted with two independently selected unsubstituted $\text{C}_1\text{-C}_3$ alkyl groups, such as those described herein. In some embodiments, Alk^{1a} can be di-substituted with unsubstituted methyl.



[0158] In some embodiments, $n-a$ can be 0. When $n-a$ is 0, those skilled in the art understand that X^{1a} is directly connected to R^{7a} . In some embodiments, $n-a$ can be 1.

[0159] In some embodiments, R^{7a} can be a substituted or unsubstituted mono-substituted amine group. For example, R^{7a} can be an amino group mono-substituted with a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, a substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkenyl, a substituted or unsubstituted $\text{C}_2\text{-C}_6$ alkynyl, a substituted or unsubstituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl, a substituted or unsubstituted monocyclic or bicyclic $\text{C}_6\text{-C}_{10}$ aryl, a substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl, a substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl, a substituted or unsubstituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl(unsubstituted $\text{C}_1\text{-C}_6$ alkyl), a substituted or unsubstituted monocyclic or bicyclic $\text{C}_6\text{-C}_{10}$ aryl(unsubstituted $\text{C}_1\text{-C}_6$ alkyl), a substituted or unsubstituted monocyclic or bicyclic 5 to 10 membered heteroaryl(unsubstituted $\text{C}_1\text{-C}_6$ alkyl) or a substituted or unsubstituted monocyclic or bicyclic 3 to 10 membered heterocyclyl(unsubstituted $\text{C}_1\text{-C}_6$ alkyl). Examples of suitable mono-substituted amine groups include, but are not limited to $-\text{NH}(\text{methyl})$, $-\text{NH}(\text{isopropyl})$, $-\text{NH}(\text{cyclopropyl})$, $-\text{NH}(\text{phenyl})$, $-\text{NH}(\text{benzyl})$ and $-\text{NH}(\text{pyridine-3-yl})$.

[0160] In some embodiments, R^{7a} can be a substituted or unsubstituted di-substituted amine group. For example, R^{7a} 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).

[0161] In some embodiments, R^{7a} can be selected from a substituted or unsubstituted N-carbamyl, a substituted or unsubstituted C-amido and a substituted or unsubstituted N-amido.

[0162] In some embodiments, R^{7a} can be a substituted or unsubstituted C₃-C₁₀ cycloalkyl. In some embodiments, R^{7a} can be a substituted or unsubstituted monocyclic C₃-C₁₀ cycloalkyl. In other embodiments, R^{7a} 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.

[0163] In some embodiments, R^{7a} can be a substituted or unsubstituted C₆-C₁₀ spirocycloalkyl. In some embodiments, R^{7a} can be a substituted C₆-C₁₀ spirocycloalkyl. In other embodiments, R^{7a} 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.

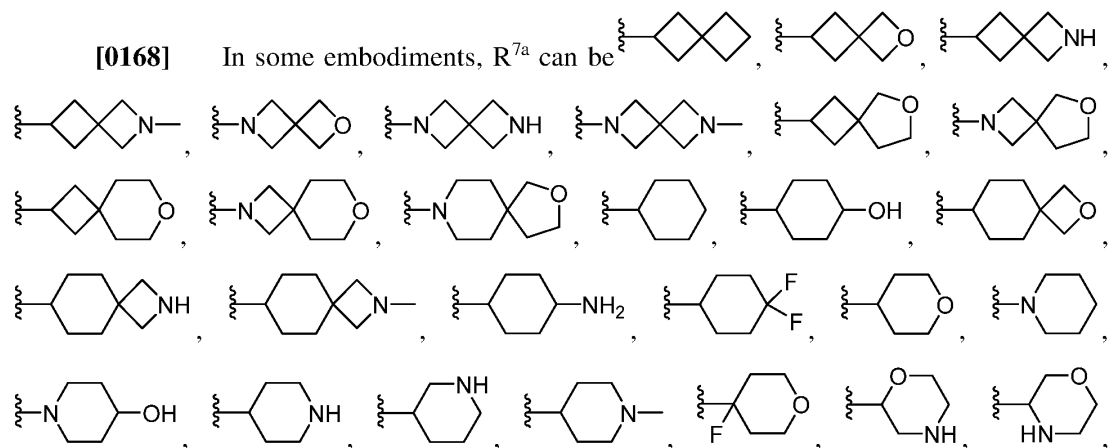
[0164] In some embodiments, R^{7a} can be a substituted or unsubstituted 3 to 10 membered heterocyclyl. In some embodiments, R^{7a} can be a substituted 3 to 10 membered heterocyclyl. In other embodiments, R^{7a} can be an unsubstituted 3 to 10 membered heterocyclyl. In some embodiments, R^{7a} can be a substituted or unsubstituted monocyclic 3 to 10 membered heterocyclyl. In other embodiments, R^{7a} 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.

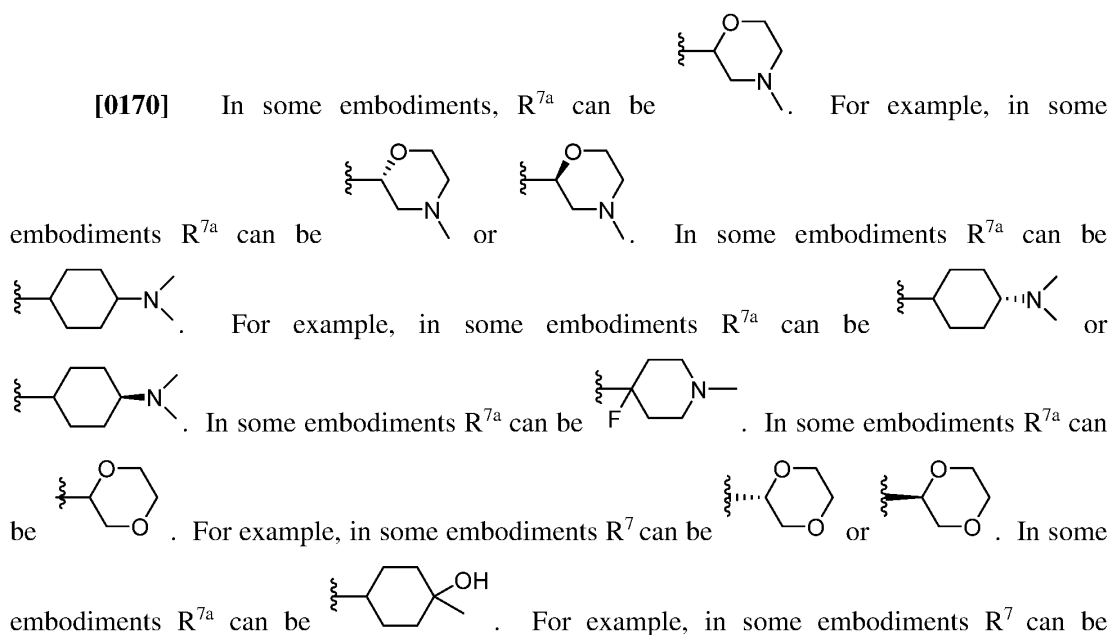
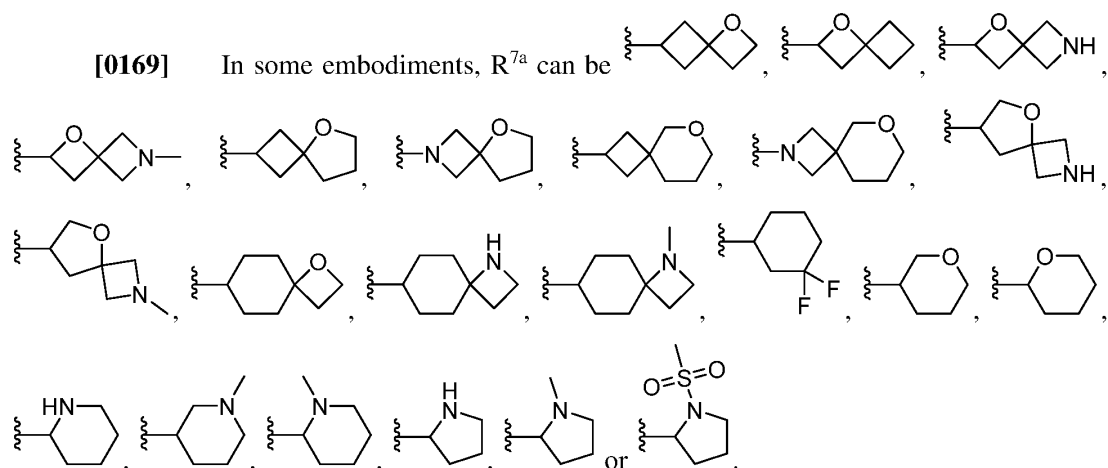
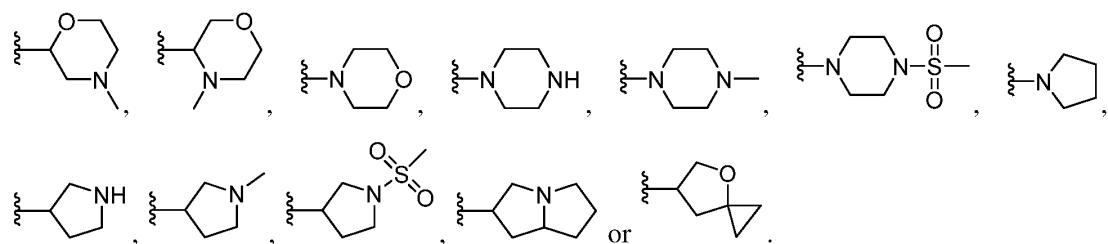
[0165] In some embodiments, R^{7a} can be a substituted or unsubstituted 6 to 10 membered spiro heterocyclyl. In some embodiments, R^{7a} can be a substituted 6 to 10 membered spiro heterocyclyl. In other embodiments, R^{7a} can be an unsubstituted 6 to 10 membered spiro heterocyclyl. In some embodiments, R^{7a} can be a substituted or unsubstituted azaspirohexane,

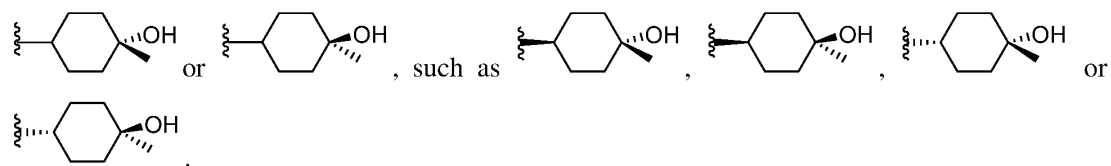
azaspiroheptane, azaspirooctane, oxaspirohexane, oxaspiroheptane, oxaspirooctane, diazaspirohexane, diazaspiroheptane, diazaspirooctane, dioxaspirohexane, dioxaspiroheptane, dioxaspirooctane, oxa-azaspirohexane, oxa-azaspiroheptane or oxa-azaspirooctane. Suitable substituted or unsubstituted 3 to 10 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.

[0166] In some embodiments, R^{7a} can be hydroxy or amino.

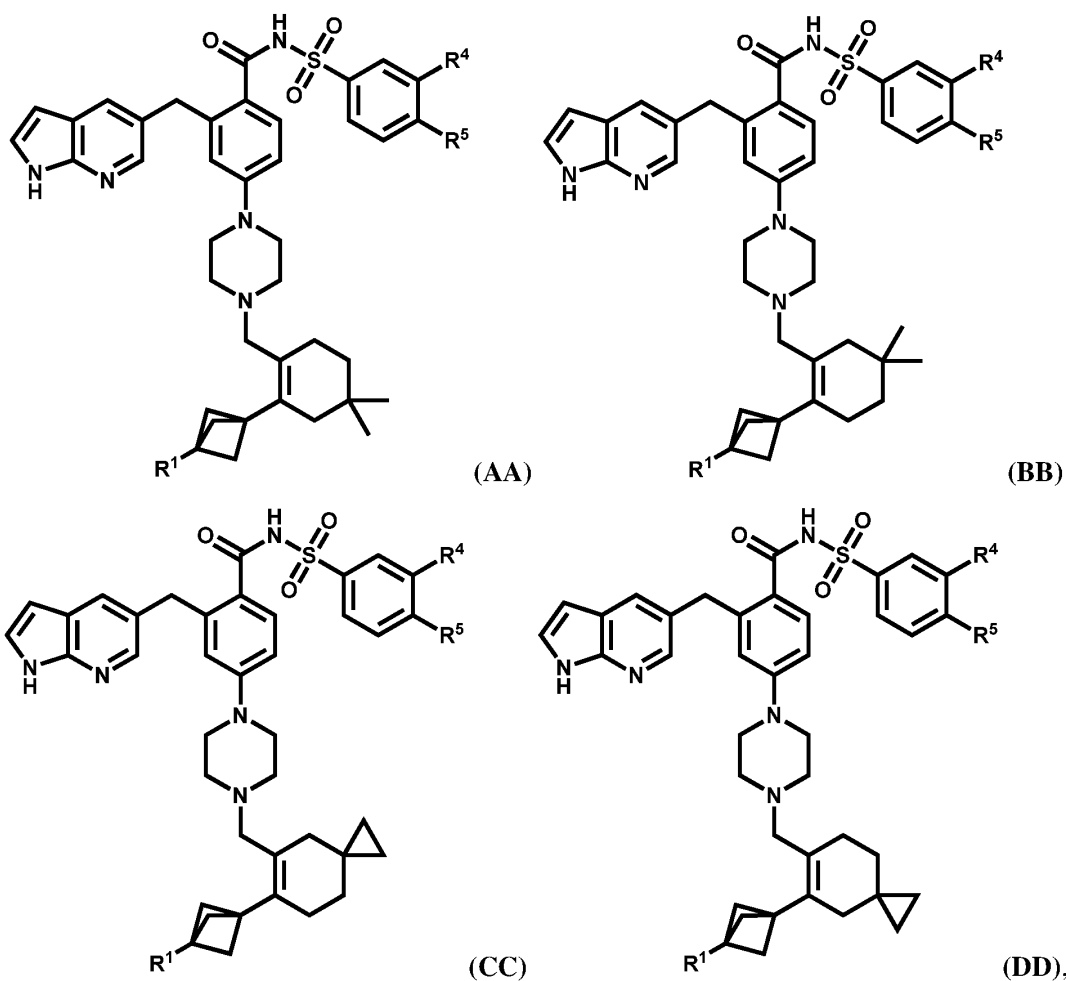
[0167] In some embodiments, R^{7a} can be unsubstituted. In other embodiments, R^7 can be substituted. In some embodiments, R^{7a} can be substituted with 1 or 2 substituents independently selected from an unsubstituted C_1 - C_6 alkyl (such as those described herein), an unsubstituted C_1 - C_6 alkoxy (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^{7a} can be substituted with 1 or 2 substituents independently selected from any of the aforementioned substituents.







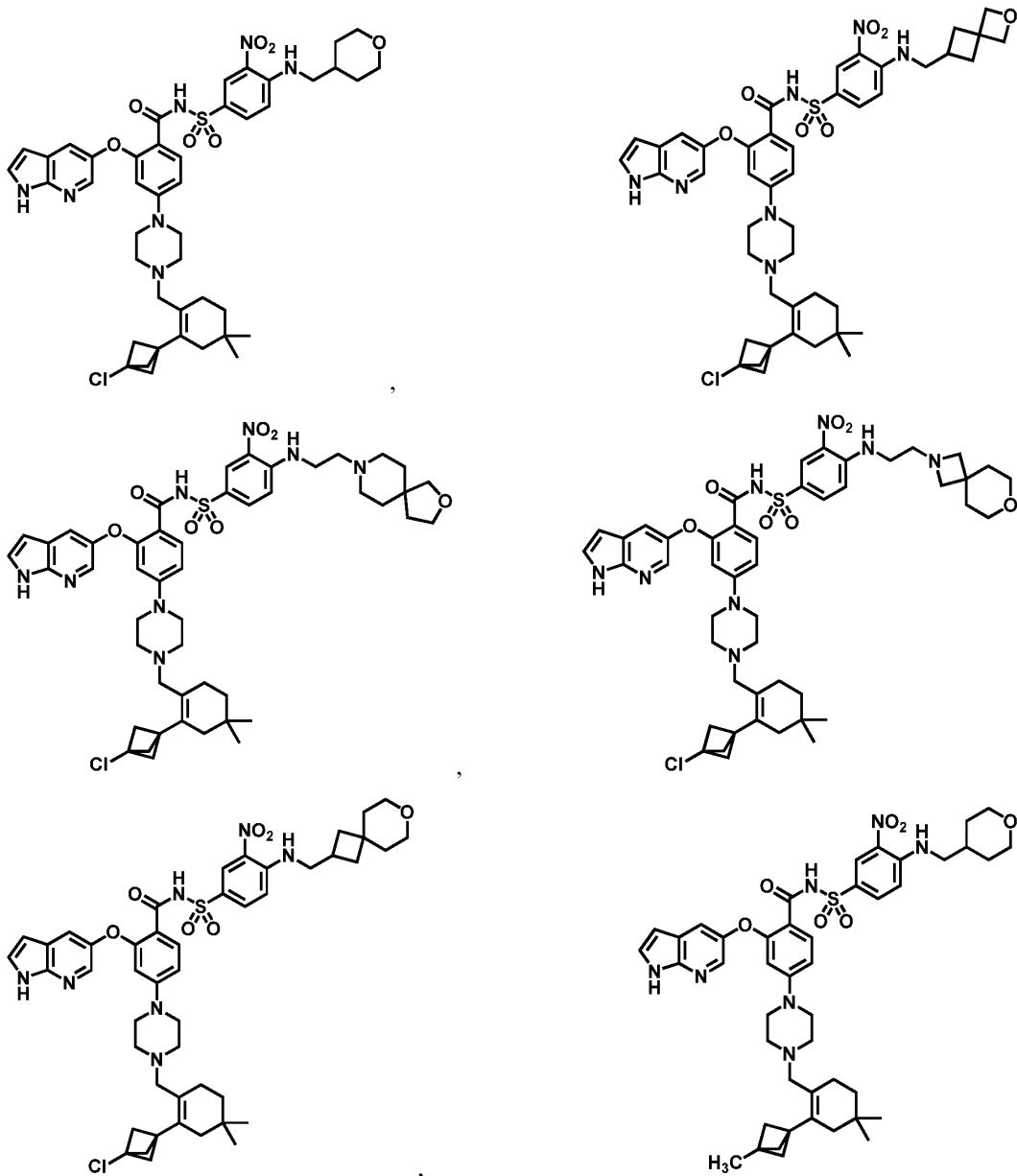
[0171] In some embodiments, Compound (B), or a pharmaceutically acceptable salt thereof, can be selected from a compound of Formula (AA), Formula (BB), Formula (CC) and Formula (DD):

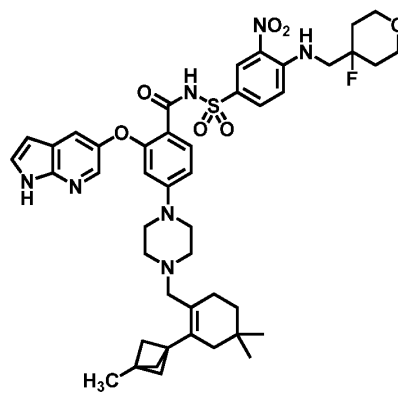
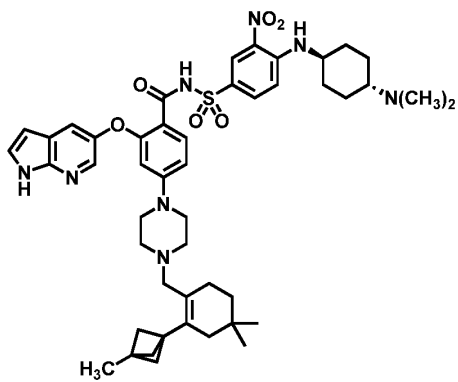
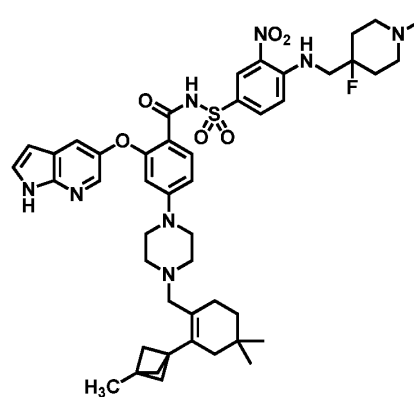
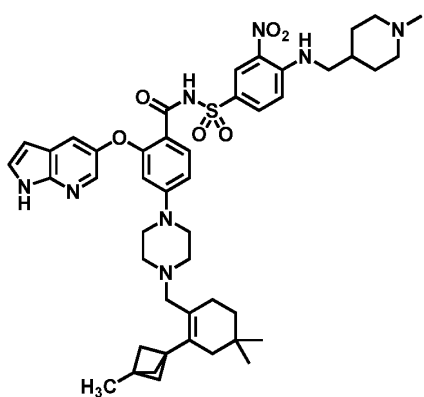
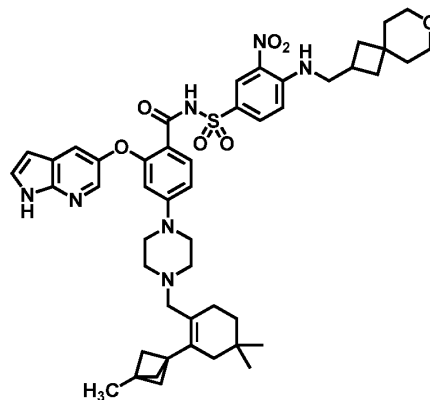
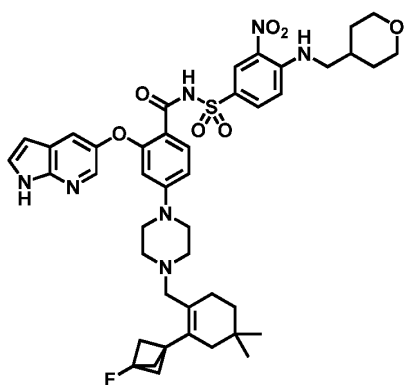


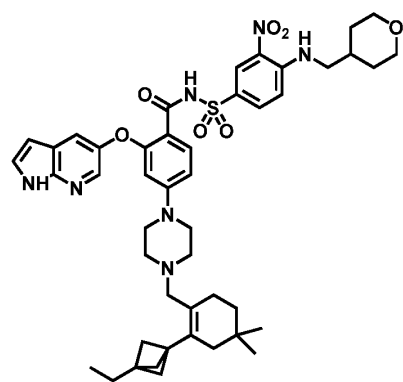
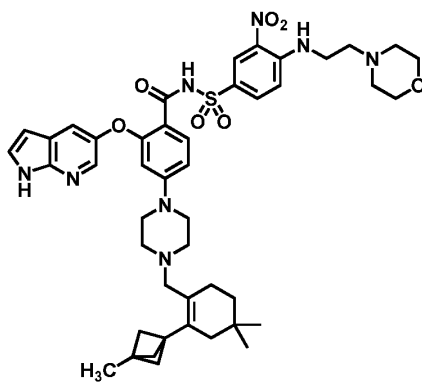
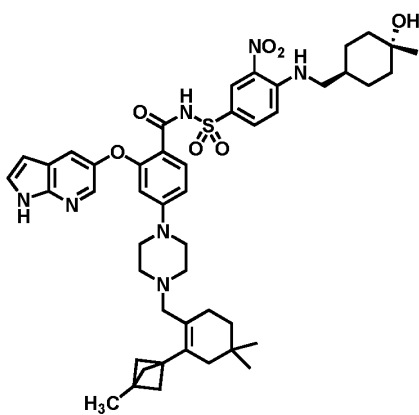
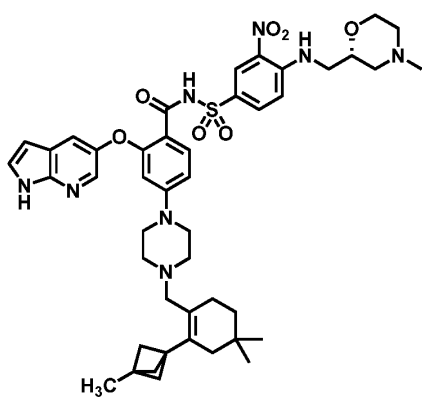
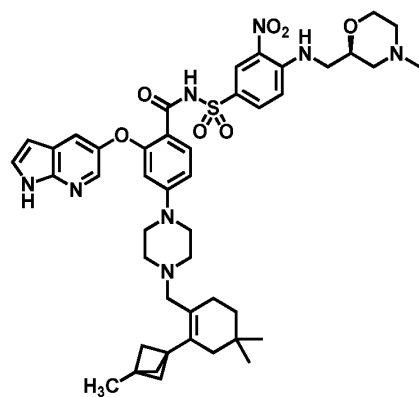
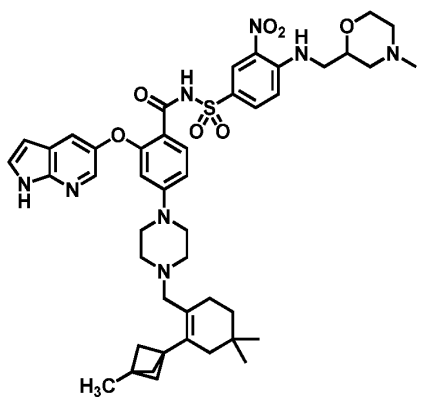
or pharmaceutically acceptable salts of any of the foregoing.

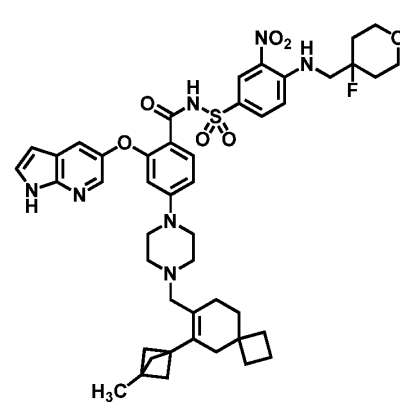
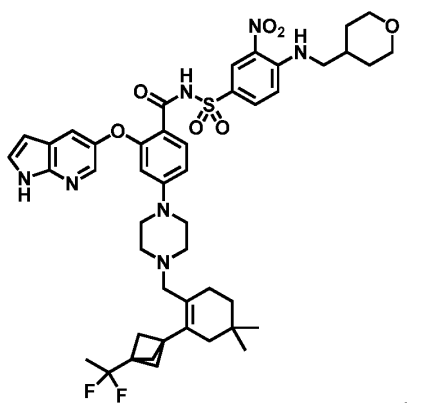
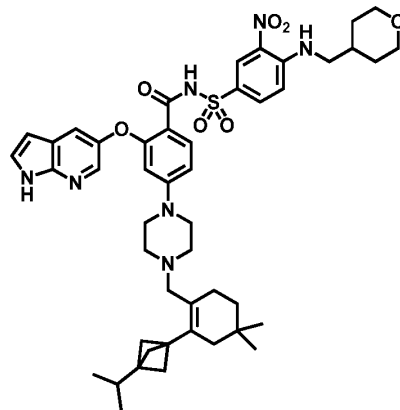
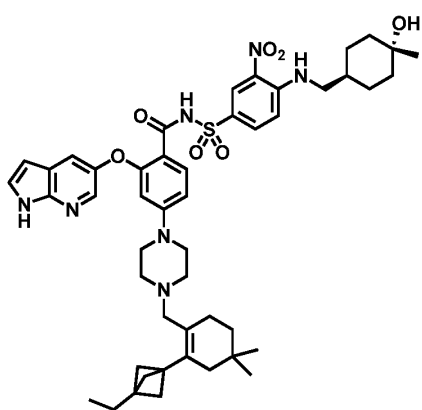
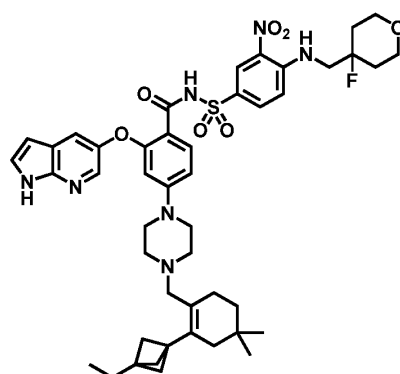
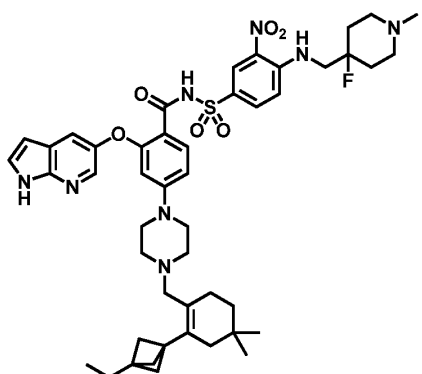
[0172] A non-limiting list of Bcl-2 inhibitors of Compound (B) are described herein, and include those provided in Figure 1.

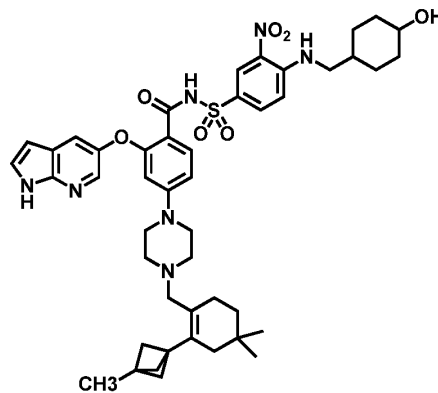
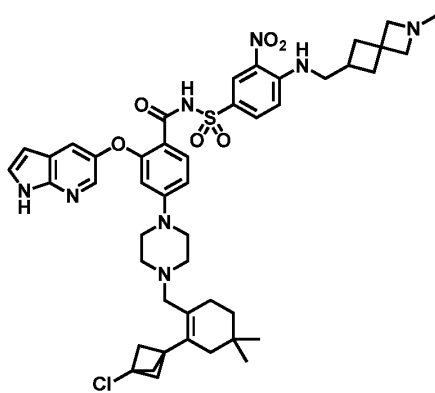
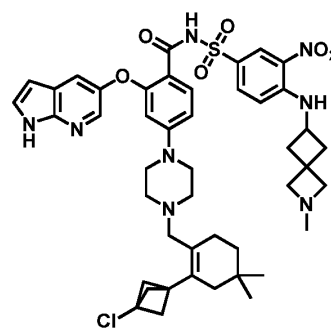
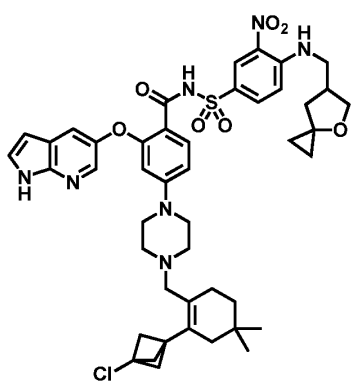
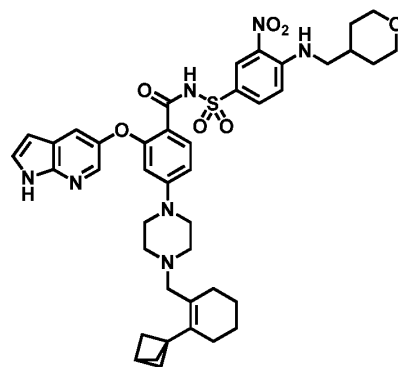
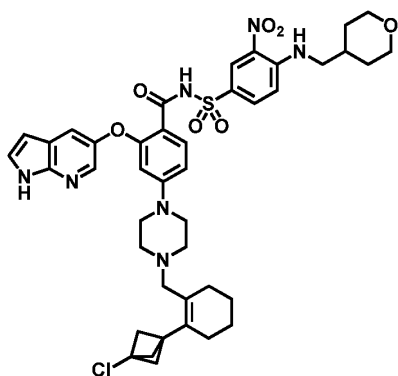
[0173] Examples of Compound (B) include the following:

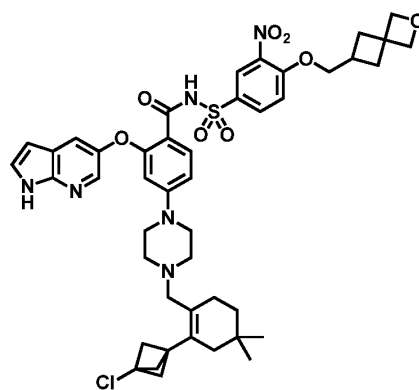
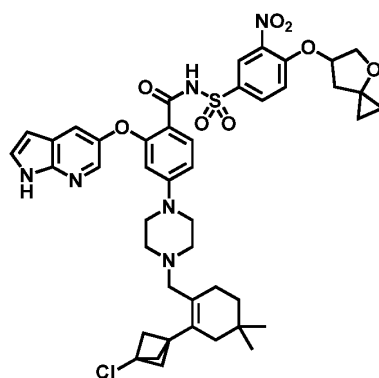
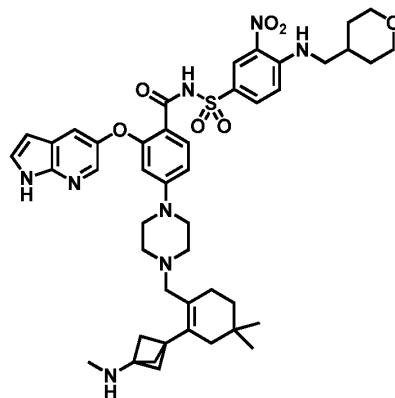


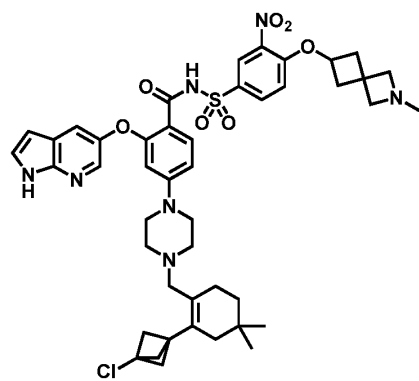
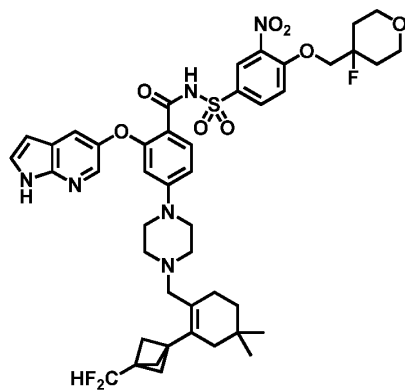
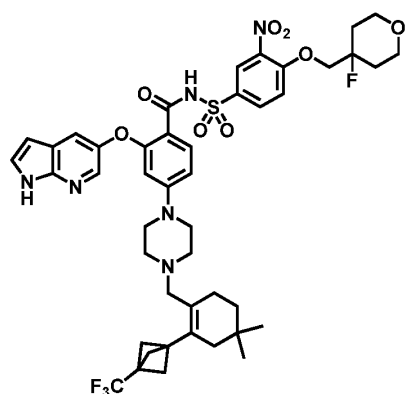
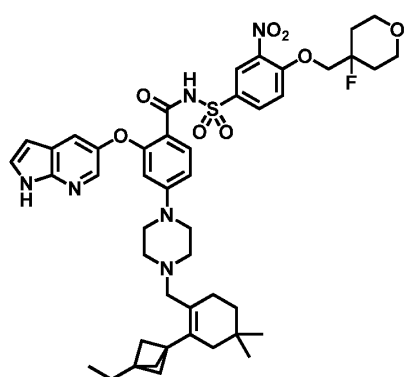
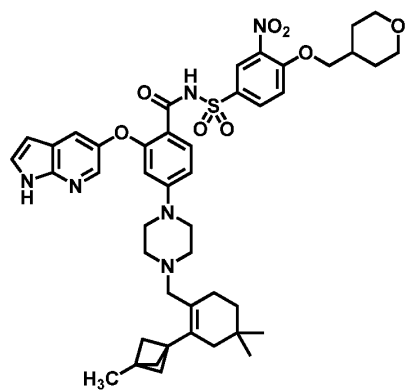
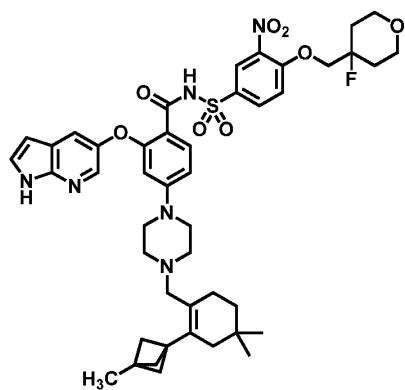


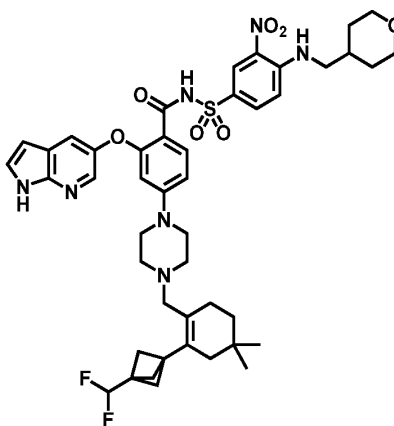
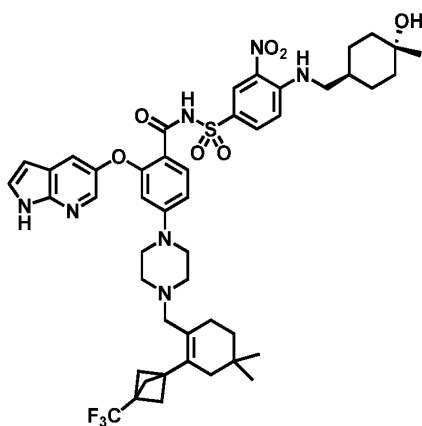
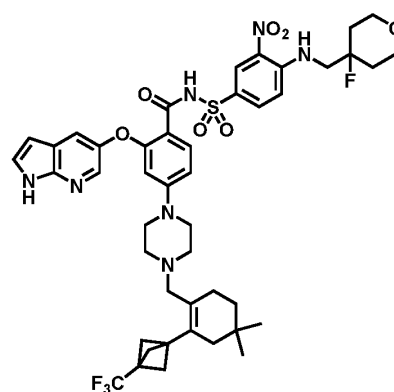
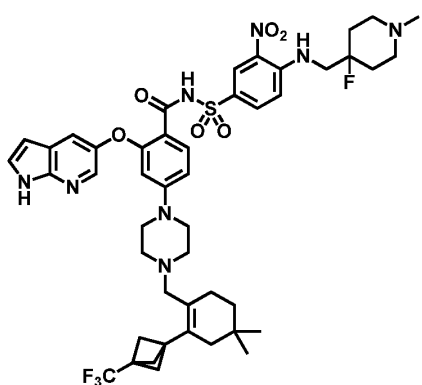
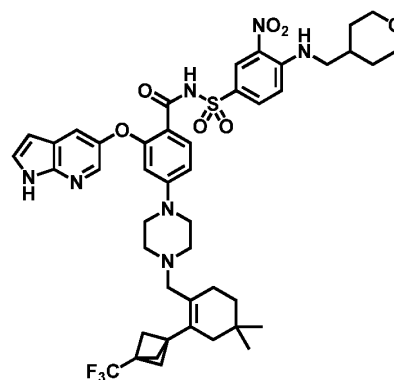
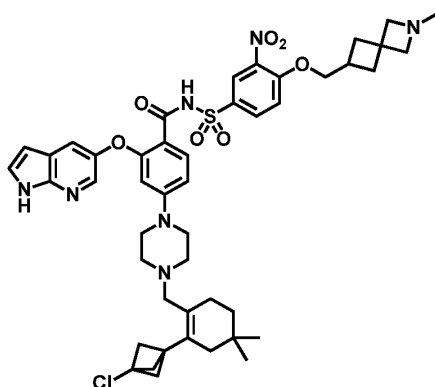


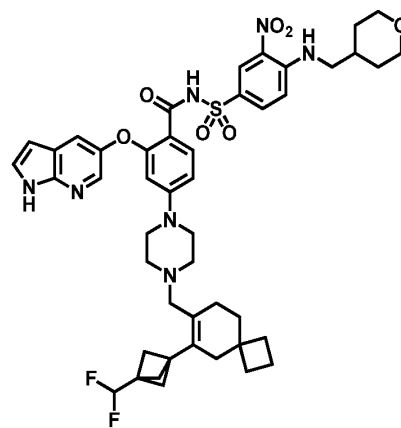
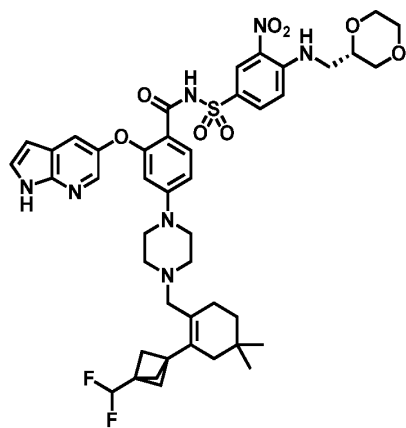
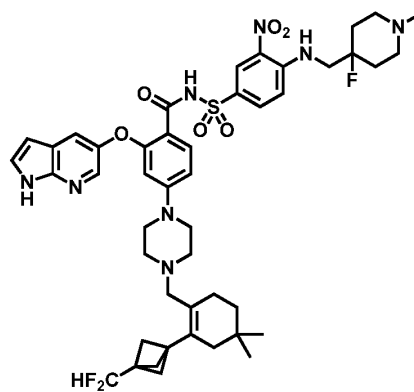
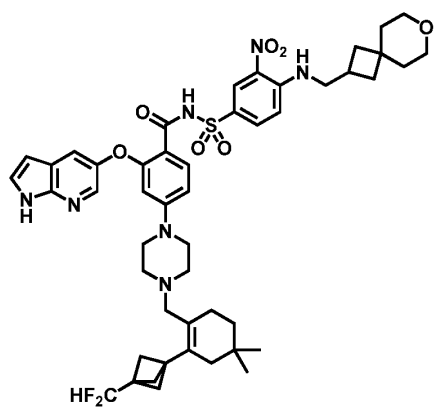
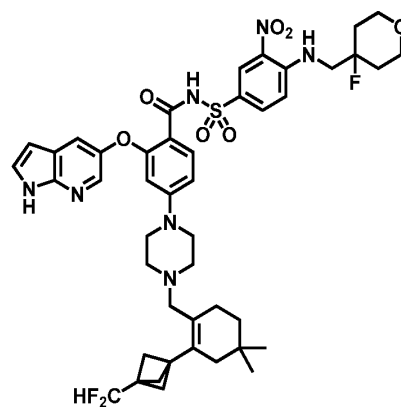
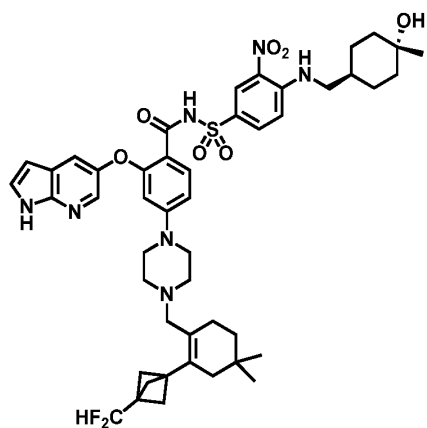


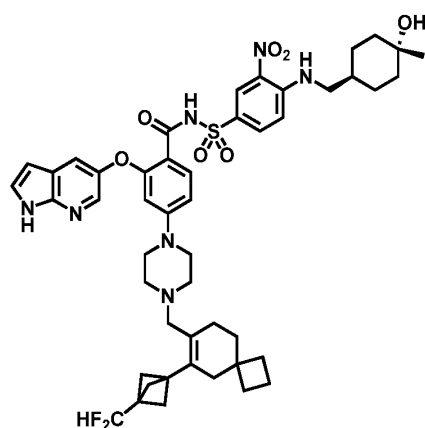




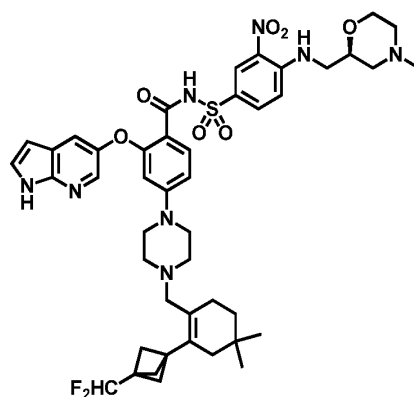








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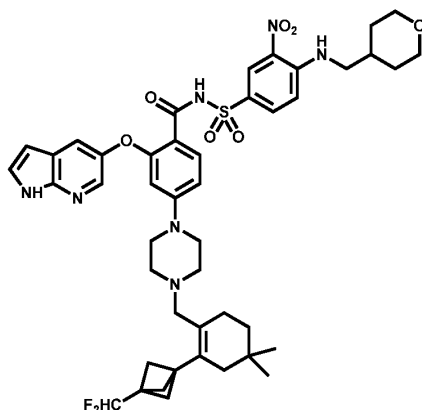


, or a

pharmaceutically acceptable salt of any of the foregoing.

[0174] Compound (B), 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 (B) is a Bcl-2 inhibitor.

[0175] Embodiments of combinations of Compound (A), including pharmaceutically acceptable salts and salt forms thereof (such as Form A and/or Form C), and Compound (B), including pharmaceutically acceptable salts thereof, are provided in Table 1. In Table 1, “A” represents Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and the numbers represent a compound as provided in Figure 1, including pharmaceutically acceptable salts thereof. For example, in Table 1, a combination represented by 1:A corresponds



to a combination of

and Compound (A), including

pharmaceutically acceptable salts of any of the foregoing.

Table 1

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

[0176] The order of administration of compounds in a combination described herein can vary. In some embodiments, Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and/or Compound (C), 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 and salt forms thereof, and/or Compound (C), 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 and salt forms thereof, and/or Compound (C), 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 and salt forms thereof, and/or Compound (C), 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 and salt forms thereof, and/or Compound (C), including pharmaceutically acceptable salts thereof, can be administered subsequent to the administration of all Compound (B), or a pharmaceutically acceptable salt thereof.

[0177] 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.

[0178] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts and salt forms 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. In other embodiments, a combination as described herein of Compound (C), 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 Compound (B), or a pharmaceutically acceptable salt thereof.

[0179] 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.

[0180] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in an additive effect. In other embodiments, a combination as described herein of Compound (C), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in an additive effect.

[0181] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in a synergistic effect. In other embodiments, a combination as described herein of Compound (C), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in a synergistic effect.

[0182] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in a strongly synergistic effect. In other embodiments, a combination as described herein of Compound (C), including pharmaceutically acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, can result in a strongly synergistic effect.

[0183] In some embodiments, a combination as described herein of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, is not antagonistic. In other embodiments, a combination as described herein of Compound (C), including pharmaceutically

acceptable salts thereof, and one or more of Compound (B), or pharmaceutically acceptable salts thereof, is not antagonistic.

[0184] 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.

[0185] 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

[0186] Compound (A), including pharmaceutically acceptable salts and salt forms thereof, can be provided in a pharmaceutical composition. Compound (B), including pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition.

Similarly, Compound (C), including pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition.

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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.

[0191] In some embodiments, Compounds (B), along with pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition that includes Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and/or Compound (C), 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 and salt forms thereof. In still other embodiments, Compounds (B), along with pharmaceutically acceptable salts thereof, can be administered in a pharmaceutical composition that is separate from a pharmaceutical composition that includes Compound (C), including pharmaceutically acceptable salts thereof.

[0192] 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.

[0193] 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.

[0194] 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 and salt forms thereof, can be administered orally. In some embodiments, Compound (C), including pharmaceutically acceptable salts thereof, can be administered orally. In some embodiments, Compound (A), including pharmaceutically acceptable salts and salt forms 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 and salt forms thereof, can be provided to a subject by a different route of administration as Compound (B), along with pharmaceutically acceptable salts thereof. In still other embodiments, Compound (C), 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 yet still other embodiments, Compound (C), 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.

[0195] 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.

[0196] 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

[0197] As provided herein, in some embodiments, a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms 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. In some embodiments, a combination of compounds that includes an effective amount of Compound (C),

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.

[0198] In some embodiments, the disease or condition can be selected from a breast cancer, a cervical cancer, an ovarian cancer, an uterine cancer, a vaginal cancer, a vulvar cancer, a bladder cancer, a brain cancer, a bone marrow cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor. In other embodiments, the disease or condition can be selected from a breast cancer, a cervical cancer, an ovarian cancer, an uterine cancer, a vaginal cancer, and a vulvar cancer.

[0199] 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.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] Various types of breast cancer are known. In some embodiments, the breast cancer can be ER positive breast cancer. In some embodiments, the breast cancer can be ER positive, HER2-negative breast cancer. In some embodiments, the breast cancer can be local breast cancer (as used herein, “local” breast cancer means the cancer has not spread to other areas of the body). In other embodiments, the breast cancer can be metastatic breast cancer. A subject can have a breast cancer that has not been previously treated.

[0204] In some cases, following breast cancer treatment, a subject can relapse or have reoccurrence of breast cancer. As used herein, the terms “relapse” and “reoccurrence” are used in their normal sense as understood by those skilled in the art. Thus, the breast cancer can be recurrent breast cancer. In some embodiments, the subject has relapsed after a previous treatment for breast cancer. For example, the subject has relapsed after receiving one or more treatments with a SERM, a SERD and/or aromatase inhibitor, such as those described herein.

[0205] Within ESR1, several amino acid mutations have been identified. Mutations in ESR1 have been proposed as playing a role in resistance. There are several therapies for inhibiting estrogen receptors, including selective ER modulators (SERM), selective ER degraders (SERD) and aromatase inhibitors. One issue that can arise from the aforementioned cancer therapies is the development of resistance to the cancer therapy. Acquired resistance to

cancer therapy, such as endocrine therapy, has been noted in nearly one-third of women treated with tamoxifen and other endocrine therapies. See Alluri et al., “Estrogen receptor mutations and their role in breast cancer progression” *Breast Cancer Research* (2014) 16:494. Researchers have suspected mutations in the estrogen receptor as one of the reasons for acquired resistance to cancer therapy, such as endocrine therapy. Thus, there is a need for compounds that can treat breast cancer wherein the cancer has one or more mutations within ESR1.

[0206] Some embodiments disclosed herein are relate to the use of a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, in the manufacture for a medicament for treating breast cancer in a subject in need thereof, wherein the breast cancer has at least one point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α). Other embodiments relate herein are directed to the use of a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, for treating breast cancer in a subject in need thereof, wherein the breast cancer has at least one point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α). Still other embodiments disclosed herein are relate to a method of treating breast cancer in a subject in need thereof with a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, wherein the breast cancer has at least one point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α).

[0207] In some embodiments, the mutation can be in the ligand binding domain (LBD) of ESR1. In some embodiments, one or more mutations can be at an amino acid selected from: A593, S576, G557, R555, L549, A546, E542, L540, D538, Y537, L536, P535, V534, V533, N532, K531, C530, H524, E523, M522, R503, L497, K481, V478, R477, E471, S463, F461, S432, G420, V418, D411, L466, S463, L453, G442, M437, M421, M396, V392, M388, E380, G344, S338, L370, S329, K303, A283, S282, E279, G274, K252, R233, P222, G160, N156, P147, G145, F97, N69, A65, A58 and S47. In some embodiments, one or more mutations

can be at an amino acid selected from: D538, Y537, L536, P535, V534, S463, V392 and E380. In some embodiments, one or more mutations can be at an amino acid selected from: D538 and Y537.

[0208] In some embodiments, one or more mutations can be selected from: K303R, D538G, Y537S, E380Q, Y537C, Y537N, A283V, A546D, A546T, A58T, A593D, A65V, C530L, D411H, E279V, E471D, E471V, E523Q, E542G, F461V, F97L, G145D, G160D, G274R, G344D, G420D, G442R, G557R, H524L, K252N, K481N, K531E, L370F, L453F, L466Q, L497R, L536H, L536P, L536Q, L536R, L540Q, L549P, M388L, M396V, M421V, M437I, M522I, N156T, N532K, N69K, P147Q, P222S, P535H, R233G, R477Q, R503W, R555H, S282C, S329Y, S338G, S432L, S463P, S47T, S576L, V392I, V418E, V478L, V533M, V534E, Y537D and Y537H.

[0209] Some embodiments disclosed herein are relate to the use of a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, in the manufacture for a medicament for treating breast cancer in a subject in need thereof, wherein the breast cancer does not include at least one point mutation (for example, a point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α)). Other embodiments relate herein are directed to the use of a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, for treating breast cancer in a subject in need thereof, wherein the breast cancer does not include has at least one point mutation, such as a point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α). Still other embodiments disclosed herein are relate to a method of treating breast cancer in a subject in need thereof with a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts and salt forms thereof, and an effective amount of one or more of Compound (B), or a pharmaceutically acceptable salt thereof, wherein the breast cancer does not include has at least one point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α) (for example, a point mutation within the Estrogen Receptor 1 (ESR1) that encodes Estrogen receptor alpha (ER α)).

[0210] As provided herein, several studies have shown that a potential cause of resistance in ER-positive breast cancer is due to acquired mutations in ESR1 due to endocrine therapy. In some embodiments, the subject had been previously treated with one or more selective ER modulators. For example, subject had been treated previously with one or more selected ER modulators selected from tamoxifen, raloxifene, ospemifene, bazedoxifene, toremifene and lasofoxifene, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the subject had been treated previously with one or more selective ER degraders, such as fulvestrant, (E)-3-[3,5-Difluoro-4-[(1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]prop-2-enoic acid (AZD9496), (R)-6-(2-(ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (elacestrant, RAD1901), (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid (Brilanestrant, ARN-810, GDC-0810), (E)-3-(4-((2-(2-(1,1-difluoroethyl)-4-fluorophenyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylic acid (LSZ102), (E)-N,N-dimethyl-4-((2-((5-((Z)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide (H3B-6545), (E)-3-(4-((2-(4-fluoro-2,6-dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylic acid (rintodestrant, G1T48), D-0502, SHR9549, ARV-471, 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol (giredestrant, GDC-9545), (S)-8-(2,4-dichlorophenyl)-9-(4-((1-(3-fluoropropyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (SAR439859), N-[1-(3-fluoropropyl)azetidin-3-yl]-6-[(6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl]pyridin-3-amine (AZD9833), OP-1250 and LY3484356, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the subject had been treated previously with one or more aromatase inhibitors. The aromatase inhibitors can be a steroidal aromatase inhibitor or a non-steroidal aromatase inhibitor. For example, the one or more aromatase inhibitors can be selected from (exemestane (steroidal aromatase inhibitor), testolactone (steroidal aromatase inhibitor); anastazole (non-steroidal aromatase inhibitor) and letrozole (non-steroidal aromatase inhibitor), including pharmaceutically acceptable salts of any of the foregoing.

[0211] In some embodiments, the breast cancer can be present in subject, wherein the subject can be a woman. As women approach middle-age, a woman can be in a stage of

menopause. In some embodiments, the subject can be a premenopausal woman. In other embodiments, the subject can be a perimenopausal woman. In still other embodiments, the subject can be a menopausal woman. In yet still other embodiments, the subject can be a postmenopausal woman. In other embodiments, the breast cancer can be present in a subject, wherein the subject can be a man. The serum estradiol level of the subject can vary. In some embodiments, the serum estradiol level (E2) of the subject can be in the range of >15 pg/mL to 350 pg/mL. In other embodiments, the serum estradiol level (E2) of the subject can be ≤ 15 pg/mL. In other embodiments, the serum estradiol level (E2) of the subject can be ≤ 10 pg/mL.

[0212] 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.

[0213] 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), (B) and/or (C), 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)

[0214] 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.

[0215] 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.

[0216] 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

[0217] 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.

Xenograft Tumor Models

[0218] Example 1: MCF-7 cells were grown in DMEM Medium supplemented with 15% heat inactivated fetal bovine serum at 37 °C in an atmosphere of 5% CO₂ in air. BALB/c nude mice were implanted subcutaneously on the 2nd right mammary fat pad with a single cell suspension of 95% viable tumor cells (1.5×10^7) in 200 μ L DMEM Matrigel mixture (1:1 ratio) without serum. When tumors reached approximately 172 mm³, animals were randomly distributed into treatment groups of 10 animals each and dosed orally, once a day for 21 days as follows: vehicle at the same volume as the single agent treatment; Compound A (alternatively referred to as “Compound (A)” in the specification and figures) at 10 mg/kg; Compound 5 at 200 mg/kg; and the combination treatment of Compound A 10 mg/kg) and Compound 5 (200 mg/kg). In addition, estradiol benzoate injections were given subcutaneously (40 μ g/ 20 μ L, twice weekly) to all treatment groups. 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 T₀ and C₀ are the mean tumor volumes of the treated and control animals at the start of the experiment. 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 2 and Table 2 illustrate that the combination of Compound A and Compound 5 is more effective in reducing tumor size than each compound alone. Compound A as a single agent or in combination with Compound 5 produced significant antitumor activity with TGI values of 81%, and 106% respectively. Compound 5 showed a minor antitumor activity with a TGI of 25%.

Table 2

COMPOUND	TGI % (DAY 21)	TUMOR REGRESSION % (DAY 21)
Compound 5	25	0
Compound A	81	0
Compound 5 + Compound A	106	11

[0219] Example 2: MCF-7 cells were grown in DMEM Medium supplemented with 15% heat inactivated fetal bovine serum at 37 °C in an atmosphere of 5% CO₂ in air. BALB/c nude mice were implanted subcutaneously on the 2nd right mammary fat pad with a single cell suspension of 95% viable tumor cells (1.5×10^7) in 200 μ L DMEM Matrigel mixture (1:1 ratio) without serum. When tumors reached approximately 226 mm³, animals were randomly distributed into treatment groups of 8 animals each and dosed orally, once a day for 24 days as follows: vehicle at same volume as the single agent treatment; Compound A at 5 mg/kg; Compound 5 at 200 mg/kg; and the combination treatment of Compound A (5 mg/kg) and Compound 5 (200 mg/kg). In addition, estradiol benzoate injections were given subcutaneously (40 μ g/ 20 μ L, twice weekly) to all treatment groups. 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. TGI and Tumor regression values were calculated using the equations provided in Example 1. In Figure 3, the top line (indicated with circles) represents the data for Vehicle, and the second line from the top (indicated with circles) represents data for Compound 5 (200 mg/kg). Figure 3 and Table 3 illustrate that the combination of Compound A and Compound 5 is more effective in reducing tumor size than each compound alone. Compound A as a single agent or in combination with Compound 5 produced significant antitumor activity with TGI values of 108%, and 143% respectively. Compound 5 showed a minor antitumor activity with TGI of 46%.

Table 3

COMPOUND	TGI % (DAY 24)	TUMOR REGRESSION % (DAY 24)
Compound 5	46	0
Compound A	108	8
Compound 5 + Compound A	143	44

[0220] Example 3: MCF-7 cells were grown in DMEM Medium supplemented with 15% heat inactivated fetal bovine serum at 37 °C in an atmosphere of 5% CO₂ in air. BALB/c nude mice were implanted subcutaneously on the 2nd right mammary fat pad with a single cell suspension of 95% viable tumor cells (1.5×10^7) in 200 μ L DMEM Matrigel mixture (1:1 ratio) without serum. When tumors reached approximately 143 mm³, animals were randomly distributed into treatment groups of 10 animals each and dosed orally, once a day for 28 days as follows: vehicle at same volume as the single agent treatment; Compound A at 10 mg/kg; Compound 6 at 50 mg/kg; and the combination treatment of Compound A (10 mg/kg) and Compound 6 (50 mg/kg). In addition, estradiol benzoate injections were given subcutaneously (40 μ g/ 20 μ L, twice weekly) to all treatment groups. 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. TGI and Tumor regression values were calculated using the equations provided in Example 1. Figure 4 and Table 4 illustrate that the combination of Compound A and Compound 6 is more effective in reducing tumor size than each compound alone. Compound A as a single agent or in combination with Compound 6 produced significant antitumor activity with TGI values of 120%, and 135% respectively. Compound 6 showed a minor antitumor activity with TGI of 18%.

Table 4

COMPOUND	TGI % (DAY 29)	TUMOR REGRESSION % (DAY 29)
Compound 6	18	-
Compound A	120	33
Compound 6 + Compound A	135	58

[0221] The data provided herein demonstrates that a combination of a SERD inhibitor and a Bcl-2 inhibitor described herein can be used to treat a disease or condition described herein.

[0222] 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.