FIG. 6

Abstract: Provided herein, inter alia, are compositions and methods useful for treating hyperproliferative diseases, including cancer and non-malignant hyperproliferative diseases.
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COMPOSITIONS AND METHODS FOR TREATING CANCER

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/235,453, filed September 30, 2015, which is incorporated herein by reference in its entirety and for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with government support under Grant Nos. DAMD17-03-1-0381 awarded by the United States Army, Medical Research and Materiel Command and CDMRP LC090297 awarded by the Department of Defense. The government has certain rights in the invention.

BACKGROUND

[0003] Lung cancer is the leading cause of cancer death in women and men in the U.S. It is estimated that there will be more than 230,000 patients diagnosed with lung cancer this year, with more than 160,000 deaths, and non-small cell lung cancer (NSCLC) will account for more than three quarters of these cases (1). Survival rates of NSCLC, the predominant type of lung cancer are unacceptably low, and new approaches to treat and prevent this disease are urgently needed.

[0004] The poor prognosis of advanced non-small cell lung cancer (NSCLC) is due, in part, to emergence of tumor resistance to chemotherapy (1). Recent data indicate that human tumors contain a small subset of cancer stem cells (CSC) responsible for drug resistance and tumor maintenance (2-5). If such minute subsets of CSC drive tumor formation and drug resistance, therapies targeting the bulk tumor mass but not CSC may fail.

[0005] Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with development of hamartomatous lesions in many organs (71-74). Some lesions grow progressively and require clinical intervention. TSC is due to mutations in either TSC1 or TSC2 genes. TSC1 (hamartin)/TSC2 (tuberin) protein complexes serve a critical role in negatively regulating mTOR complex 1 (mTORC1) which exerts downstream effects on cell transcription, translation,
metabolism and proliferation. mTORC1 is constitutively active in cells lacking either TSC1 or TSC2 and in hamartomas of TSC patients. New therapeutic approaches to control the growth of TSC-related proliferative diseases are urgently needed.

[0006] Breast cancer is a worldwide health concern with about 1,000,000 million new cases each year. In the clinic, endocrine therapy is an important intervention in women with breast cancers that express estrogen receptor (ER), and treatment with tamoxifen has enhanced patient survival. The success of endocrine therapy is dependent on tight regulation of breast cell growth by steroids and growth factor receptors (27) most patients eventually stop responding to anti-estrogen therapy. Resistance to tamoxifen (TAM) and aromatase inhibitors represents a major drawback to treatment of hormone-dependent breast cancer, and new options for endocrine therapy are urgently needed to reverse this outcome (28-30).

[0007] At diagnosis, about 70% of breast cancer patients have tumors that express estrogen receptors (ER) and/or progesterone receptors (PR). Patients with ER+ tumors can be treated with hormonal therapy such as tamoxifen which was the first effective targeted therapy for breast cancer. However, all advanced ER+ tumors eventually develop endocrine resistance, and there is an urgent need for new interventions to stop endocrine resistance.

[0008] Subversion of growth factor receptors often occurs in malignancy, and members of the HER family are often implicated in cancer (31). Overexpression of HER-2 or related HER receptors occurs in two-thirds of sporadic breast tumors, while HER-2 over-expression/amplification is found in 25-30% of breast cancers (30-33), is generally a marker of poor prognosis (7), and it associates with failure of antiestrogen therapy in the clinic (28, 34-38, 69-72). It is generally held that biologic activity of estrogen in breast cells is mediated by its binding with high-affinity ER in the nucleus (27, 39).

[0009] Two systems that transmit extracellular signals into the machinery of the cell nucleus are the signaling pathways that activate nuclear factor κB (NF-κB) and estrogen receptor (ER). These two transcription factors induce expression of genes that control cell fates, including proliferation and cell death (apoptosis). Estrogen receptor (ER) and nuclear factor-kappaB (NFκB), a major regulator of pathways central to malignant progression, are known to be mutually inhibitory at several molecular levels. Some ER-positive breast cancers SERMS such as tamoxifen may
stimulate cell growth and survival (62). Recent investigations elucidated a previously unsuspected effect of ER (63).

[0010] The aromatic plant known as feverfew (Tanacetum parthenium) contains a family of compounds known as sesquiterpene lactones, particularly parthenolide. Disclosed herein, inter alia, are solutions to these and other problems in the art.

BRIEF SUMMARY OF THE INVENTION

[0011] In a first aspect is provided a compound, or a pharmaceutically acceptable salt thereof, having the formula:

![Chemical structure](image)

(I). $L^1$ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. $L^2$ is a bond, substituted or unsubstituted heteroalkylene, $\text{--NH--}$, or $\text{--O--}$. $R^1$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. $R^2$ is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0012] In another aspect is provided a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

[0013] In another aspect is provided a method of treating cancer in a patient in need of the treatment, the method including administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments) to the patient.

[0014] In another aspect is provided a method of treating a non-malignant hyperproliferative disease in a patient in need of the treatment, the method including administering a therapeutically
effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments) to the patient.

[0015] In another aspect is provided a method of inhibiting cancer cell growth or survival including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

[0016] In another aspect is provided a method of modulating the level of activity of NF-κB in a cell including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

[0017] In another aspect is provided a method of modulating the level of activity of TSC1 in a cell including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

[0018] In another aspect is provided a method of modulating the level of activity of TSC2 in a cell including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

[0019] In another aspect is provided a method of modulating the level of activity of mTOR in a cell including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

BRIEF DESCRIPTION OF THE DRAWINGS


[0021] FIG. 2: Parthenolides inhibit proliferation of MDAMB231 triple negative breast cancer cells. Parthenolide analogues JD211-JD216 were tested for antitumor activity using triple-negative breast cancer cells (MDA-MB-231) in vitro. Doses ranged from 0-50 micromolar and tumor cell proliferation was assessed using established methods. Antitumor effects and particularly JD213, JD214, JD215 and JD216 were greater than that observed with dimethylamino-parthenolide (DMAPT). This was most notable at lower compound dose at 10 micromolar. These findings indicate that novel compounds such as JD213, JD214, JD215 and JD216 are more promising.
candidates for anticancer therapy then DMAPT because these cancers are more sensitive to compounds other than DMAPT.

[0022] FIG. 3. H1975 NSCLC Cell proliferation (% control) as a function of parthenolide analog dose (uM). Reagents: JD200, JD201, JD202, JD203, JD211, JD212, JD213, JD214, JD215, JD216. Correlation of observed curve to reagent is indicated by arrow.

[0023] FIG. 4. A549 NSCLC Cell proliferation (% control) as a function of parthenolide analog dose (uM). Reagents: JD200, JD201, JD202, JD203, JD211, JD212, JD213, JD214, JD215, JD216. Correlation of observed curve to reagent is indicated by arrow.

[0024] FIG. 5. Selected parthenolide analogs inhibit proliferation of MDA-MD-231 triple-negative breast cancer cells. Cell proliferation (% control) as a function of parthenolide analog dose (uM). Reagents: JD200, JD201, JD202, JD203, JD211, JD212, JD213, JD214, JD215, JD216. Correlation of observed curve to reagent is indicated by arrow.

[0025] FIG. 6. PTL analog JD216 does not significantly alter the proliferation of human umbilical vein endothelial cells (HUVEC) in vitro when dosed at 100-nM or at doses up to 10-uM (not shown). In contrast, PTL analog JD216 does effectively suppress MDA-MB-231 human triple-negative breast cancer cell proliferation at a 100-nM dose (0.1-uM) in vitro as compared to control (P<0.001).

DETAILED DESCRIPTION

I. Definitions

[0026] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0027] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH$_2$O- is equivalent to -OCH$_2$-.
The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched non-cyclic carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C₁-C₁₀ means one to ten carbons).

Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds (alkenyl) or triple bonds (alkynyl). An alkenyl may include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. An alkynyl may include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotlyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethylvinyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated.

The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylen) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylen” is a shorter chain alkyl or alkylen group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched non-cyclic chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized). The heteroatom(s) (e.g., O, N, P, S, and Si) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl
group is attached to the remainder of the molecule. Examples include, but are not limited
to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂,
-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=CH-N-OCH₃, -CH=CH-N(CH₃)₂-CH₃,
-O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. A heteroalkyl moiety may include one
heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different
carbonyls of another term, means, unless otherwise stated, a heteroalkyl including at least one double bond. A heteroalkyl may optionally include more than one double bond and/or one or more triple bonds in additional to the one or more double bonds. The term “heteroalkynyl,” by itself or in combination with
another term, means, unless otherwise stated, a heteroalkyl including at least one triple bond. A heteroalkynyl may optionally include more than one triple bond and/or one or more double bonds in additional to the one or more triple bonds.

[0031] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless
otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited
by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking
groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)₂R'- represents
both -C(O)₂R'- and -R'C(O)₂-. As described above, heteroalkyl groups, as used herein, include those
groups that are attached to the remainder of the molecule through a heteroatom, such
as -C(O)R', -C(O)NR', -NR'R', -OR', -SR', and/or -SO₂R'. Where “heteroalkyl” is recited, followed
by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific
heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R' or the like.

[0032] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, non-aromatic cyclic versions of "alkyl" and "heteroalkyl," respectively, wherein the carbons making up the ring or rings do not necessarily need to be bonded to a hydrogen due to all carbon valencies participating in bonds with non-hydrogen atoms.

Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, 3-hydroxy-cyclobut-3-enyl-1,2, dione, 1H-1,2,4-triazolyl-5(4H)-one, 4H-1,2,4-triazolyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. A heterocycloalkyl moiety may include one ring heteroatom (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include two optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include three optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include four optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include five optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include up to 8 optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. The terms "cycloalkenyl" and "cycloalkynyl," by themselves or in combination with other terms, mean, unless otherwise stated, non-aromatic cyclic versions of "alkenyl" and "alkynyl," respectively. The terms "heterocycloalkenyl" and "heterocycloalkynyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "heteroalkenyl" and "heteroalkynyl," respectively.
[0033] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0034] The term “acyl” means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0035] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalinyll,
3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene” and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Non-limiting examples of heteroaryl groups include pyridinyl, pyrimidinyl, thiophenyl, thienyl, furanyl, indolyl, benzoazadiazolyl, benzodioxolyl, benzodioxanylyl, thianaphthanyl, pyrrolopyridinyl, indazolyl, quinolinyl, quinoxalinyl, pyridopyrazinyl, quinazolinonyl, benzoisoxazolyl, imidazopyridinyl, benzofuranyl, benzothienyl, benzothiophenyl, phenyl, naphthyl, biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furylthienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, isoquinolyl, thiadiazolyl, oxadiazolyl, pyrrolyl, diazolyl, triazolyl, tetrazolyl, benzothiadiazolyl, isothiazolyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, benzotriazolyl, benzoxazolyl, or quinolyl. The examples above may be substituted or unsubstituted and divalent radicals of each heteroaryl example above are non-limiting examples of heteroarylene.

[0036] A fused ring heterocycloalkyl-aryl is an aryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-heteroaryl is a heteroaryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-cycloalkyl is a heterocycloalkyl fused to a cycloalkyl. A fused ring heterocycloalkyl-heterocycloalkyl is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring heterocycloalkyl-aryl, fused ring heterocycloalkyl-heteroaryl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substituents described herein.

[0037] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0038] The term “alkylsulfonyl,” as used herein, means a moiety having the formula -S(O)₂-R', where R' is a substituted or unsubstituted alkyl group as defined above. R’ may have a specified number of carbons (e.g., “C₁-C₄ alkylsulfonyl”).

[0039] Each of the above terms (e.g., “alkyl”, “heteroalkyl”, “cycloalkyl”, “heterocycloalkyl”, “aryl”, and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.
Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkylnyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR',

=N-OR', =NR'R", =SR', =halogen, =SiR'R"R"", =OC(O)R', =C(O)R', =CO2R', =CONR'R", =OC(O)NR'R" , =NR"C(O)R', =NR'C(O)NR"R", =NR"C(O)2R', =NR-C(NR'R"R")=NR"", =NR-C(NR'R")=NR"", =S(O)R', =S(O)2R', =S(O)2NR'R", =NRSO2R', =NR'NR"R"", =ONR'R", =NR'CR"NR"R"", =CN, =NO2, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), triphosphate (or derivatives thereof), in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrroldinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF3 and -CH2CF3) and acyl (e.g., -C(O)CH3, -C(O)CF3, -C(O)CH2OCH3, and the like).

Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', =NR'R", =SR', =halogen, =SiR'R"R"", =OC(O)R', =C(O)R', =CO2R', =CONR'R", =OC(O)NR'R", =NR"C(O)R', =NR'-C(O)NR"R", =NR"C(O)2R', =NR-C(NR'R"R")=NR"", =NR-C(NR'R")=N

R"", =S(O)R', =S(O)2R', =S(O)2NR'R", =NRSO2R', =NR'NR"R"", =ONR'R", =NR'CR"NR"R"", =CN, =NO2, =R', =N3, =CH(Ph)2, fluoro(C1-C4)alkoxy, and fluoro(C1-C4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"", and R"" are preferably independently selected from hydrogen,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0042] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0043] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(=O)-(CRR')₉-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)₉-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CRR')₉-X'- (C"R"R")₉-Y-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'. The substituents R, R', R'', and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.
As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include, oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF₃, -CH₂F, -CHF₂, -CCl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NH₂, -NHC=(O) NNH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, -OCH₂F, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo,
halogen, -CF₃, -CH₂F, -CHF₂, -CCl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NH₂, -NHC=(O) NNH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, -OCH₂F, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CF₃, -CH₂F, -CHF₂, -CCl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -N O₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NH₂, -NHC=(O) NNH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, -OCH₂F, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, , and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo,
halogen, -CF₃, -CH₂F, -CHF₂, -CCl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NH₂, -NHC=(O) NNH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, -OCH₂F,
unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0046] A “size-limited substituent” or “size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0047] A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0048] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.
[0049] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C1-C20 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C1-C20 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C3-C8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C6-C10 arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0050] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C1-C8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C1-C8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C3-C7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C6-C10 arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section below.
The term “pharmaceutically acceptable salts” is meant to include salts of the active compunds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al., Journal of Pharmaceutical Science 66:1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.
The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

As used herein, the term “salt” refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and
(L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0058] As used herein, the term “isomers” refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0059] The term “tautomer,” as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0060] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0061] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0062] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by $^{13}$C- or $^{14}$C-enriched carbon are within the scope of this invention.

[0063] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ($^3$H), iodine-125 ($^{125}$I), or carbon-14 ($^{14}$C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0064] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.
The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[nt]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C1-C20 alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C1-C20 alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as “R-substituted.” Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

The terms “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement, remission, diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient, slowing in the rate of degeneration or decline, making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters, including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, certain methods herein treat hyperproliferative disorders, such as cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or non-malignant hyperproliferative diseases (e.g. hamartomatous lesion,
angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma). For example certain methods herein treat cancer by decreasing or reducing or preventing the occurrence, growth, metastasis, or progression of cancer or by decreasing or reducing or preventing a symptom of cancer. Symptoms of cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) would be known or may be determined by a person of ordinary skill in the art. The term “treating” and conjugations thereof, include prevention of an injury, pathology, condition, or disease (e.g. preventing the development of one or more symptoms of cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer).

[0068] An “effective amount” is an amount sufficient to accomplish a stated purpose (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce one or more symptoms of a disease or condition). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An “activity decreasing amount,” as used herein, refers to an amount of antagonist (inhibitor) required to decrease the activity of an enzyme or protein relative to the absence of the inhibitor (antagonist). An “activity increasing amount,” as used herein,
refers to an amount of agonist (activator) required to increase the activity of an enzyme or protein relative to the absence of the activator (agonist). A "function disrupting amount," as used herein, refers to the amount of antagonist (inhibitor) required to disrupt the function of an enzyme or protein relative to the absence of the inhibitor (antagonist). A "function increasing amount," as used herein, refers to the amount of agonist (activator) required to increase the function of an enzyme or protein relative to the absence of the activator (agonist). The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) means that the disease (e.g. cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, a symptom of a disease or condition associated with an increase in NFκB activity may be a symptom that results (entirely or partially) from an increase in NFκB activity (e.g. increase in NFκB phosphorylation or activity of phosphorylated NFκB or activity of NFκB or increase in activity of an NFκB signal transduction or signaling pathway). As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a disease associated with increased NFκB activity or NFκB pathway activity (e.g. phosphorylated NFκB activity or pathway), may be treated with an agent (e.g. compound as described herein) effective for decreasing the level of activity of NFκB activity or
NFκB pathway or phosphorylated NFκB activity or pathway. For example, a disease associated with phosphorylated NFκB, may be treated with an agent (e.g. compound as described herein) effective for decreasing the level of activity of phosphorylated NFκB or a downstream component or effector of phosphorylated NFκB. For example, a disease associated with NFκB, may be treated with an agent (e.g. compound as described herein) effective for decreasing the level of activity of NFκB or a downstream component or effector of NFκB.

[0070] “Control” or “control experiment” is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects.

[0071] “Contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated, however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture. The term “contacting” may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme (e.g. NFκB, phosphorylated NFκB, mTOR, mTORC1, TSC1, TSC2, or component of NFκB pathway, phosphorylated NFκB pathway, pathway activated by NFκB phosphorylation, mTOR pathway, mTORC1 pathway, TSC1 pathway, or TSC2 pathway). In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g. NFκB pathway, phosphorylated NFκB pathway, pathway activated by NFκB phosphorylation, mTOR pathway, mTORC1 pathway, TSC1 pathway, or TSC2 pathway).

[0072] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor (e.g. antagonist) interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In some embodiments inhibition refers to reduction of a disease or symptoms of
disease. In some embodiments, inhibition refers to a reduction in the activity of a signal transduction pathway or signaling pathway. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In some embodiments, inhibition refers to a decrease in the activity of a signal transduction pathway or signaling pathway (e.g. NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway). Thus, inhibition may include, at least in part, partially or totally decreasing stimulation, decreasing or reducing activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein increased in a disease (e.g. level of NFκB activity or protein or level of phosphorylated NFκB or level or activity of a component of an NFκB pathway or level of phosphorylated NFκB activity or protein or level or activity of a component of a phosphorylated NFκB pathway or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway, wherein each is associated with a hyperproliferative disease, for example cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or a non-malignant hyperproliferative disease (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma)). Inhibition may include, at least in part, partially or totally decreasing stimulation, decreasing or reducing activation, or deactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway) that may modulate the level of another protein or increase cell survival (e.g. decrease in phosphorylated NFκB pathway activity may increase cell survival in cells that may or may not have an increase in phosphorylated NFκB pathway activity relative to a non-disease control or decrease in
NFκB pathway activity may increase cell survival in cells that may or may not have an increase in NFκB pathway activity relative to a non-disease control).

[0073] As defined herein, the term “activation”, “activate”, “activating” and the like in reference to a protein-activator (e.g. agonist) interaction means positively affecting (e.g. increasing) the activity or function of the protein (e.g. NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway) relative to the activity or function of the protein in the absence of the activator (e.g. compound described herein). In some embodiments, activation refers to an increase in the activity of a signal transduction pathway or signaling pathway (e.g. NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTORC1 pathway or TSC1 pathway or TSC2 pathway). Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease (e.g. level of NFκB activity or level of protein or activity decreased by phosphorylation of NFκB or protein associated with cancer (e.g. leukemia, lung cancer; epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer). Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway) that may modulate the level of another protein or increase cell survival (e.g. increase in NFκB activity may increase cell survival in cells that may or may not have a reduction in NFκB activity relative to a non-disease control).

[0074] The term “modulator” refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule. In some embodiments, a modulator of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by
NFκB phosphorylation or mTOR pathway or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway is a compound that reduces the severity of one or more symptoms of a disease associated with NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway (e.g. disease associated with an increase or decrease in the level of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway, for example cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or a non-malignant hyperproliferative disease (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma) or a disease that is not caused by NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway but may benefit from modulation of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway activity (e.g. decreasing or increasing in level of activity of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway). In embodiments, a modulator of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway is an anti-cancer agent.

[0075] "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a compound or pharmaceutical
composition, as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0076] “Disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. In some embodiments, the disease is a disease associated with (e.g. caused by) an increase in the level of activity or amount of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway. In some embodiments, the disease is a disease associated with (e.g. caused by) a decrease in the level of activity or amount of NFκB or phosphorylated NFκB or NFκB pathway or phosphorylated NFκB pathway or pathway activated by NFκB phosphorylation or mTOR pathway or mTOR or mTORC1 pathway or mTORC1 or TSC1 or TSC1 pathway or TSC2 or TSC2 pathway. In some embodiments, the disease is cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer). In some embodiments, the disease is a non-malignant hyperproliferative disease (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma).

[0077] Examples of diseases, disorders, or conditions include, but are not limited to, cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer). In some instances, “disease” or “condition” refers to cancer. In some further instances, “cancer” refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, melanomas, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, liver cancer, including hepatocarcinoma, lymphoma, including B-acute
lymphoblastic lymphoma, non-Hodgkin’s lymphomas (e.g., Burkitt’s, Small Cell, and Large Cell lymphomas), Hodgkin’s lymphoma, leukemia (including AML, ALL, and CML), and/or multiple myeloma. In some further instances, “cancer” refers to lung cancer, breast cancer, ovarian cancer, leukemia, lymphoma, melanoma, pancreatic cancer, sarcoma, bladder cancer, bone cancer, brain cancer, cervical cancer, colon cancer, esophageal cancer, gastric cancer, liver cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, prostate cancer, metastatic cancer, or carcinoma. In embodiments “cancer” refers to a cancer resistant to an anti-cancer therapy (e.g. treatment with an anti-cancer agent (e.g. platinum-based compound, cisplatin, carboplatin, hormonal therapy, hormonal therapeutic agent, tamoxifen, trastuzumab, or an aromatase inhibitor)).

[0078] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals, including leukemia, lymphoma, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound, pharmaceutical composition, or method provided herein include lymphoma, sarcoma, bladder cancer, bone cancer, brain tumor, cervical cancer, colon cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, leukemia, prostate cancer, breast cancer (e.g. ER positive, ER negative, chemotherapy resistant, herceptin resistant, HER2 positive, doxorubicin resistant, tamoxifen resistant, ductal carcinoma, ductal carcinoma in situ (DCIS), triple negative, lobular carcinoma, primary, metastatic), ovarian cancer, pancreatic cancer, liver cancer (e.g. hepatocellular carcinoma), lung cancer (e.g. non-small cell lung carcinoma, squamous cell lung carcinoma, adenocarcinoma, large cell lung carcinoma, small cell lung carcinoma, carcinoïd, sarcoma, cisplatin resistant lung cancer, carboplatin resistant lung cancer, platinum-based compound resistant lung cancer), glioblastoma multiforme, glioma, or melanoma. Additional examples include, cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus or Medulloblastoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoïd, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary
thymid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, Paget’s Disease of the Nipple, Phyllodes Tumors, Lobular Carcinoma, Ductal Carcinoma, cancer of the pancreatic stellate cells, cancer of the hepatic stellate cells, or prostate cancer.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic).


The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound, pharmaceutical composition, or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma,
chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectatic sarcoma.

[0081] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, or superficial spreading melanoma.

[0082] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloïd carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, ductal carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoïdes, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal

[0083] The term “non-malignant hyperproliferative disease” is used in accordance with its plain ordinary meaning and refers to a disease including a growth that is not cancerous. Examples of a non-malignant hyperproliferative disease include a hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma.

[0084] The term “signaling pathway” as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components.

[0085] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such
as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxyethyl cellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0086] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0087] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent or chemotherapeutic). The compound of the invention can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and
aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Rex. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0088] Pharmaceutical compositions provided by the present invention include compositions wherein the active ingredient (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, inter alia, on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating
the activity of a target molecule (e.g. NFκB, phosphorylated NFκB, mTOR, mTORC1, TSC1, TSC2 or component of NFκB pathway, phosphorylated NFκB pathway, pathway activated by NFκB phosphorylation, mTOR pathway, mTORC1 pathway, TSC1 pathway, or TSC2 pathway), and/or reducing, eliminating, or slowing the progression of disease symptoms (e.g. symptoms of cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or a non-malignant hyperproliferative disease (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma)). Determination of a therapeutically effective amount of a compound of the invention is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

[0089] The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g. symptoms of cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or a non-malignant hyperproliferative disease (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma)), kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' invention. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

[0090] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.
[0091] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0092] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached.

[0093] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0094] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0095] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or a
non-malignant hyperproliferative disease (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma), or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0096] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) or non-malignant hyperproliferative diseases (e.g. hamartomatous lesion, angiomyolipoma, lymphangioleiomyomatosis, tuberous sclerosis complex, a hamartia, or a hamartoma) such as surgery.

[0097] The term “NFκB” or “NF-κB” refers to a protein complex controlling DNA transcription commonly referred to in the art as “nuclear factor kappa-light-chain-enhancer of activated B cells” including individual proteins thereof and homologs thereof. In embodiments, “NFκB” refers to the human protein. Included in the term “NFκB” are the wildtype and mutant forms of the protein. In embodiments, the term “NFκB” refers to the monomeric protein. In embodiments, the term “NFκB” refers to a dimer of NFκB (e.g. homodimer or heterodimer). In some embodiments, the term “NFκB” refers to a functional complex including NFκB proteins (e.g. homodimer or heterodimer). In embodiments, the term “NFκB” refers to the human protein also known as NFκB1, corresponding to Entrez 4790, OMIM 164011, RefSeq NM_003998, GI:259155300, and/or UniProt P19838. In embodiments, the term “NFκB” refers to an NFκB dimer (e.g. homodimer or
heterodimer) including the human protein corresponding to Entrez 4790, OMIM 164011, RefSeq NM_003998, GI:259155300, and/or UniProt P19838. In embodiments, the term “NFkB” refers to the human protein also known as RelA or p65, corresponding to Entrez 5970, OMIM 164014, RefSeq NM_021975, GI:223468675, and/or UniProt Q04206. In embodiments, the term “NFkB” refers to an NFkB dimer (e.g. homodimer or heterodimer) including the human protein corresponding to Entrez 5970, OMIM 164014, RefSeq NM_021975, GI:223468675, and/or UniProt Q04206. In embodiments, the term “NFkB” refers to the human protein also known as NFkB2, corresponding to Entrez 4791, OMIM 164012, RefSeq NM_002502, GI:570359567, and/or UniProt Q00653. In embodiments, the term “NFkB” refers to an NFkB dimer (e.g. homodimer or heterodimer) including the human protein corresponding to Entrez 4791, OMIM 164012, RefSeq NM_002502, GI:570359567, and/or UniProt Q00653. In embodiments, the term “NFkB” refers to the human protein also known as RelB, corresponding to Entrez 5971, OMIM 604758, RefSeq NM_006509, GI:317575683, and/or UniProt Q01201. In embodiments, the term “NFkB” refers to an NFkB dimer (e.g. homodimer or heterodimer) including the human protein corresponding to Entrez 5971, OMIM 604758, RefSeq NM_006509, GI:317575683, and/or UniProt Q01201. In embodiments, the term “NFkB” refers to the human protein also known as c-Rel, corresponding to Entrez 5966, OMIM 164910, RefSeq NM_002908, GI:619534180, and/or UniProt Q04864. In embodiments, the term “NFkB” refers to the complex of human NFkB1 and RelA. In embodiments, “NFkB” refers to the complex of human NFkB1 and NFkB2. In embodiments, “NFkB” refers to the complex of human NFkB1 and RelB. In embodiments, “NFkB” refers to the complex of human NFkB1 and c-Rel. In embodiments, “NFkB” refers to the complex of human NFkB2 and RelA. In embodiments, “NFkB” refers to the complex of human NFkB2 and RelB. In embodiments, “NFkB” refers to the complex of human NFkB2 and c-Rel. In embodiments, “NFkB” refers to the complex of human RelA and RelB. In embodiments, “NFkB” refers to the complex of human RelA and c-Rel. In embodiments, “NFkB” refers to the complex of human RelB and c-Rel. In embodiments, “NFkB” refers to the homodimer of human NFkB1. In embodiments, “NFkB” refers to the homodimer of human NFkB2. In embodiments, “NFkB” refers
to the homodimer of human RelA. In embodiments, “NFκB” refers to the homodimer of human RelB. In embodiments, “NFκB” refers to the homodimer of human c-Rel. In embodiments, the reference numbers above for “NFκB” refer to the protein, and associated nucleic acids, known as of the date of filing of this application. The term “TSC1” or “hamartin” refers to the protein “tuberous sclerosis protein 1”. In embodiments, “TSC1” refers to the human protein. Included in the term “TSC2” are the wildtype and and mutant forms of the protein. In embodiments, “TSC1” refers to the protein associated with Entrez Gene 7248, OMIM 605284, UniProt Q92574, RefSeq (protein) NP_000359, and/or GI:4507693. In embodiments, the reference numbers immediately above refer to the protein, and associated nucleic acids, known as of the date of filing of this application. The term “TSC2” or “tuberin” refers to the protein “tuberous sclerosis protein 2”. In embodiments, “TSC2” refers to the human protein. Included in the term “TSC2” are the wildtype and and mutant forms of the protein. In embodiments, “TSC2” refers to the protein associated with Entrez Gene 7249, OMIM 191092, UniProt P49815, RefSeq (protein) NP_000539, and/or GI:116256352. In embodiments, the reference numbers immediately above refer to the protein, and associated nucleic acids, known as of the date of filing of this application. The term “mTOR” refers to the protein “mammalian target of rapamycin”. In embodiments, “mTOR” refers to the human protein. Included in the term “mTOR” are the wildtype and mutant forms of the protein. In embodiments, “mTOR” refers to the protein associated with Entrez Gene 2475, OMIM 601231, UniProt P42345, RefSeq (protein) NP_004949, and/or GI:4826730. In embodiments, the reference numbers immediately above refer to the protein, and associated nucleic acids, known as of the date of filing of this application.

[0098] “Anti-cancer agent” is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244,
GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiopeta, nitrosoureas, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiopeta), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitine, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxuridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds or platinum containing agents (e.g. cisplatin, oxaloplatin, carboplatin), anthracyclenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossypol, genasense, polyphenol E, Chlorofusin, all-trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone, acularubicin, acylfulvene; adecyphenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid, amrubicin, amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides;
aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PtBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflade; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capcetabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cectropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; colfimycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ofosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodiodemmin B; deslorelin; dexamethasone; dextifosamide; dextrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azaeytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifuridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflostimeth; elemene; emitefur; epirubicin; epiristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunic hydrochloride; forfenimex; forimestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoarclidones; imiquimod; immunostimulant peptides; insulain-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol; 4-; iroplacl; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenogristim; lentinam sulfate; leptomatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprolrelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum
compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody; human chorionic gonadotrophin; monophosphoryl lipid A+mycobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytoine inducer; ormaplatin; osaterone; oxaliplatin; oxanomycin; palauamine; palmitoyl rhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentroazole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors; microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethyelrie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine dimethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin
D; spiromustine; spleonopterin; sponisatatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipamide; stromelysin inhibitors; sulfidosine; superactive vasoactive intestinal peptide antagonist; suradista; suramine; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoiethin; thrombopoiethin mimetic; thymalfasin; thymopoeitin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetylaradine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus–derived growth inhibitory factor; urokinase receptor antagonists; vaptoreotide; variloin B; vector system; erythrocyte gene therapy; velaresol; veramine; veridins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanotere ; zeniplatin; zilascorb; zinostatin stimulamer; Adriamycin, Daicinomycin, Bleomycin, Vinblastin, Cisplatin, acivicin, aclacubicin; acodazole hydrochloride; acronine; adozelecin; aldesleukin; altretamine; ambomycin; amantantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropririmine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carbofatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazone; daunorubicin hydrochloride; decitabine; dexornaplatin; dezaguamine; dezaguamine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflomithine hydrochloride; elsamitracin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbuloxide; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriezin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rIL sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-1b; interferon alfa-3; interferon beta-1a, interferon gamma-1b; iproplatin; irinotecan hydrochloride;
lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphanal; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamicin; ormaplatin; oxisuran; pegaspargase; pemiycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfironycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulfenfur; talisomycin; tecegalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; toeroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vaperotide; vertoporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol. TM (i.e. paclitaxel), Taxotere TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XXA-296), ABT-751 (Abbott, i.e. E-7010), Altorhrytins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatin (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZA-1027), Vincristine sulfate, Cryptophycin 52 (i.e. LY-355703), Vitilevuamide, Tubulysin A, Canadensol,
Centaurein (i.e. NSC-106969), Oncocidin A1 (i.e. BTO-956 and DIME), Fijianolide B, Laulimalide, Narcosine (also known as NSC-5366), Nascapine, Hemiasterlin, Vanadocene acetylacetone, Monsatrol, Inanocine (i.e. NSC-698666), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, Diazonamide A, Taccalonolide A, Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), Myoseverin B, Resverastatin phosphate sodium, steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoroxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamycin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, iraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pertinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, hormonal therapies, or the like.

[0099] The term "platinum-based compound" or “platinum containing agent” as used herein refers to a compound comprising a heavy metal complex containing a central atom of platinum surrounded by organic and/or inorganic functionalities. Non-limiting examples of platinum-based compounds include oxaliplatin, cisplatin, carboplatin, pharmaceutically acceptable salts thereof, stereoisomers
thereof, derivatives thereof, analogs thereof, and combinations thereof. Included within platinum-based compounds are platinum-based drugs.

[0100] "Hormonal therapy" or "hormone therapy" is used in accordance with its plain ordinary meaning and refers to the treatment of a disease (e.g. cancer) by administration of an agent (e.g. compound) that modulates the production or activity of a hormone, the activity of a protein that is modulated by a hormone, or a signaling pathway that is modulated by a hormone or the activity of a hormone. An agent used in hormonal therapy may be referred to as a "hormonal therapy agent" or "hormonal therapeutic agent". Hormonal therapeutic agents include, but are not limited to, estrogens, androgens, antiestrogens, antiandrogens, endocrine therapies, steroids (e.g., dexamethasone), finasteride, fulvestrant, aromatase inhibitors (e.g. exemestane, anastrozole, aminoglutethimide, testolactone, letrozole, vorozole, formestane, or fadrozole), tamoxifen, and gonadotropin-releasing hormone agonists (GnRH) such as goserelin.

[0101] "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0102] "Therapy resistant" cancers, tumor cells, and tumors refer to cancers that have become resistant to one or more cancer therapies including, but not limited to, an anti-cancer agent, a chemotherapy (e.g. a chemotherapeutic), a hormonal therapy (e.g. a hormonal therapeutic agent), a radiotherapy, an immunotherapy, and/or combinations thereof.

[0103] Additionally, the compounds described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), and radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, etc.).
In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as $^{37}$Sc, $^{64}$Cu, $^{67}$Cu, $^{89}$Sr, $^{86}$Y, $^{87}$Y, $^{99}$Y, $^{105}$Rh, $^{111}$In, $^{111}$mSn, $^{149}$Pm, $^{153}$Sm, $^{166}$Ho, $^{177}$Lu, $^{186}$Re, $^{188}$Re, $^{211}$At, and $^{212}$Bi, optionally conjugated to antibodies directed against tumor antigens.

The term “cancer stem cell” is used in accordance with its plain ordinary meaning within cancer biology and cell biology and refers to cancer cells with characteristics associated with non-cancerous stem cells, including for example the ability of self-renewal and the ability to differentiate into all cell types that make up a cancer sample (e.g. tumor or cancer cells). The term “cancer progenitor cell” is used in accordance with its plain ordinary meaning within cancer biology and cell biology and refers to cancer cells with characteristics associated with non-cancerous progenitor cells. In embodiments, cancer stem cells and/or cancer progenitor cells may be identified by the presence (or absence) of cell markers (e.g. CD133 (PROM1), CD44 (PGP1), CD24 (HSA), EpCAM (epithelial cell adhesion molecule), ESA (epithelial specific antigen)), THY1 (CD90), ATP-binding cassette B5 (ABCB5), Hoechst33342, CD34, and/or ALDH1 (aldehyde dehydrogenase). In embodiments, lung cancer stem/progenitor cells may be identified by the presence of CD133 and ALDH1 (e.g. high levels of ALDH1 compared to non-lung cancer stem/progenitor cells).

A "stem cell" is a cell characterized by the ability of self-renewal through mitotic cell division and the potential to differentiate into a tissue or an organ. Among mammalian stem cells, embryonic and somatic stem cells can be distinguished. Embryonic stem cells reside in the blastocyst and give rise to embryonic tissues, whereas somatic stem cells reside in adult tissues for the purpose of tissue regeneration and repair.

"Self renewal" refers to the ability of a cell to divide and generate at least one daughter cell with the self-renewing characteristics of the parent cell. The second daughter cell may commit to a particular differentiation pathway. For example, a self-renewing hematopoietic stem cell can divide and form one daughter stem cell and another daughter cell committed to differentiation in the myeloid or lymphoid pathway. A committed progenitor cell has typically lost the self-renewal capacity, and upon cell division produces two daughter cells that display a more differentiated (i.e., restricted) phenotype. Non-self renewing cells refer to cells that undergo cell division to produce
daughter cells, neither of which have the differentiation potential of the parent cell type, but instead generates differentiated daughter cells.

[0108] The term "pluripotent" or "pluripotency" refers to cells with the ability to give rise to progeny that can undergo differentiation, under appropriate conditions, into cell types that collectively exhibit characteristics associated with cell lineages from the three germ layers (endoderm, mesoderm, and ectoderm). Pluripotent stem cells can contribute to tissues of a prenatal, postnatal or adult organism. A standard art-accepted test, such as the ability to form a teratoma in 8-12 week old SCID mice, can be used to establish the pluripotency of a cell population. However, identification of various pluripotent stem cell characteristics can also be used to identify pluripotent cells.

[0109] "Pluripotent stem cell characteristics" refer to characteristics of a cell that distinguish pluripotent stem cells from other cells. Expression or non-expression of certain combinations of molecular markers are examples of characteristics of pluripotent stem cells. More specifically, human pluripotent stem cells may express at least some, and optionally all, of the markers from the following non-limiting list: SSEA-3, SSEA-4, TRA-1-60, TRA-1-81, TRA-2-49/6E, ALP, Sox2, E-cadherin, UTF-1, Oct4, Lin28, Rex1, and Nanog. Cell morphologies associated with pluripotent stem cells are also pluripotent stem cell characteristics.

[0110] The terms "induced pluripotent stem cell," "iPS" and the like refer to a pluripotent stem cell artificially derived from a non-pluripotent cell. A "non-pluripotent cell" can be a cell of lesser potency to self-renew and differentiate than a pluripotent stem cell. Cells of lesser potency can be, but are not limited to adult stem cells, tissue specific progenitor cells, primary or secondary cells.

[0111] An adult stem cell is an undifferentiated cell found in an individual after embryonic development. Adult stem cells multiply by cell division to replenish dying cells and regenerate damaged tissue. An adult stem cell has the ability to divide and create another cell like itself or to create a more differentiated cell. Even though adult stem cells are associated with the expression of pluripotency markers such as Rex1, Nanog, Oct4 or Sox2, they do not have the ability of pluripotent stem cells to differentiate into the cell types of all three germ layers. Adult stem cells have a limited ability to self-renew and generate progeny of distinct cell types. Adult stem cells can include hematopoietic stem cell, a cord blood stem cell, a mesenchymal stem cell, an epithelial stem cell, a
skin stem cell or a neural stem cell. A tissue specific progenitor refers to a cell devoid of self-renewal potential that is committed to differentiate into a specific organ or tissue. A primary cell includes any cell of an adult or fetal organism apart from egg cells, sperm cells and stem cells. Examples of useful primary cells include, but are not limited to, skin cells, bone cells, blood cells, cells of internal organs and cells of connective tissue. A secondary cell is derived from a primary cell and has been immortalized for long-lived *in vitro* cell culture.

[0112] The term “triple negative breast cancer” or “triple negative” when applied to a type of breast cancer is used in accordance with its plain ordinary meaning within cancer biology and refers to a breast cancer including cancer cells that have a reduced expression (e.g., no expression or no detectable expression by standard methods) of estrogen receptor, progesterone receptor, and Her2/neu.

II. Compounds

[0113] In a first aspect is provided a compound, or a pharmaceutically acceptable salt thereof, having the formula:

![](image)

(I). $L^1$ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. $L^2$ is a bond, substituted or unsubstituted heteroalkylene, –NH–, or –O–. $R^1$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. $R^2$ is hydrogen, –OH, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0114] In another aspect is provided a compound, or a pharmaceutically acceptable salt thereof, having the formula:
C₁-C₄ alkylene, or substituted or unsubstituted 2 to 3 membered heteroalkylene. L¹ is a bond, substituted or unsubstituted heteroalkylene, -NH-, or -O-. R¹ is hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. R² is hydrogen, -OH, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

L¹, L², R¹, and R² are as described herein.

In embodiments, L¹ is substituted propylene. In embodiments, L¹ is unsubstituted propylene. In embodiments, L¹ is substituted methylene. In embodiments, L¹ is unsubstituted methylene. In embodiments, L¹ is a bond. In embodiments, L¹ is -C(CH₃)₂-.

In embodiments, L² is -O(CH₂)₂-. In embodiments, L² is -O-. In embodiments, L² is -NH(CH₂)₂-. In embodiments, L² is a bond. In embodiments, L² is -O(CH₂)-.

The symbol z₁ is an integer from 0 to 3. In embodiments, z₁ is 3. In embodiments, z₁ is 2. In embodiments, z₁ is 1. In embodiments, z₁ is 0.

In embodiments, R¹ is independently hydrogen, -CX³, -CN, -COOH, -CONH₂, -CHX², -CH₂X, R⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^4-substituted or unsubstituted cycloalkyl (e.g., C_3-C_6, C_3-C_6, C_4-C_6, or C_5-C_6), R^4-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^4-substituted or unsubstituted aryl (e.g., C_6-C_10 or phenyl), or R^4-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^1 is independently -F, -Cl, -Br, or -I. In embodiments, R^1 is independently hydrogen. In embodiments, R^1 is independently unsubstituted methyl. In embodiments, R^1 is independently unsubstituted ethyl. In embodiments, R^1 is independently hydrogen, -C\text{X}^1\text{H}, -CN, -COOH, -CONH\text{H}_2, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_6, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_10 or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^1 is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1 is substituted or unsubstituted 3 to 6 membered heteroalkyl. In embodiments, R^1 is substituted or unsubstituted 4 to 6 membered heteroalkyl. In embodiments, R^1 is independently hydrogen, R^4-substituted or unsubstituted alkyl, R^4-substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1 is R^4-substituted or unsubstituted 3 to 6 membered heteroalkyl. In embodiments, R^1 is R^4-substituted or unsubstituted 4 to 6 membered heteroalkyl. In embodiments, R^1 is hydrogen. In embodiments, R^1 is -CH\text{H}_3. In embodiments, R^1 is hydrogen, R^4-substituted or unsubstituted C_1-C_6 alkyl, R^4-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^4-substituted or unsubstituted C_3-C_6 cycloalkyl, R^4-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^4-substituted or unsubstituted phenyl, or R^4-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is unsubstituted C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted C_1-C_2 alkyl. In embodiments, R^1 is unsubstituted C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted C_1-C_3 alkyl. In embodiments, R^1 is unsubstituted C_1-C_2 alkyl. In embodiments, R^1 is unsubstituted C_2-C_3 alkyl. In embodiments, R^1 is unsubstituted C_3-C_6 alkyl. In embodiments, R^1 is unsubstituted C_4-C_6 alkyl. In embodiments, R^1 is R^4-substituted or unsubstituted C_1-C_6 alkyl. In embodiments, R^1 is R^4-substituted or unsubstituted C_1-C_5 alkyl. In embodiments, R^1 is R^4-substituted or unsubstituted C_1-C_6.
C₄ alkyl. In embodiments, R¹ is R⁴-substituted or unsubstituted C₁-C₃ alkyl. In embodiments, R¹ is unsubstituted methyl. In embodiments, R¹ is unsubstituted ethyl. In embodiments, R¹ is unsubstituted propyl. In embodiments, R¹ is unsubstituted isopropyl. In embodiments, R¹ is unsubstituted butyl. In embodiments, R¹ is unsubstituted isobutyl. In embodiments, R¹ is unsubstituted tert-butyl. In embodiments, R¹ is independently hydrogen, -CX₁⁻³, -CHX¹⁻², -CH₂X¹, or R⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is independently hydrogen, -CX₁⁻³, -CHX¹⁻², -CH₂X¹, or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is independently -CX₁⁻³, -CHX¹⁻², -CH₂X¹, or unsubstituted alkyl (e.g., C₁-C₄ or C₁-C₂).

10 [0121] R⁴ is independently halogen, oxo, -CX¹⁻³, -CHX¹⁻², -CH₂X¹, -OCX¹⁻³, -OCHX²⁻³, -OCH₂X⁴⁻³, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₃H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X¹ is independently halogen. In embodiments, X¹ is independently -F.

[0122] In embodiments, R⁴ is independently halogen, oxo, -CX¹⁻³, -CHX¹⁻², -CH₂X¹, -OCX¹⁻³, -OCHX²⁻³, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₃H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH₃, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted 3 to 6 membered heteroalkyl, substituted or unsubstituted 4 to 6 membered heteroalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R⁴ is independently halogen, oxo, -CX¹⁻³, -CHX¹⁻², -CH₂X¹, -OCX¹⁻³, -OCHX²⁻³, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₃H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH₃, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R⁴ is independently substituted or unsubstituted 3 to 6 membered heteroalkyl. In
embodiments, \( R^4 \) is independently substituted or unsubstituted 4 to 6 membered heteroalkyl. In embodiments, \( R^4 \) is independently substituted or unsubstituted phenyl. In embodiments, \( R^4 \) is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, \( R^4 \) is independently substituted or unsubstituted \( C_1-C_6 \) alkyl. In embodiments, \( R^4 \) is independently substituted or unsubstituted \( C_1-C_5 \) alkyl. In embodiments, \( R^4 \) is independently substituted or unsubstituted \( C_1-C_4 \) alkyl. In embodiments, \( R^4 \) is independently substituted or unsubstituted \( C_1-C_3 \) alkyl. In embodiments, \( R^4 \) is independently unsubstituted \( C_1-C_6 \) alkyl. In embodiments, \( R^4 \) is independently unsubstituted \( C_1-C_5 \) alkyl. In embodiments, \( R^4 \) is independently unsubstituted \( C_1-C_4 \) alkyl. In embodiments, \( R^4 \) is independently unsubstituted methyl. In embodiments, \( R^4 \) is independently unsubstituted ethyl. In embodiments, \( R^4 \) is independently unsubstituted propyl. In embodiments, \( R^4 \) is independently unsubstituted isopropyl. In embodiments, \( R^4 \) is independently unsubstituted butyl. In embodiments, \( R^4 \) is independently unsubstituted isobutyl. In embodiments, \( R^4 \) is independently unsubstituted tert-butyl.

15 | [0123] | In embodiments, \( R^4 \) is independently halogen, oxo, \(-\text{CX}^4\), \(-\text{CHX}^4\), \(-\text{CH}_2\text{X}^4\), \(-\text{OCX}^4\), \(-\text{OCHX}^4\), \(-\text{OCH}_2\text{X}^4\), \(-\text{CN}\), \(-\text{SO}(\text{O})\text{CH}_3\), \(-\text{OH}\), \(-\text{NH}_2\), \(-\text{COOH}\), \(-\text{CONH}_2\), \(-\text{NO}_2\), \(-\text{C}(\text{O})\text{CH}_3\), \(-\text{CH}_2\text{CH}_3\), \(-\text{CH}_2\text{OH}\), \(-\text{SH}\), \(-\text{SO}_2\text{H}\), \(-\text{SO}_3\text{H}\), \(-\text{SO}_2\text{NH}_2\), \(-\text{SO}_2\text{CH}_3\), \(-\text{NHNH}_2\), \(-\text{ONH}_2\), \(-\text{NHC}(\text{O})\text{NHNH}_2\), \(-\text{NHC}(\text{O})\text{NH}_2\), \(-\text{NHSO}_2\text{H}\), \(-\text{NHC}(\text{O})\text{H}\), \(-\text{NHC}(\text{O})\text{OH}\), \(-\text{NOOH}\), \(-\text{OCH}_3\), \(-\text{OCF}_3\), \(-\text{OCHF}_2\), \( R^5 \)-substituted or unsubstituted alkyl, \( R^5 \)-substituted or unsubstituted heteroalkyl, \( R^5 \)-substituted or unsubstituted cycloalkyl, \( R^5 \)-substituted or unsubstituted heterocycloalkyl, \( R^5 \)-substituted or unsubstituted aryl, or \( R^5 \)-substituted or unsubstituted heteroaryl. In embodiments, \( R^5 \) is independently halogen, oxo, \(-\text{CF}_3\), \(-\text{CCl}_3\), \(-\text{CN}\), \(-\text{SO}(\text{O})\text{CH}_3\), \(-\text{OH}\), \(-\text{NH}_2\), \(-\text{COOH}\), \(-\text{CONH}_2\), \(-\text{NO}_2\), \(-\text{C}(\text{O})\text{CH}_3\), \(-\text{CH}_2\text{CH}_3\), \(-\text{CH}_2\text{OH}\), \(-\text{SH}\), \(-\text{SO}_3\text{H}\), \(-\text{SO}_2\text{H}\), \(-\text{SO}_2\text{NH}_2\), \(-\text{SO}_2\text{CH}_3\), \(-\text{NHNH}_2\), \(-\text{ONH}_2\), \(-\text{NHC}(\text{O})\text{NHNH}_2\), \(-\text{NHC}(\text{O})\text{NH}_2\), \(-\text{NHSO}_2\text{H}\), \(-\text{NHC}(\text{O})\text{H}\), \(-\text{NHC}(\text{O})\text{OH}\), \(-\text{NOOH}\), \(-\text{OCH}_3\), \(-\text{OCF}_3\), \(-\text{OCHF}_2\), \( R^5 \)-substituted or unsubstituted \( C_1-C_6 \) alkyl, \( R^5 \)-substituted or unsubstituted 2 to 6 membered heteroalkyl, \( R^5 \)-substituted or unsubstituted \( C_3-C_6 \) cycloalkyl, \( R^5 \)-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, \( R^5 \)-substituted or unsubstituted phenyl, or \( R^5 \)-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, \( R^4 \) is independently halogen, \( R^5 \)-substituted or unsubstituted \( C_1-C_6 \) alkyl or \( R^5 \)-substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, \( R^4 \) is independently \( R^5 \)-substituted or unsubstituted 3 to 6
membered heteroalkyl. In embodiments, R^1 is independently R^5-substituted or unsubstituted 4 to 6 membered heteroalkyl. In embodiments, R^4 is independently R^5-substituted or unsubstituted C_{1-6} alkyl. In embodiments, R^4 is independently R^5-substituted or unsubstituted C_{1-5} alkyl. In embodiments, R^4 is independently R^5-substituted or unsubstituted C_{1-4} alkyl. In embodiments, R^4 is independently R^5-substituted or unsubstituted C_{1-3} alkyl. In embodiments, R^4 is independently unsubstituted methyl. In embodiments, R^4 is independently unsubstituted ethyl. In embodiments, R^4 is independently unsubstituted propyl. In embodiments, R^4 is independently unsubstituted isopropyl. In embodiments, R^4 is independently unsubstituted butyl. In embodiments, R^4 is independently unsubstituted isobutyl. In embodiments, R^4 is independently unsubstituted tert-butyl.

[0124] In embodiments, R^2 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^2 is –OH. In embodiments, R^2 is independently hydrogen, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl. In embodiments, R^2 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^2 is substituted or unsubstituted phenyl. In embodiments, R^2 is hydrogen. In embodiments, R^2 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^2 is substituted or unsubstituted 5 membered heteroaryl. In embodiments, R^2 is substituted or unsubstituted 6 membered heteroaryl. In embodiments, R^2 is unsubstituted phenyl. In embodiments, R^2 is unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^2 is unsubstituted 5 membered heteroaryl. In embodiments, R^2 is unsubstituted 6 membered heteroaryl.

[0125] In embodiments, R^2 is substituted or unsubstituted pyrrolyl. In embodiments, R^2 is substituted or unsubstituted pyrazolyl. In embodiments, R^2 is substituted or unsubstituted imidazolyl. In embodiments, R^2 is substituted or unsubstituted oxazolyl. In embodiments, R^2 is substituted or unsubstituted isoxazolyl. In embodiments, R^2 is substituted or unsubstituted thiazolyl. In embodiments, R^2 is substituted or unsubstituted furyl. In embodiments, R^2 is substituted or unsubstituted thieryl. In embodiments, R^2 is substituted or unsubstituted pyridyl. In embodiments, R^2 is substituted or unsubstituted pyrimidyl. In embodiments, R^2 is substituted or unsubstituted pyrazinyl. In embodiments, R^2 is substituted or unsubstituted pyridazinyl. In embodiments, R^2 is substituted or unsubstituted 1,2,3-triazinyl. In embodiments, R^2 is substituted or unsubstituted 1,2,4-triazinyl. In embodiments, R^2 is substituted or unsubstituted 1,3,5-triazinyl. In embodiments,
R² is substituted pyrrolyl. In embodiments, R² is substituted pyrazolyl. In embodiments, R² is substituted imidazolyl. In embodiments, R² is substituted oxazolyl. In embodiments, R² is substituted isoxazolyl. In embodiments, R² is substituted thiazolyl. In embodiments, R² is substituted furyl. In embodiments, R² is substituted thienyl. In embodiments, R² is substituted pyridyl. In embodiments, R² is substituted pyrimidyl. In embodiments, R² is substituted pyrazinyl. In embodiments, R² is substituted pyridazinyl. In embodiments, R² is substituted 1,2,3-triazinyl. In embodiments, R² is substituted 1,2,4-triazinyl. In embodiments, R² is substituted 1,3,5-triazinyl. In embodiments, R² is R³-substituted pyrrolyl. In embodiments, R² is R³-substituted pyrazolyl. In embodiments, R² is R³-substituted imidazolyl. In embodiments, R² is R³-substituted oxazolyl. In embodiments, R² is R³-substituted isoxazolyl. In embodiments, R² is R³-substituted thiazolyl. In embodiments, R² is R³-substituted furyl. In embodiments, R² is R³-substituted thienyl. In embodiments, R² is R³-substituted pyridyl. In embodiments, R² is R³-substituted pyrimidyl. In embodiments, R² is R³-substituted pyrazinyl. In embodiments, R² is R³-substituted pyridazinyl. In embodiments, R² is R³-substituted 1,2,3-triazinyl. In embodiments, R² is R³-substituted 1,2,4-triazinyl. In embodiments, R² is R³-substituted 1,3,5-triazinyl. In embodiments, R² is unsubstituted pyrrolyl. In embodiments, R² is unsubstituted pyrazolyl. In embodiments, R² is unsubstituted imidazolyl. In embodiments, R² is unsubstituted oxazolyl. In embodiments, R² is unsubstituted isoxazolyl. In embodiments, R² is unsubstituted thiazolyl. In embodiments, R² is unsubstituted furyl. In embodiments, R² is unsubstituted thienyl. In embodiments, R² is unsubstituted pyridyl. In embodiments, R² is unsubstituted pyrimidyl. In embodiments, R² is unsubstituted pyrazinyl. In embodiments, R² is unsubstituted pyridazinyl. In embodiments, R² is unsubstituted 1,2,3-triazinyl. In embodiments, R² is unsubstituted 1,2,4-triazinyl. In embodiments, R² is unsubstituted 1,3,5-triazinyl.

[0126] In embodiments, R² is substituted or unsubstituted 1-pyrrolyl. In embodiments, R² is substituted or unsubstituted 2-pyrrolyl. In embodiments, R² is substituted or unsubstituted 3-pyrrolyl. In embodiments, R² is substituted or unsubstituted 3-pyrazolyl. In embodiments, R² is substituted or unsubstituted 3-imidazolyl. In embodiments, R² is substituted or unsubstituted 2-imidazolyl. In embodiments, R² is substituted or unsubstituted 3-pyrazolyl. In embodiments, R² is substituted or unsubstituted 4-imidazolyl. In embodiments, R² is substituted or unsubstituted 4-imidazolyl. In embodiments, R² is substituted or unsubstituted 2-oxazolyl. In embodiments, R² is substituted or unsubstituted 4-oxazolyl. In embodiments, R² is substituted or unsubstituted 5-oxazolyl. In embodiments, R² is substituted or unsubstituted 5-oxazolyl.
substituted or unsubstituted 3-isoxazolyl. In embodiments, R² is substituted or unsubstituted 4-isoxazolyl. In embodiments, R² is substituted or unsubstituted 5-isoxazolyl. In embodiments, R² is substituted or unsubstituted 2-thiazolyl. In embodiments, R² is substituted or unsubstituted 4-thiazolyl. In embodiments, R² is substituted or unsubstituted 5-thiazolyl. In embodiments, R² is substituted or unsubstituted 2-furyl. In embodiments, R² is substituted or unsubstituted 3-furyl. In embodiments, R² is substituted or unsubstituted 2-thienyl. In embodiments, R² is substituted or unsubstituted 2-thienyl. In embodiments, R² is substituted or unsubstituted 3-thienyl. In embodiments, R² is substituted or unsubstituted 2-pyridyl. In embodiments, R² is substituted or unsubstituted 3-pyridyl. In embodiments, R² is substituted or unsubstituted 4-pyridyl. In embodiments, R² is substituted or unsubstituted 2-pyrimidyl. In embodiments, R² is substituted or unsubstituted 4-pyrimidyl. In embodiments, R² is substituted or unsubstituted 5-pyrimidyl. In embodiments, R² is substituted or unsubstituted 6-pyrimidyl. In embodiments, R² is substituted or unsubstituted 2-pyrazinyl. In embodiments, R² is substituted or unsubstituted 3-pyrazinyl. In embodiments, R² is substituted or unsubstituted 3-pyrazinyl. In embodiments, R² is substituted or unsubstituted 4-pyrazinyl. In embodiments, R² is substituted or unsubstituted 1,2,3-triazinyl. In embodiments, R² is substituted or unsubstituted 1,2,4-triazinyl. In embodiments, R² is substituted or unsubstituted 1,3,5-triazinyl.

[0127] In embodiments, R² is substituted 1-pyrrolyl. In embodiments, R² is substituted 2-pyrrolyl. In embodiments, R² is substituted 3-pyrrolyl. In embodiments, R² is substituted 3-pyrazolyl. In embodiments, R² is substituted 2-imidazolyl. In embodiments, R² is substituted 4-imidazolyl. In embodiments, R² is substituted 5-imidazolyl. In embodiments, R² is substituted 2-oxazolyl. In embodiments, R² is substituted 4-oxazolyl. In embodiments, R² is substituted 5-oxazolyl. In embodiments, R² is substituted 3-isoxazolyl. In embodiments, R² is substituted 4-isoxazolyl. In embodiments, R² is substituted 5-isoxazolyl. In embodiments, R² is substituted 2-thiazolyl. In embodiments, R² is substituted 4-thiazolyl. In embodiments, R² is substituted 5-thiazolyl. In embodiments, R² is substituted 2-furyl. In embodiments, R² is substituted 3-furyl. In embodiments, R² is substituted 2-thienyl. In embodiments, R² is substituted 3-thienyl. In embodiments, R² is substituted 2-pyridyl. In embodiments, R² is substituted 3-pyridyl. In embodiments, R² is substituted 4-pyridyl. In embodiments, R² is substituted 2-pyrimidyl. In embodiments, R² is substituted 3-pyrimidyl. In embodiments, R² is substituted 4-pyrimidyl. In embodiments, R² is substituted 5-pyrimidyl. In embodiments, R² is substituted 6-pyrimidyl. In embodiments, R² is substituted 2-pyrazinyl. In embodiments, R² is substituted 3-pyrazinyl.
substituted 3-pyrazinyl. In embodiments, R² is substituted 3-pyridazinyl. In embodiments, R² is substituted 4-pyridazinyl. In embodiments, R² is substituted 1,2,3-triazinyl. In embodiments, R² is substituted 1,2,4-triazinyl. In embodiments, R² is substituted 1,3,5-triazinyl.

[0128] In embodiments, R² is R³-substituted 1-pyrrolyl. In embodiments, R² is R³-substituted 2-pyrrolyl. In embodiments, R² is R³-substituted 3-pyrrolyl. In embodiments, R² is R³-substituted 3-pyrazolyl. In embodiments, R² is R³-substituted 2-imidazolyl. In embodiments, R² is R³-substituted 4-imidazolyl. In embodiments, R³ is R³-substituted 5-imidazolyl. In embodiments, R³ is R³-substituted 2-oxazolyl. In embodiments, R³ is R³-substituted 4-oxazolyl. In embodiments, R³ is R³-substituted 5-oxazolyl. In embodiments, R³ is R³-substituted 3-isoxazolyl. In embodiments, R³ is R³-substituted 4-isoxazolyl. In embodiments, R³ is R³-substituted 5-isoxazolyl. In embodiments, R³ is R³-substituted 2-thiazolyl. In embodiments, R³ is R³-substituted 4-thiazolyl. In embodiments, R³ is R³-substituted 5-thiazolyl. In embodiments, R³ is R³-substituted 2-furanyl. In embodiments, R³ is R³-substituted 3-furanyl. In embodiments, R³ is R³-substituted 2-thienyl. In embodiments, R³ is R³-substituted 3-thienyl. In embodiments, R³ is R³-substituted 2-pyridyl. In embodiments, R³ is R³-substituted 3-pyridyl. In embodiments, R³ is R³-substituted 4-pyridyl. In embodiments, R³ is R³-substituted 2-pyrimidyl. In embodiments, R³ is R³-substituted 4-pyrimidyl. In embodiments, R³ is R³-substituted 5-pyrimidyl. In embodiments, R³ is R³-substituted 6-pyrimidyl. In embodiments, R³ is R³-substituted 2-pyrazinyl. In embodiments, R³ is R³-substituted 3-pyrazinyl. In embodiments, R³ is R³-substituted 3-pyridazinyl. In embodiments, R³ is R³-substituted 1,2,3-triazinyl. In embodiments, R³ is R³-substituted 1,2,4-triazinyl. In embodiments, R³ is R³-substituted 1,3,5-triazinyl.

[0129] In embodiments, R² is unsubstituted 1-pyrrolyl. In embodiments, R² is unsubstituted 2-pyrrolyl. In embodiments, R² is unsubstituted 3-pyrrolyl. In embodiments, R² is unsubstituted 3-pyrazolyl. In embodiments, R² is unsubstituted 2-imidazolyl. In embodiments, R² is unsubstituted 4-imidazolyl. In embodiments, R² is unsubstituted 2-oxazolyl. In embodiments, R² is unsubstituted 4-oxazolyl. In embodiments, R² is unsubstituted 5-oxazolyl. In embodiments, R² is unsubstituted 3-isoxazolyl. In embodiments, R² is unsubstituted 4-isoxazolyl. In embodiments, R² is unsubstituted 5-isoxazolyl. In embodiments, R² is unsubstituted 2-thiazolyl. In embodiments, R² is unsubstituted 4-thiazolyl. In embodiments, R² is unsubstituted 5-thiazolyl. In embodiments, R² is unsubstituted 2-furanyl. In embodiments, R² is unsubstituted 3-furanyl. In embodiments, R² is unsubstituted 2-thienyl. In embodiments, R² is unsubstituted 3-thienyl. In embodiments, R² is unsubstituted 2-pyridyl. In embodiments, R² is unsubstituted 3-pyridyl. In embodiments, R² is unsubstituted 4-pyridyl. In embodiments, R² is unsubstituted 2-pyrimidyl. In embodiments, R² is unsubstituted 4-pyrimidyl. In embodiments, R² is unsubstituted 5-pyrimidyl. In embodiments, R² is unsubstituted 6-pyrimidyl. In embodiments, R² is unsubstituted 2-pyrazinyl. In embodiments, R² is unsubstituted 3-pyrazinyl. In embodiments, R² is unsubstituted 3-pyridazinyl. In embodiments, R² is unsubstituted 1,2,3-triazinyl. In embodiments, R² is unsubstituted 1,2,4-triazinyl. In embodiments, R² is unsubstituted 1,3,5-triazinyl.
unsubstituted 5-thiazoly. In embodiments, R\textsuperscript{3} is unsubstituted 2-furyl. In embodiments, R\textsuperscript{2} is unsubstituted 3-furyl. In embodiments, R\textsuperscript{2} is unsubstituted 2-thienyl. In embodiments, R\textsuperscript{2} is unsubstituted 3-thienyl. In embodiments, R\textsuperscript{2} is unsubstituted 2-pyridyl. In embodiments, R\textsuperscript{2} is unsubstituted 3-pyridyl. In embodiments, R\textsuperscript{2} is unsubstituted 4-pyridyl. In embodiments, R\textsuperscript{2} is unsubstituted 2-pyrimidyl. In embodiments, R\textsuperscript{2} is unsubstituted 4-pyrimidyl. In embodiments, R\textsuperscript{2} is unsubstituted 5-pyrimidyl. In embodiments, R\textsuperscript{2} is unsubstituted 6-pyrimidyl. In embodiments, R\textsuperscript{2} is unsubstituted 2-pyrazinyl. In embodiments, R\textsuperscript{2} is unsubstituted 3-pyrazinyl. In embodiments, R\textsuperscript{2} is unsubstituted 3-pyridazinyl. In embodiments, R\textsuperscript{2} is unsubstituted 4-pyridazinyl. In embodiments, R\textsuperscript{2} is unsubstituted 1,2,3-triazinyl. In embodiments, R\textsuperscript{2} is unsubstituted 1,2,4-triazinyl. In embodiments, R\textsuperscript{2} is unsubstituted 1,3,5-triazinyl.

[0130] In embodiments, R\textsuperscript{2} is hydrogen, R\textsuperscript{3}-substituted or unsubstituted cycloalkyl, R\textsuperscript{3}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{3}-substituted or unsubstituted aryl, or R\textsuperscript{3}-substituted or unsubstituted heteroaryl. In embodiments, R\textsuperscript{2} is independently hydrogen, R\textsuperscript{3}-substituted or unsubstituted C\textsubscript{4}-C\textsubscript{6} cycloalkyl, R\textsuperscript{3}-substituted or unsubstituted 4 to 6 membered heterocycloalkyl, R\textsuperscript{3}-substituted or unsubstituted phenyl, or R\textsuperscript{3}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently hydrogen. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted or unsubstituted C\textsubscript{4}-C\textsubscript{6} cycloalkyl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted or unsubstituted 4 to 6 membered heterocycloalkyl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted or unsubstituted phenyl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently unsubstituted C\textsubscript{4}-C\textsubscript{6} cycloalkyl. In embodiments, R\textsuperscript{2} is unsubstituted 4 to 6 membered heterocycloalkyl. In embodiments, R\textsuperscript{2} is unsubstituted phenyl. In embodiments, R\textsuperscript{2} is unsubstituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted or unsubstituted cycloalkyl or independently R\textsuperscript{3}-substituted heterocycloalkyl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted phenyl or independently R\textsuperscript{3}-substituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted phenyl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted 5 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently R\textsuperscript{3}-substituted 6 membered heteroaryl. In embodiments, R\textsuperscript{2} is independently unsubstituted phenyl. In embodiments, R\textsuperscript{2} is independently...
unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently unsubstituted 5 membered heteroaryl. In embodiments, R² is independently unsubstituted 6 membered heteroaryl.

[0131] R³ is independently halogen, oxo, –CX³, –CHX³, –CH₂X³, –OCX³, –OCHX³, –OCH₂X³, –CN, –S(O)CH₃, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –C(O)CH₃, –CH₂CH₃,

–CH₂CH₂OH, –SH, –SO₂H, –SO₃H, –SO₂NH₂, –SO₂CH₃, –NHNH₂, –ONH₂, –NHC=(O)NHNH₂, –NHC=(O)NH₂, –NH.SO₂H, –NHC=(O)H, –NH.C(O)OH, –NHOH, –OCH₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. Two adjacent R³ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X³ is independently halogen. In embodiments, X³ is independently –F.

[0132] In embodiments, R³ is independently halogen, oxo, –CX³, –CHX³, –CH₂X³, –OCX³, –OCHX³, –OCH₂X³, –CN, –S(O)CH₃, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –C(O)CH₃,

–CH₂CH₃, –CH₂CH₂OH, –SH, –SO₂H, –SO₃H, –SO₂NH₂, –SO₂CH₃, –NHNH₂, –ONH₂, –NHC=(O)NHNH₂, –NHC=(O)NH₂, –NH.SO₂H, –NHC=(O)H, –NH.C(O)OH, –NHOH, –OCH₃, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, R³ is independently –OH. In embodiments, R³ is independently –F. In embodiments, R³ is independently –Cl. In embodiments, R³ is independently –Br. In embodiments, R³ is independently –I. In embodiments, R³ is independently –SH. In embodiments, R³ is independently –NH₂. In embodiments, R³ is independently –NO₂.

[0133] In embodiments, R³ is independently halogen, oxo, –CX³, –CHX³, –CH₂X³, –OCX³, –OCHX³, –OCH₂X³, –CN, –S(O)CH₃, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –C(O)CH₃,

–CH₂CH₃, –CH₂CH₂OH, –SH, –SO₂H, –SO₃H, –SO₂NH₂, –SO₂CH₃, –NHNH₂, –ONH₂, –NHC=(O)NHNH₂, –NHC=(O)NH₂, –NH.SO₂H, –NHC=(O)H, –NH.C(O)OH, –NHOH, –OCH₃, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₅-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6
membered heteroaryl. In embodiments, $R^3$ is independently halogen, oxo, $-CX^3$, $-CHX^3$, $-CH_2X^3$, $-OCX^3$, $-OCHX^3$, $-OCH_2X^3$, $-CN$, $-S(O)CH_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-C(O)CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-SH$, $-SO_2H$, $-SO_3H$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHNNH_2$, $-ONH_2$, $-NHC=(O)NNHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NO_2$, $-OCH_3$, $R^6$-substituted or unsubstituted $C_1$-$C_6$ alkyl, $R^6$-substituted or unsubstituted 2 to 6 membered heteroaryl, $R^6$-substituted or unsubstituted $C_3$-$C_6$ cycloalkyl, $R^6$-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, $R^6$-substituted or unsubstituted phenyl, or $R^6$-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0134] In embodiments, $R^3$ is independently halogen, oxo, $-CX^3$, $-CHX^3$, $-CH_2X^3$, $-OCX^3$, $-OCHX^3$, $-OCH_2X^3$, $-CN$, $-S(O)CH_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-C(O)CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-SH$, $-SO_2H$, $-SO_3H$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHNNH_2$, $-ONH_2$, $-NHC=(O)NNHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NO_2$, $-OCH_3$, $R^6$-substituted or unsubstituted alkyl, $R^6$-substituted or unsubstituted heteroaryl, $R^6$-substituted or unsubstituted cycloalkyl, $R^6$-substituted or unsubstituted heterocycloalkyl, $R^6$-substituted or unsubstituted aryl, or $R^6$-substituted or unsubstituted heteroaryl. In embodiments, two adjacent $R^3$ substituents may optionally be joined to form an $R^6$-substituted or unsubstituted cycloalkyl, $R^6$-substituted or unsubstituted heterocycloalkyl, $R^6$-substituted or unsubstituted aryl, or $R^6$-substituted or unsubstituted heteroaryl. In embodiments, $R^3$ is independently $R^6$-substituted or unsubstituted cycloalkyl or $R^6$-substituted or unsubstituted heterocycloalkyl. In embodiments, $R^3$ is independently $R^6$-substituted or unsubstituted phenyl or $R^6$-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^3$ is independently $R^6$-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^3$ is independently $R^6$-substituted phenyl. In embodiments, $R^3$ is independently $R^6$-substituted 5 to 6 membered heteroaryl. In embodiments, $R^3$ is independently $R^6$-substituted 5 membered heteroaryl. In embodiments, $R^3$ is independently $R^6$-substituted 6 membered heteroaryl. In embodiments, $R^3$ is independently unsubstituted phenyl. In embodiments, $R^3$ is independently unsubstituted 5 membered heteroaryl. In embodiments, $R^3$ is independently unsubstituted 6 membered heteroaryl.

[0135] $R^6$ is independently halogen, oxo, $-CX^6$, $-CHX^6$, $-CH_2X^6$, $-OCX^6$, $-OCHX^6$, $-OCH_2X^6$, $-CN$, $-S(O)CH_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-C(O)CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-SH$, $-SO_2H$, $-SO_3H$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHNNH_2$, $-ONH_2$, $-NHC=(O)NNHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NO_2$, $-OCH_3$, $R^6$-substituted or unsubstituted alkyl, $R^6$-substituted or unsubstituted heteroaryl, $R^6$-substituted or unsubstituted cycloalkyl, $R^6$-substituted or unsubstituted heterocycloalkyl, $R^6$-substituted or unsubstituted aryl, or $R^6$-substituted or unsubstituted heteroaryl.
-CH₂CH₂OH, -SH, -SO₂H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X⁶ is independently halogen. In embodiments, X⁶ is independently -F.

[0136] In embodiments, R⁶ is independently halogen, oxo, -CX⁶₃, -CHX⁶₂, -CH₂X⁶, -OCX⁶₃, -OCHX⁶₂, -OCH₂X⁶, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC(O)OH, -NHOH, -OCH₃, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R⁶ is independently halogen, oxo, -CX⁶₃, -CHX⁶₂, -CH₂X⁶, -OCX⁶₃, -OCHX⁶₂, -OCH₂X⁶, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC(O)OH, -NHOH, -OCH₃, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0137] In embodiments, R⁶ is independently hydrogen, halogen, substituted or unsubstituted C₁-C₆ alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R⁶ is substituted or unsubstituted 3 to 6 membered heteroalkyl. In embodiments, R⁶ is substituted or unsubstituted 4 to 6 membered heteroalkyl. In embodiments, R⁶ is independently substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R⁶ is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R⁶ is independently substituted or unsubstituted C₁-C₃ alkyl. In embodiments, R⁶ is independently unsubstituted C₁-C₆ alkyl. In embodiments, R⁶ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R⁶ is independently unsubstituted C₁-C₃ alkyl.

[0138] In embodiments, R⁶ is independently halogen, oxo, -CX⁶₃, -CHX⁶₂, -CH₂X⁶, -OCX⁶₃, -OCHX⁶₂, -OCH₂X⁶, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃,
-CH$_2$CH$_3$, -CH$_2$CH$_2$OH, -SH, -SO$_2$H, -SO$_2$H, -SO$_2$NH$_2$, -SO$_2$CH$_3$, -NHNH$_2$, -ONH$_2$, 
-NHC=(O)NHNH$_2$, -NHC=(O)NH$_2$, -NHSO$_2$H, -NHC=(O)H, -NHC(OH)$_2$, -NHOH, -OCH$_3$, 
R$^7$-substituted or unsubstituted alkyl, R$^7$-substituted or unsubstituted heteroalkyl, R$^7$-substituted or unsubstituted cycloalkyl, R$^7$-substituted or unsubstituted heterocycloalkyl, R$^7$-substituted or unsubstituted aryl, or R$^7$-substituted or unsubstituted heteroaryl.

[0139] In embodiments, R$^6$ is independently halogen, oxo, -CX$^6$, -CHX$^6$, -CH$_2$X$^6$, -OCX$^6$, -OCHX$^6$, -CN, -S(O)CH$_3$, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -C(O)CH$_3$, -CH$_2$CH$_3$, -CH$_2$CH$_2$OH, -SH, -SO$_2$H, -SO$_2$H, -SO$_2$NH$_2$, -SO$_2$CH$_3$, -NHNH$_2$, -ONH$_2$, -NHC=(O)NHNH$_2$, -NHC=(O)NH$_2$, -NHSO$_2$H, -NHC=(O)H, -NHC(OH)$_2$, -NHOH, -OCH$_3$, 
R$^7$-substituted or unsubstituted C$_1$-C$_6$ alkyl, R$^7$-substituted or unsubstituted 2 to 6 membered heteroalkyl, R$^7$-substituted or unsubstituted C$_3$-C$_6$ cycloalkyl, R$^7$-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R$^7$-substituted or unsubstituted phenyl, or R$^7$-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0140] In embodiments, R$^6$ is independently hydrogen, halogen, R$^7$-substituted or unsubstituted C$_1$-C$_6$ alkyl or R$^7$-substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R$^6$ is independently halogen, R$^7$-substituted or unsubstituted 3 to 6 membered heteroalkyl. In embodiments, R$^6$ is independently R$^7$-substituted or unsubstituted 4 to 6 membered heteroalkyl.

[0141] R$^5$ is independently halogen, oxo, -CX$^5$, -CHX$^5$, -CH$_2$X$^5$, -OCX$^5$, -OCHX$^5$, -OCH$_2$X$^5$, -CN, -S(O)CH$_3$, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -C(O)CH$_3$, -CH$_2$CH$_3$, -CH$_2$CH$_2$OH, -SH, -SO$_2$H, -SO$_2$H, -SO$_2$NH$_2$, -SO$_2$CH$_3$, -NHNH$_2$, -ONH$_2$, -NHC=(O)NHNH$_2$, -NHC=(O)NH$_2$, -NHSO$_2$H, -NHC=(O)H, -NHC(OH)$_2$, -NHOH, -OCH$_3$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. X$^5$ is independently halogen. In embodiments, X$^5$ is independently -F. In embodiments, R$^5$ is independently hydrogen. In embodiments, R$^5$ is independently unsubstituted C$_1$-C$_6$ alkyl. In embodiments, R$^5$ is independently unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R$^5$ is independently unsubstituted 3 to 6 membered heteroalkyl. In embodiments, R$^5$ is independently unsubstituted 4 to 6 membered heteroalkyl. In embodiments, R$^5$ is independently unsubstituted phenyl. In embodiments, R$^5$ is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, R$^5$ is independently halogen, oxo, -
CX₅⁺, −CHX₅⁻, −CH₂X₅⁻, −OCX₅⁻, −OCHX₅⁻, −OCH₂X₃⁻, −CN, −S(O)CH₃, −OH, −NH₂, −COOH,
−CONH₂, −NO₂, −C(O)CH₃, −CH₂CH₃, −CH₂CH₂OH, −SH, −SO₃H, −SO₄H, −SO₂NH₂, −SO₂CH₃,
−NHNH₂, −ONH₂, −NHC=(O)NHNH₂, −NHC=(O)NH₂, −NH₂SO₃H, −NHC=(O)H, −NHC(O)OH,
−NOH, −OCH₃, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl,
unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted
phenyl, or unsubstituted 5 to 6 membered heteroaryl.

R⁷ is independently halogen, oxo, −CX₃⁻, −CHX₃⁻, −CH₂X₇⁻, −OCX₃⁻, −OCHX₇⁻, −
OCH₂X₇⁻, −CN, −S(O)CH₃, −OH, −NH₂, −COOH, −CONH₂, −NO₂, −C(O)CH₃, −CH₂CH₃,
−CH₂CH₂OH, −SH, −SO₃H, −SO₄H, −SO₂NH₂, −SO₂CH₃, −NHNH₂, −ONH₂, −NHC=(O)NHNH₂,
−NHC=(O)NH₂, −NH₂SO₃H, −NHC=(O)H, −NHC(O)OH, −NOH, −OCH₃, unsubstituted alkyl,
unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted
aryl, or unsubstituted heteroaryl. X⁷ is independently halogen. In embodiments, X⁷ is
independently -F. In embodiments, R² is independently hydrogen. In embodiments, R⁷ is
independently unsubstituted C₁-C₆ alkyl. In embodiments, R⁷ is independently unsubstituted 2 to 6
membered heteroalkyl. In embodiments, R² is independently unsubstituted 3 to 6 membered
heteroalkyl. In embodiments, R² is independently unsubstituted 4 to 6 membered heteroalkyl. In
embodiments, R² is independently unsubstituted phenyl. In embodiments, R² is independently
unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently halogen, oxo, −
CX₃⁻, −CHX₃⁻, −CH₂X₇⁻, −OCX₃⁻, −OCHX₇⁻, −CN, −S(O)CH₃, −OH, −NH₂, −COOH,
−CONH₂, −NO₂, −C(O)CH₃, −CH₂CH₃, −CH₂CH₂OH, −SH, −SO₃H, −SO₄H, −SO₂NH₂, −SO₂CH₃,
−NHNH₂, −ONH₂, −NHC=(O)NHNH₂, −NHC=(O)NH₂, −NH₂SO₃H, −NHC=(O)H, −NHC(O)OH,
−NOH, −OCH₃, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl,
unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted
phenyl, or unsubstituted 5 to 6 membered heteroaryl.

L₁ is a bond, R⁸-substituted or unsubstituted C₁-C₄ alkylene (e.g., C₁-C₄, C₁-C₃, or C₁-C₂), or R⁸-substituted or unsubstituted 2 to 3 membered heteroalkylene. In
embodiments, L₁ is a bond, unsubstituted C₁-C₄ alkylene (e.g., C₁-C₄, C₁-C₃, or C₁-C₂), or
unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L₁ is independently R⁸-substituted
or unsubstituted methylene. In embodiments, L₁ is independently R⁸-substituted or unsubstituted
ethylene. In embodiments, L₁ is independently R⁸-substituted methylene. In embodiments, L₁ is
independently R^8-substituted ethylene. In embodiments, L^1 is independently unsubstituted methylene. In embodiments, L^1 is independently unsubstituted ethylene. In embodiments, L^1 is –C(R^8)=. In embodiments, L^1 is –CH(R^8)=. In embodiments, L^1 is –C(CH_2R^8)=. In embodiments, L^1 is –CH(CH_2R^8)=. In embodiments, L^1 is –C(CH_2CH_3)=. In embodiments, L^1 is –CH(CH_2CH_3)=.

[0144] In embodiments, R^8 is independently oxo, halogen, -CX^3, -CHX^2, -CH_2X, -OCX^3, -OCH_2X^2, -OCHX, -CN, -OH, -NH_2, -COOH, -CONH_2, -SH, -NHNH_2, -ONH_2, -NHC(O)NHNH_2, -NHC(O)NH_2, -NHC(O)H, -NHC(O)OH, -NHOH, R^9-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), R^9-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^9-substituted or unsubstituted cycloalkyl (e.g., C_3-C_6, C_3-C_6, C_4-C_6, or C_5-C_6), R^9-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^9-substituted or unsubstituted aryl (e.g., C_6-C_10 or phenyl), or R^9-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^8 is independently –F, –Cl, –Br, or –I. In embodiments, R^8 is independently unsubstituted methyl. In embodiments, R^8 is independently unsubstituted ethyl. In embodiments, R^8 is independently oxo, halogen, -CX^3, -CHX^2, -CH_2X, -OCX^3, -OCH_2X^2, -OCHX, -CN, -OH, -NH_2, -COOH, -CONH_2, -SH, -NHNH_2, -ONH_2, -NHC(O)NHNH_2, -NHC(O)NH_2, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_6, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_10 or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0145] R^9 is independently oxo, halogen, -CX^3, -CHX^2, -CH_2X, -OCX^3, -OCH_2X^2, -OCHX, -CN, -OH, -NH_2, -COOH, -CONH_2, -SH, -NHNH_2, -ONH_2, -NHC(O)NHNH_2, -NHC(O)NH_2, -NHC(O)H, -NHC(O)OH, -NHOH, R^10-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), R^10-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^10-substituted or unsubstituted cycloalkyl (e.g., C_3-C_6, C_3-C_6, C_4-
C₆, or C₅₋C₆), R¹⁰-substituted or unsubsti tuted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6
membered, 4 to 5 membered, or 5 to 6 membered), R¹⁰-substituted or unsubsti tuted aryl (e.g., C₆-C₁₀
or phenyl), or R¹⁰-substituted or unsubsti tuted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered,
or 5 to 6 membered). X⁰ is independently –F, –Cl, –Br, or –I. In embodiments, R⁹ is independently
hydrogen. In embodiments, R⁹ is independently unsubsti tuted methyl. In embodiments, R⁹ is
independently unsubsti tuted ethyl. In embodiments, R⁹ is independently o xo,
halogen, -CX⁹, -CHX⁹, -CH₂X⁹, -OCX⁹, -OCH₂X⁹, -OCHX⁹, -CN, -OH, -NH₂, -COOH, -CONH₂,
-SH, -NHNH₂, -ONH₂, -NHC(O)NH₂, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH,
unsubsti tuted alkyl (e.g., C₁₋C₈, C₁₋C₆, C₁₋C₄, or C₁₋C₂), unsubsti tuted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubsti tuted
cycloalkyl (e.g., C₃₋C₈, C₃₋C₆, C₄₋C₆, or C₅₋C₆), unsubsti tuted heterocycloalkyl (e.g., 3 to
6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubsti tuted aryl (e.g.,
C₆-C₁₀ or phenyl), or unsubsti tuted heteroaryl. (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6
membered).

[0146] R¹⁰ is independently o xo,
halogen, -CX¹⁰, -CHX¹⁰, -CH₂X¹⁰, -OCX¹⁰, -OCH₂X¹⁰, -OCHX¹⁰, -CN, -OH, -NH₂, -COOH, -CONH₂,
-SH, -NHNH₂, -ONH₂, -NHC(O)NH₂, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH,
unsubsti tuted alkyl (e.g., C₁₋C₈, C₁₋C₆, C₁₋C₄, or C₁₋C₂), unsubsti tuted alkyl (e.g., C₁₋C₈, C₁₋C₆, C₁₋C₄, or C₁₋C₂), unsubsti tuted heteroalkyl (e.g., 2 to
8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubsti tuted
cycloalkyl (e.g., C₃₋C₈, C₃₋C₆, C₄₋C₆, or C₅₋C₆), unsubsti tuted heterocycloalkyl (e.g., 3 to
6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubsti tuted aryl (e.g.,
C₆-C₁₀ or phenyl), or unsubsti tuted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6
membered). X¹⁰ is independently –F, –Cl, –Br, or –I. In embodiments, R¹⁰ is independently
unsubsti tuted methyl. In embodiments, R¹⁰ is independently unsubsti tuted ethyl.

[0147] R² is hydro gen, –OH, R³-substituted or unsubsti tuted cycloalkyl (e.g., C₃₋C₈, C₃₋C₆, C₄₋C₆,
or C₅₋C₆), R³-substituted or unsubsti tuted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered,
4 to 5 membered, or 5 to 6 membered), R³-substituted or unsubsti tuted aryl (e.g., C₆-C₁₀ or phenyl),
or R³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0148] R³ is independently halogen, oxo, -CX³, -CHX³, -CH₂X³, -OCX³, -OCHX³, -OCH₂X³, -CN, -SOᵢ₆R¹⁴, -SO₃NR¹¹R¹², -NHNR¹¹R¹², -ONR¹¹R¹², -NHC=(O)NHNR¹¹R¹², -NHC=(NR¹⁴)NR¹¹R¹², -N(O)₃, -NR¹¹R¹², -C(O)R¹³, -C(O)-OR¹³, -C(O)NR¹¹R¹², -OR¹⁴, -NR¹¹SO₂R¹⁴, -NR¹¹C(O)-OR¹³, -NR¹¹OR¹³, substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₅-C₆, C₄-C₅, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R³ is independently halogen, oxo, -CX³, -CHX³, -CH₂X³, -OCX³, -OCHX³, -OCH₂X³, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NH₂, -ONH₂, -NHC=(O)NH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH₃, R⁶-substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₂), R⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R⁶-substituted or unsubstituted cycloalkyl (e.g., C₅-C₆, C₄-C₅, C₅-C₆), R⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R³ is independently halogen, oxo, -CX³, -CHX³, -CH₂X³, -OCX³, -OCHX³, -OCH₂X³, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NH₂, -ONH₂, -NHC=(O)NH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH₃, R⁶-substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₂), R⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R⁶-substituted or unsubstituted cycloalkyl (e.g., C₅-C₆, C₄-C₅, C₅-C₆), R⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
R^6-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), R^6-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^6-substituted or unsubstituted aryl (e.g., C_6-C_10 or phenyl), or R^6-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^3 is independently halogen, oxo, –CX^3, –CHX^3, –CHX^3, –OCX^3, –OCHX^3, –OCH2X^3, –CN, –S(O)CH_3, –OH, –NH_2, –COOH, –CONH_2, –ONO_2, –C(O)CH_3, –CH_2CH_3, –CH_2CH_2OH, –SH, –SO_2H, –SO_4H, –SO_2NH_2, –SO_2CH_3, –NHNH_2, –ONH_2, –NHC(O)NH_2, –NH(N)=C(O)NH_2, –NHSO_2H, –NH=NHC(O)H, –NHC(O)OH, –NOH, –OCH_3, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_10 or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). Two adjacent R^3 substituents may optionally be joined to form a R^6-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), R^6-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^6-substituted or unsubstituted aryl (e.g., C_6-C_10 or phenyl), or R^6-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^3 is independently halogen. In embodiments, X^3 is independently -F. n3 is an integer from 0 to 4. m3 is 1 or 2. v3 is 1 or 2. In embodiments, n3 is 0. In embodiments, n3 is 1. In embodiments, n3 is 2. In embodiments, n3 is 3. In embodiments, n3 is 4. In embodiments, m3 is 1. In embodiments, m3 is 2. In embodiments, v3 is 1. In embodiments, v3 is 2. 

[0149] R^{11} is independently hydrogen, –CX^{11}, –CN, –COOH, –CONH_2, –CHX^{11}, –CH_2X^{11}, substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_10 or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{11} is independently hydrogen, –CX^{11}, –CN, –COOH, –CONH_2, –CHX^{11}, –CH_2X^{11},
R^{11A}-substituted or unsubstituted alkyl (e.g., C_{1}-C_{8}, C_{1}-C_{6}, C_{1}-C_{4}, or C_{1}-C_{2}), R^{11A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{11A}-substituted or unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C_{4}-C_{6}, or C_{5}-C_{6}), R^{11A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{11A}-substituted or unsubstituted aryl (e.g., C_{6}-C_{10} or phenyl), or R^{11A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{11} is independently –F, -Cl, -Br, or -I. In embodiments, R^{11} is independently hydrogen. In embodiments, R^{11} is independently unsubstituted methyl. In embodiments, R^{11} is independently unsubstituted ethyl. In embodiments, R^{11} is independently hydrogen, -CX^{11}, -CN, -COOH, -CONH_{2}, unsubstituted alkyl (e.g., C_{1}-C_{8}, C_{1}-C_{6}, C_{1}-C_{4}, or C_{1}-C_{2}), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C_{4}-C_{6}, or C_{5}-C_{6}), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_{6}-C_{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0150] In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or unsubstituted heterocycloalkyl or R^{11A}-substituted or unsubstituted heteroaryl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{11A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or unsubstituted piperazinyl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or unsubstituted piperidinyl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or unsubstituted pyrrolidinyl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or unsubstituted azetidinyl. In embodiments, R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{11A}-substituted or
unsubstituted morpholinyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{11A}-substituted or unsubstituted azeridinyl.

[0151] R\textsuperscript{11A} is independently oxo, halogen, -CX\textsuperscript{11A}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -SH, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC(O)NHNH\textsubscript{2},

-CHX\textsuperscript{11A}, -H, -NHC(O).NH\textsubscript{2}, -NHC(O).OH, -NHOH, -CHX\textsuperscript{11A}, -CH\textsubscript{2}X\textsuperscript{11A}, -OCX\textsuperscript{11A}, -OCH\textsubscript{2}X\textsuperscript{11A}, -OH

-CHX\textsuperscript{11A}, R\textsuperscript{11B}-substituted or unsubstituted alkyl (e.g., C\textsubscript{1}-C\textsubscript{8}, C\textsubscript{1}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}), R\textsuperscript{11B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R\textsuperscript{11B}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}), R\textsuperscript{11B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R\textsuperscript{11B}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{10} or phenyl), or R\textsuperscript{11B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

X\textsuperscript{11A} is independently -F, -Cl, -Br, or -I. In embodiments, R\textsuperscript{11A} is independently oxo, halogen, -CX\textsuperscript{11A}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -SH, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC(O)NHNH\textsubscript{2},

-CHX\textsuperscript{11A}, -H, -NHC(O).NH\textsubscript{2}, -NHC(O).OH, -NHOH, -CHX\textsuperscript{11A}, -CH\textsubscript{2}X\textsuperscript{11A}, -OCX\textsuperscript{11A}, -OCH\textsubscript{2}X\textsuperscript{11A}, -OH

-CHX\textsuperscript{11A}, unsubstituted alkyl (e.g., C\textsubscript{1}-C\textsubscript{8}, C\textsubscript{1}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0152] R\textsuperscript{11B} is independently oxo, halogen, -CX\textsuperscript{11B}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -SH,

-NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC(O)NHNH\textsubscript{2},

-NHC(O).NH\textsubscript{2}, -NHC(O).OH, -NHOH, -CHX\textsuperscript{11B}, -CH\textsubscript{2}X\textsuperscript{11B}, -OCX\textsuperscript{11B}, -OCH\textsubscript{2}X\textsuperscript{11B}, -OH

-CHX\textsuperscript{11B}, R\textsuperscript{11C}-substituted or unsubstituted alkyl (e.g., C\textsubscript{1}-C\textsubscript{8}, C\textsubscript{1}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}), R\textsuperscript{11C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R\textsuperscript{11C}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}), R\textsuperscript{11C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R\textsuperscript{11C}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
C₁₀ or phenyl), or R¹¹C-substituted or unsubstituted heteroaryl (e.g., 5 to 10 members, 5 to 9 members, or 5 to 6 members). X¹¹B is independently –F, –Cl, –Br, or –I. In embodiments, R¹¹B is independently oxo, halogen, -CX¹¹B, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, –NHNH₂, –ONH₂, –NHC(O)NHNH₂, –NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX¹¹B, -CH₂X¹¹B, -OCX¹¹B, -OCH₂X¹¹B, -OCHX¹¹B, unsubstituted alkyl (e.g., C₁⁻C₈, C₁⁻C₆, C₁⁻C₄, or C₁⁻C₂), unsubstituted heteroalkyl (e.g., 2 to 8 members, 2 to 6 membered, 4 to 6 members, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₅⁻C₈, C₅⁻C₆, C₄⁻C₆, or C₅⁻C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆⁻C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

R¹¹C is independently oxo, halogen, -CX¹¹C, -CHX¹¹C, -CH₂X¹¹C, -OCX¹¹C, -OCH₂X¹¹C, -OCHX¹¹C, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, –NHNH₂, –ONH₂, –NHC(O)NHNH₂, –NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C₁⁻C₈, C₁⁻C₆, C₁⁻C₄, or C₁⁻C₂), unsubstituted heteroalkyl (e.g., 2 to 8 members, 2 to 6 membered, 4 to 6 members, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃⁻C₈, C₃⁻C₆, C₄⁻C₆, or C₅⁻C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆⁻C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹¹C is independently –F, –Cl, –Br, or –I.

R¹² is independently hydrogen, -CX¹², -CN, -COOH, -CONH₂, -CHX¹², -CH₂X¹², substituted or unsubstituted alkyl (e.g., C₁⁻C₈, C₁⁻C₆, C₁⁻C₄, or C₁⁻C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 members, 2 to 6 membered, 4 to 6 members, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃⁻C₈, C₃⁻C₆, C₄⁻C₆, or C₅⁻C₆), substituted or unsubstituted heterocycloalkyl (e.g., C₃⁻C₈, C₃⁻C₆, C₄⁻C₆, or C₅⁻C₆), substituted or unsubstituted aryl (e.g., C₆⁻C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹² is independently hydrogen, -CX¹², -CN, -COOH, -CONH₂, -CHX¹², -CH₂X¹², R¹²A-substituted or unsubstituted alkyl (e.g., C₁⁻C₈, C₁⁻C₆, C₁⁻C₄, or C₁⁻C₂), R¹²A-substituted or
unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R\textsuperscript{12A}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}), R\textsuperscript{12A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R\textsuperscript{12A}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{10} or phenyl), or R\textsuperscript{12A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X\textsuperscript{12} is –F, –Cl, –Br, or –I. In embodiments, R\textsuperscript{12} is independently hydrogen. In embodiments, R\textsuperscript{12} is independently unsubstituted methyl. In embodiments, R\textsuperscript{12} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{12} is independently hydrogen, -CX\textsuperscript{12}, -CN, -COOH, -CONH\textsubscript{2}, unsubstituted alkyl (e.g., C\textsubscript{1}-C\textsubscript{8}, C\textsubscript{1}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or unsubstituted heterocycloalkyl or R\textsuperscript{12A}-substituted or unsubstituted heteroaryl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R\textsuperscript{12A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or unsubstituted piperazinyl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or unsubstituted piperidinyl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or unsubstituted pyrrolidinyl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or unsubstituted azetidinyl. In embodiments, R\textsuperscript{12} and R\textsuperscript{11} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{12A}-substituted or
unsubstituted morpholinyl. In embodiments, $R^{12}$ and $R^{11}$ substituents bonded to the same nitrogen atom may optionally be joined to form a $R^{12A}$-substituted or unsubstituted azeridinyl.

[0156] $R^{12A}$ is independently oxo, halogen, -CX$^{12A}_3$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -SH, -NHNH$_2$, -ONH$_2$, -NHC(O)NH$_2$,

- NHC(O)NH$_2$, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX$^{12A}_2$, -CH$_2$X$^{12A}$, -OCX$^{12A}_3$, -OCH$_2$X$^{12A}$, -OCHX$^{12A}_2$, $R^{12B}$-substituted or unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_6$, C$_1$-C$_4$, or C$_1$-C$_2$), $R^{12B}$-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{12B}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_1$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), $R^{12B}$-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{12B}$-substituted or unsubstituted aryl (e.g., C$_6$-C$_{10}$ or phenyl), or $R^{12B}$-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{12A}$ is independently -F, -Cl, -Br, or -I. In embodiments, $R^{12A}$ is independently oxo, halogen, -CX$^{12A}_3$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -SH, -NHNH$_2$, -ONH$_2$, -NHC(O)NH$_2$,

- NHC(O)NH$_2$, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX$^{12A}_2$, -CH$_2$X$^{12A}$, -OCX$^{12A}_3$, -OCH$_2$X$^{12A}$, -OCHX$^{12A}_2$, unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_6$, C$_1$-C$_4$, or C$_1$-C$_2$), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C$_6$-C$_{10}$ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0157] $R^{12B}$ is independently oxo, halogen, -CX$^{12B}_3$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -SH, -NHNH$_2$, -ONH$_2$, -NHC(O)NH$_2$,

- NHC(O)NH$_2$, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX$^{12B}_2$, -CH$_2$X$^{12B}$, -OCX$^{12B}_3$, -OCH$_2$X$^{12B}$, -OCHX$^{12B}_2$, $R^{12C}$-substituted or unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_6$, C$_1$-C$_4$, or C$_1$-C$_2$), $R^{12C}$-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{12C}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), $R^{12C}$-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{12C}$-substituted or unsubstituted aryl (e.g., C$_6$-
C_{10} or phenyl), or R^{12C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 members, 5 to 9
membered, or 5 to 6 membered). X^{12B} is independently –F, –Cl, –Br, or –I. In embodiments, R^{12B} is
independently oxo, halogen, –CX^{12B}, –CN, –OH, –NH₂, –COOH, –CONH₂, –SH, –NHNH₂, –ONH₂,
–NHC(O)NHNH₂,

CHX^{12B}, unsubstituted alkyl (e.g., C₁₁₂₈, C₁₁₂₆, C₁₁₂₄, or C₁₁₂₂), unsubstituted heteroalkyl (e.g., 2
to 8 members, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
unsubstituted cycloalkyl (e.g., C₃−C₈, C₅−C₆, C₄−C₆, or C₅−C₆), unsubstituted heterocycloalkyl (e.g., 3
to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g.,
C₆−C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6
membered).

[0158] R^{12C} is independently oxo,
H, –CONH₂, –SH, –NHNH₂, –ONH₂, –NHC(O)NHNH₂,

–NHC(O)NH₂, –NHC(O)H, –NHC(O)OH, –NHOH, unsubstituted alkyl (e.g., C₁₁₂₈, C₁₁₂₆, C₁₁₂₄, or
C₁₁₂₂), unsubstituted heteroalkyl (e.g., 2 to 8 members, 2 to 6 membered, 4 to 6 membered, 2 to 3
membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃−C₈, C₅−C₆, C₄−C₆, or C₅−C₆),
unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6
membered), unsubstituted aryl (e.g., C₆−C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X^{12C} is independently –F, –Cl, –Br, or –I.

[0159] R^{13} is independently hydrogen, –CX^{13}, –CN, –COOH, –CONH₂, –CHX^{13}, –CH₂X^{13},
substituted or unsubstituted alkyl (e.g., C₁−C₈, C₁−C₆, C₁−C₄, or C₁−C₂), substituted or unsubstituted
heteroalkyl (e.g., 2 to 8 members, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5
membered), substituted or unsubstituted cycloalkyl (e.g., C₃−C₈, C₅−C₆, C₄−C₆, or C₅−C₆), substituted
or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to
6 membered), substituted or unsubstituted aryl (e.g., C₆−C₁₀ or phenyl), or substituted or
unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In
embodiments, R^{13} is independently hydrogen, –CX^{13}, –CN, –COOH, –CONH₂, –CHX^{13}, –CH₂X^{13},
R^{13A}-substituted or unsubstituted alkyl (e.g., C₁−C₈, C₁−C₆, C₁−C₄, or C₁−C₂), R^{13A}-substituted or
unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), \( \text{R}^{13A} \)-substituted or unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), \( \text{R}^{13A} \)-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), \( \text{R}^{13A} \)-substituted or unsubstituted aryl (e.g., C\(_6\)-C\(_{10}\) or phenyl), or \( \text{R}^{13A} \)-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). \( \text{X}^{13} \) is independently –F, -Cl, -Br, or -I. In embodiments, \( \text{R}^{13} \) is independently hydrogen. In embodiments, \( \text{R}^{13} \) is independently unsubstituted methyl. In embodiments, \( \text{R}^{13} \) is independently unsubstituted ethyl. In embodiments, \( \text{R}^{13} \) is independently hydrogen, -\( \text{CX}^{13}_3 \), -\( \text{CN} \), -\( \text{COOH} \), -\( \text{CONH}_2 \), unsubstituted alkyl (e.g., C\(_1\)-C\(_8\), C\(_1\)-C\(_6\), C\(_1\)-C\(_4\), or C\(_1\)-C\(_2\)), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C\(_6\)-C\(_{10}\) or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0160] \( \text{R}^{13A} \) is independently oxo, halogen, -\( \text{CX}^{13A}_3 \), -\( \text{CN} \), -\( \text{OH} \), -\( \text{NH}_2 \), -\( \text{COOH} \), -\( \text{CONH}_2 \), -\( \text{SH} \), -\( \text{NHNH}_2 \), -\( \text{ONH}_2 \), -\( \text{NHC(O)NHNH}_2 \), -\( \text{NHC(O)NH}_2 \), -\( \text{NHC(O)H} \), -\( \text{NHC(O)OH} \), -\( \text{NHOH} \), -\( \text{CHX}^{13A}_3 \), -\( \text{CH}_2\text{X}^{13A} \), -\( \text{OCX}^{13A}_3 \), -\( \text{OCH}_2\text{X}^{13A} \), -\( \text{OCHX}^{13A}_3 \), \( \text{R}^{13B} \)-substituted or unsubstituted alkyl (e.g., C\(_1\)-C\(_8\), C\(_1\)-C\(_6\), C\(_1\)-C\(_4\), or C\(_1\)-C\(_2\)), \( \text{R}^{13B} \)-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), \( \text{R}^{13B} \)-substituted or unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), \( \text{R}^{13B} \)-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), \( \text{R}^{13B} \)-substituted or unsubstituted aryl (e.g., C\(_6\)-C\(_{10}\) or phenyl), or \( \text{R}^{13B} \)-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). \( \text{X}^{13A} \) is independently –F, -Cl, -Br, or -I. In embodiments, \( \text{R}^{13A} \) is independently oxo, halogen, -\( \text{CX}^{13A}_3 \), -\( \text{CN} \), -\( \text{OH} \), -\( \text{NH}_2 \), -\( \text{COOH} \), -\( \text{CONH}_2 \), -\( \text{SH} \), -\( \text{NHNH}_2 \), -\( \text{ONH}_2 \), -\( \text{NHC(O)NHNH}_2 \), -\( \text{NHC(O)NH}_2 \), -\( \text{NHC(O)H} \), -\( \text{NHC(O)OH} \), -\( \text{NHOH} \), -\( \text{CHX}^{13A}_3 \), -\( \text{CH}_2\text{X}^{13A} \), -\( \text{OCX}^{13A}_3 \), -\( \text{OCH}_2\text{X}^{13A} \), -\( \text{OCHX}^{13A}_3 \), unsubstituted alkyl (e.g., C\(_1\)-C\(_8\), C\(_1\)-C\(_6\), C\(_1\)-C\(_4\), or C\(_1\)-C\(_2\)), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), unsubstituted heterocycloalkyl (e.g., 3
to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

R¹³B is independently oxo, halogen, -CX¹³B, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX¹³B₂, -CH₂X¹³B, -OCX¹³B, -OCH₂X¹³B, -OCHX¹³B₂, R¹³C-substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₄, or C₁-C₂), R¹³C-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R¹³C-substituted or unsubstituted cycloalkyl (e.g., C₅-C₆, C₄-C₆, or C₅-C₆), R¹³C-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R¹³C-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R¹³C-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹³B is independently –F, –Cl, –Br, or –I. In embodiments, R¹³B is independently oxo, halogen, -CX¹³B, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX¹³B₂, -CH₂X¹³B, -OCX¹³B, -OCH₂X¹³B, -OCHX¹³B₂, unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₅-C₆, C₄-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

R¹³C is independently oxo, halogen, -CX¹³C, -CHX¹³C, -CH₂X¹³C, -OCX¹³C, -OCH₂X¹³C, -OCHX¹³C, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₅-C₆, C₄-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹³C is independently –F, –Cl, –Br, or –I.

[0063] R¹⁴ is independently hydrogen, -CX¹⁴₃, -CN, -COOH, -CONH₂, -CHX¹⁴₂, -CH₂X¹⁴, substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₆, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁴ is independently hydrogen, -CX¹⁴₃, -CN, -COOH, -CONH₂, -CHX¹⁴₂, -CH₂X¹⁴, R¹⁴A-substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₆, or C₁-C₂), R¹⁴A-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R¹⁴A-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R¹⁴A-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R¹⁴A-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R¹⁴A-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁴ is independently –F, –Cl, –Br, or –I. In embodiments, R¹⁴ is independently hydrogen. In embodiments, R¹⁴ is independently unsubstituted methyl. In embodiments, R¹⁴ is independently unsubstituted ethyl. In embodiments, R¹⁴ is independently hydrogen, -CX¹⁴₃, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₆, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0064] R¹⁴A is independently oxo, halogen, -CX¹⁴₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, -NH₂H₂, -ONH₂, -NHC(O)NH₂, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NH₂OH, -CHX¹⁴₂, -CH₂X¹⁴, -OCX¹⁴₂, -OCH₂X¹⁴₂, R¹⁴B-substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₆, C₁-C₆, or C₁-C₂), R¹⁴B.
substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{14B}-substituted or unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C_{4}-C_{6}, or C_{5}-C_{6}), R^{14B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{14B}-substituted or unsubstituted aryl (e.g., C_{6}-C_{10} or phenyl), or R^{14B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{14A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{14A} is independently oxo, halogen, -CX^{14A}_{3}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -SH, -NHNH_{2}, -ONH_{2}, -NHC(O)NNHNH_{2}, -NHC(O)NH_{2}, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX^{14A}_{2}, -CH_{2}X^{14A}, -OCX^{14A}_{3}, -OCH_{2}X^{14A}, -OCHX^{14A}_{2}, unsubstituted alkyl (e.g., C_{1}-C_{8}, C_{1}-C_{6}, C_{1}-C_{4}, or C_{1}-C_{2}), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C_{4}-C_{6}, or C_{5}-C_{6}), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_{6}-C_{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0165] R^{14B} is independently oxo, halogen, -CX^{14B}_{3}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -SH, -NHNH_{2}, -ONH_{2}, -NHC(O)NNHNH_{2}, -NHC(O)NH_{2}, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX^{14B}_{2}, -CH_{2}X^{14B}, -OCX^{14B}_{3}, -OCH_{2}X^{14B}, -OCHX^{14B}_{2}, R^{14C}-substituted or unsubstituted alkyl (e.g., C_{1}-C_{8}, C_{1}-C_{6}, C_{1}-C_{4}, or C_{1}-C_{2}), R^{14C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{14C}-substituted or unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C_{4}-C_{6}, or C_{5}-C_{6}), R^{14C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{14C}-substituted or unsubstituted aryl (e.g., C_{6}-C_{10} or phenyl), or R^{14C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{14B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{14B} is independently oxo, halogen, -CX^{14B}_{3}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -SH, -NHNH_{2}, -ONH_{2}, -NHC(O)NNHNH_{2}, -NHC(O)NH_{2}, -NHC(O)H, -NHC(O)OH, -NHOH, -CHX^{14B}_{2}, -CH_{2}X^{14B}, -OCX^{14B}_{3}, -OCH_{2}X^{14B}, -OCHX^{14B}_{2}, unsubstituted alkyl (e.g., C_{1}-C_{8}, C_{1}-C_{6}, C_{1}-C_{4}, or C_{1}-C_{2}), unsubstituted heteroalkyl (e.g., 2
to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), 
unsubstituted cycloalkyl (e.g., C₃-C₈, C₅-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0166] R¹⁴C is independently oxo,
halogen, -CX¹⁴C³, -CHX¹⁴C₂, -CH₂X¹⁴C, -OCX¹⁴C³, -OCH₂X¹⁴C, -OCHX¹⁴C₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
-NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₅-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁴C is independently –F, –Cl, –Br, or –I.

[0167] In embodiments, L² is a bond, R¹⁵-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), –NH₂, or –O–. In embodiments, L² is a bond, unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), –NH₂, or –O–.

[0168] R¹⁵ is independently oxo,
halogen, -CX¹⁵³, -CHX¹⁵₂, -CH₂X¹⁵, -OCX¹⁵³, -OCH₂X¹⁵, -OCHX¹⁵₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
-NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₅-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁵ is independently oxo, halogen, -CX¹⁵³, -CHX¹⁵₂, -CH₂X¹⁵, -OCX¹⁵³, -OCH₂X¹⁵, -OCHX¹⁵₂, -CN, -OH, -NH₂, -COOH, -C
ONH$_2$, -SH, -NHNH$_2$, -ONH$_2$, -NHC(O)NHNH$_2$,
-NHC(O)NH$_2$, -NHC(O)H, -NHC(O)OH, -NHOH, R$^{16}$-substituted or unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_6$, C$_1$-C$_4$, or C$_1$-C$_2$), R$^{16}$-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R$^{16}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), R$^{16}$-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R$^{16}$-substituted or unsubstituted aryl (e.g., C$_6$-C$_{10}$ or phenyl), or R$^{16}$-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X$^{15}$ is independently –F, –Cl, –Br, or –I. In embodiments, R$^{15}$ is independently unsubstituted methyl. In embodiments, R$^{15}$ is independently unsubstituted ethyl. In embodiments, R$^{15}$ is independently o xo,
halogen, -CX$^{15}$, -CHX$^{15}$, -CH$_2$X$^{15}$, -OCH$^{15}$, -OCH$_2$X$^{15}$, -OCHX$^{15}$, -CN, -OH, -NH$_2$, -COOH, -C
ONH$_2$, -SH, -NHNH$_2$, -ONH$_2$, -NHC(O)NHNH$_2$,
-NHC(O)NH$_2$, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_6$, C$_1$-C$_4$, or C$_1$-C$_2$), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C$_6$-C$_{10}$ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0169] R$^{16}$ is independently o xo,
halogen, -CX$^{16}$, -CHX$^{16}$, -CH$_2$X$^{16}$, -OCH$^{16}$, -OCH$_2$X$^{16}$, -OCHX$^{16}$, -CN, -OH, -NH$_2$, -COOH, -C
ONH$_2$, -SH, -NHNH$_2$, -ONH$_2$, -NHC(O)NHNH$_2$,
-NHC(O)NH$_2$, -NHC(O)H, -NHC(O)OH, -NHOH, substituted or unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_6$, C$_1$-C$_4$, or C$_1$-C$_2$), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C$_6$-C$_{10}$ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R$^{16}$ is independently o xo,
halogen, -CX$^{16}$, -CHX$^{16}$, -CH$_2$X$^{16}$, -OCH$^{16}$, -OCH$_2$X$^{16}$, -OCHX$^{16}$, -CN, -OH, -NH$_2$, -COOH, -C

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ONH₂, -SH, –NHNH₂, –ONH₂, –NHC(O)NHNH₂,
–NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, R¹⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R¹⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R¹⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R¹⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R¹⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R¹⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁶ is independently –F, -Cl, -Br, or -I. In embodiments, R¹⁶ is independently unsubstituted methyl. In embodiments, R¹⁶ is independently unsubstituted ethyl. In embodiments, R¹⁶ is independently hydrogen, oxo, halogen, -CX¹⁶, -CHX¹⁶, -CH₂X¹⁶, -OCX¹⁶, -OCH₂X¹⁶, -OCHX¹⁶, -CN, -OH, -NH₂, -COOH, -C ONH₂, -SH, –NHNH₂, –ONH₂, –NHC(O)NHNH₂,
–NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0170] R¹⁷ is independently oxo,
halogen, -CX¹⁶, -CHX¹⁶, -CH₂X¹⁶, -OCX¹⁶, -OCH₂X¹⁶, -OCHX¹⁶, -CN, -OH, -NH₂, -COOH, -C ONH₂, -SH, –NHNH₂, –ONH₂, –NHC(O)NHNH₂,
–NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁷ is independently –F, -Cl, -Br, or -I. In embodiments, R¹⁷ is independently unsubstituted methyl. In embodiments, R¹⁷ is independently unsubstituted ethyl.
[0171] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

\[
\text{(III).}
\]

[0172] \( L^1, L^2, R^1, \text{ and } R^3 \) are as described herein.

[0173] The symbol \( z_2 \) is an integer from 0 to 5. In embodiments, \( z_2 \) is 5. In embodiments, \( z_2 \) is 4. In embodiments, \( z_2 \) is 3. In embodiments, \( z_2 \) is 2. In embodiments, \( z_2 \) is 1. In embodiments, \( z_2 \) is 0. It is understood that when \( z_2 \) is 0, then \( R^3 \) is hydrogen.

[0174] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

\[
\text{(IV).}
\]

[0175] \( L^1, L^2, R^1, R^3, \text{ and } z_2 \) are as described herein.

[0176] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

\[
\text{. } L^1, R^1, \text{ and } R^2 \text{ are as described herein. In embodiments,}
\]
R² is hydrogen. In embodiments, R² is unsubstituted methyl. In embodiments, R² is –CF₃. In embodiments, R¹ is hydrogen. In embodiments, R¹ is unsubstituted methyl. In embodiments, R¹ is unsubstituted ethyl. In embodiments, R¹ is –CF₃. In embodiments, L¹ is –C(CH₃)₂–. In embodiments, L¹ is –CH₂–. In embodiments, R² is R³-substituted phenyl. In embodiments, R² is R³-substituted methyl. In embodiments, R² is unsubstituted methyl. In embodiments, R² is R³-substituted C₁-C₄ alkyl. In embodiments, R² is unsubstituted C₁-C₄ alkyl.

[0177] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

[Diagram]

L¹, R¹, and R² are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

[Diagram]

L¹, R¹, and R² are as described herein. In embodiments, R² is hydrogen. In embodiments, R² is unsubstituted phenyl. In embodiments, R¹ is hydrogen. In embodiments, R¹ is unsubstituted methyl. In embodiments, R¹ is unsubstituted ethyl. In embodiments, R¹ is –CF₃. In embodiments, L¹ is –C(CH₃)₂–. In embodiments, L¹ is –CH₂–. In embodiments, R² is R³-substituted phenyl. In embodiments, R² is R³-substituted methyl. In embodiments, R² is unsubstituted methyl. In embodiments, R² is R³-substituted C₁-C₄ alkyl. In embodiments, R² is unsubstituted C₁-C₄ alkyl.

[0178] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

[Diagram]

z₂, L¹, R¹, and R³ are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the
formula: z2, L1, R1, and R3 are as described herein. In embodiments, z2 is 0. In embodiments, z2 is 1. In embodiments, R3 is halogen. In embodiments, R3 is unsubstituted methyl. In embodiments, R3 is unsubstituted ethyl. In embodiments, R3 is –CF3. In embodiments, R4 is hydrogen. In embodiments, R4 is unsubstituted methyl. In embodiments, R4 is unsubstituted ethyl. In embodiments, R4 is –CF3. In embodiments, L1 is –C(CH3)2–. In embodiments, L1 is –CH2–.

[0179] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

formula: L2, R1, and R2 are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

R2 is hydrogen. In embodiments, R2 is unsubstituted phenyl. In embodiments, R4 is hydrogen. In embodiments, R4 is unsubstituted methyl. In embodiments, R4 is unsubstituted ethyl. In embodiments, R4 is –CF3. In embodiments, L2 is –O–. In embodiments, L2 is –OCH2–. In embodiments, R2 is R3-substituted phenyl. In embodiments, R2 is R3-substituted methyl. In embodiments, R2 is unsubstituted methyl. In embodiments, R2 is R3-substituted C1–C4 alkyl. In embodiments, R2 is unsubstituted C1–C4 alkyl. In embodiments, L2 is not –O–. In embodiments, L2

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is not −OCH$_3$−. In embodiments, −L$^2$R$^2$ is not −OH. In embodiments, −L$^2$R$^2$ is not −OCH$_2$Ph. In embodiments, the compound is not JD211.

[0180] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

L$^2$, R$^1$, and R$^2$ are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

L$^2$, R$^1$, and R$^2$ are as described herein. In embodiments, R$^2$ is hydrogen. In embodiments, R$^2$ is unsubstituted phenyl. In embodiments, R$^1$ is hydrogen. In embodiments, R$^1$ is unsubstituted methyl. In embodiments, R$^1$ is unsubstituted ethyl. In embodiments, R$^1$ is −CF$_3$. In embodiments, L$^2$ is −O−. In embodiments, L$^2$ is −OCH$_2$−. In embodiments, R$^2$ is R$^3$-substituted phenyl. In embodiments, R$^2$ is R$^3$-substituted methyl. In embodiments, R$^2$ is unsubstituted methyl. In embodiments, R$^2$ is R$^3$-substituted C$_1$-C$_4$ alkyl. In embodiments, R$^2$ is unsubstituted C$_1$-C$_4$ alkyl. In embodiments, L$^2$ is not −O−. In embodiments, L$^2$ is not −OCH$_2$−. In embodiments, −L$^2$R$^2$ is not −OH. In embodiments, −L$^2$R$^2$ is not −OCH$_2$Ph. In embodiments, the compound is not JD212.
In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: \[ \text{L}, \text{L}^1, \text{L}^2, \text{and R}^2 \text{ are as described herein.} \]

In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: \[ \text{L}^1, \text{L}^2, \text{and R}^2 \text{ are as described herein.} \]

\( R^2 \) is hydrogen. In embodiments, \( R^2 \) is unsubstituted phenyl. In embodiments, \( L^1 \) is \(-\text{C}(\text{CH}_3)_2\text{–} \). In embodiments, \( L^1 \) is \(-\text{CH}_2\text{–} \). In embodiments, \( L^2 \) is \(-\text{O}\text{–} \). In embodiments, \( L^2 \) is \(-\text{OCH}_2\text{–} \). In embodiments, \( R^2 \) is \( R^3 \)-substituted phenyl. In embodiments, \( R^2 \) is \( R^3 \)-substituted methyl. In embodiments, \( R^2 \) is unsubstituted methyl. In embodiments, \( R^2 \) is \( R^3 \)-substituted \( C_1\text{-}C_4 \) alkyl. In embodiments, \( R^2 \) is unsubstituted \( C_1\text{-}C_4 \) alkyl.

In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: \[ \text{L}^1 \text{ and } \text{R}^2 \text{ are as described herein.} \]

In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: \[ \text{L}^1 \text{ and } \text{R}^2 \text{ are as described herein.} \]

In embodiments, \( \text{R}^2 \) is hydrogen. In embodiments, \( \text{R}^2 \) is unsubstituted phenyl. In embodiments, \( \text{L}^1 \) is \(-\text{C}(\text{CH}_3)_2\text{–} \). In embodiments, \( \text{L}^1 \) is \(-\text{CH}_2\text{–} \). In embodiments, \( \text{R}^2 \) is \( R^3 \)-substituted phenyl. In embodiments, \( \text{R}^2 \) is \( R^3 \)-substituted phenyl. In embodiments, \( \text{R}^2 \) is
R³-substituted methyl. In embodiments, R² is unsubstituted methyl. In embodiments, R² is R³-substituted C₁-C₄ alkyl. In embodiments, R² is unsubstituted C₁-C₄ alkyl.

[0183] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: 

\[ \text{structure image} \]

L¹ and R² are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: 

\[ \text{structure image} \]

L¹ and R² are as described herein. In embodiments, R² is hydrogen. In embodiments, R² is unsubstituted phenyl. In embodiments, L¹ is \(-\text{C(CH₃)}₂\)-. In embodiments, L¹ is \(-\text{CH₂}-\). In embodiments, R² is R³-substituted phenyl. In embodiments, R² is R³-substituted methyl. In embodiments, R² is unsubstituted methyl. In embodiments, R³ is R³-substituted C₁-C₄ alkyl. In embodiments, R² is unsubstituted C₁-C₄ alkyl.

[0184] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: 

\[ \text{structure image} \]

L² and R² are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula: 

\[ \text{structure image} \]

L² and R² are as described herein. In embodiments, R² is hydrogen. In embodiments, R² is unsubstituted phenyl. In embodiments, L² is \(-\text{O}-\). In
embodiments, $L^2$ is $-\text{OCH}_2-$. In embodiments, $R^2$ is $R^3$-substituted phenyl. In embodiments, $R^3$ is $R^3$-substituted methyl. In embodiments, $R^2$ is unsubstituted methyl. In embodiments, $R^2$ is $R^3$-substituted C$_1$-C$_4$ alkyl. In embodiments, $R^2$ is unsubstituted C$_1$-C$_4$ alkyl.

[0185] In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

$L^2$ and $R^2$ are as described herein. In embodiments, the compound or a pharmaceutically acceptable salt thereof, has the formula:

$L^2$ and $R^2$ are as described herein. In embodiments, $R^2$ is hydrogen. In embodiments, $R^2$ is unsubstituted phenyl. In embodiments, $L^2$ is $-\text{O}-$. In embodiments, $L^2$ is $-\text{OCH}_2-$. In embodiments, $R^2$ is $R^3$-substituted phenyl. In embodiments, $R^3$ is $R^3$-substituted methyl. In embodiments, $R^2$ is unsubstituted methyl. In embodiments, $R^2$ is $R^3$-substituted C$_1$-C$_4$ alkyl. In embodiments, $R^2$ is unsubstituted C$_1$-C$_4$ alkyl.

[0186] In embodiments, the compound is selected from the group consisting of:

JD211,

JD212,

JD213,

JD214,
JD215, and JD216. In embodiments, the compound is

JD211. In embodiments, the compound is

JD212. In embodiments, the compound is

JD213. In embodiments, the compound is

JD214. In embodiments, the compound is

JD215. In embodiments, the compound is

JD216.
[0187] In embodiments, the compound is not JD211. In embodiments, the compound is not JD212. In embodiments, the compound is not JD213. In embodiments, the compound is not JD214. In embodiments, the compound is not JD215. In embodiments, the compound is not JD216.

[0188] In embodiments, $R^2$ is not hydrogen. In embodiments, $R^2$ is not unsubstituted phenyl. In embodiments, $R^1$ is not hydrogen. In embodiments, $R^1$ is not unsubstituted methyl. In embodiments, $R^1$ is not unsubstituted ethyl. In embodiments, $R^1$ is not $-\text{CF}_3$. In embodiments, $L^2$ is not $-\text{O}^-$. In embodiments, $L^2$ is not $-\text{OCH}_2^-$. In embodiments, $-L^2R^2$ is not $-\text{OH}$. In embodiments, $-L^2R^2$ is not $-\text{OCH}_3\text{Ph}$. In embodiments, $L^1$ is not $-\text{C(CH}_3)_2^-$. In embodiments, $L^1$ is not $-\text{CH}_2^-$. 

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In some embodiments, the compound is a compound described herein, including in an aspect, embodiment, example, table, figure, or claim.

III. Pharmaceutical Compositions

In another aspect is provided a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

In embodiments of the pharmaceutical compositions, the compound (e.g. as described herein, including embodiments), or pharmaceutically acceptable salt thereof, is included in a therapeutically effective amount. In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent (e.g. therapeutic agent). In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent (e.g. therapeutic agent) in a therapeutically effective amount. In embodiments, the second agent is an agent for treating cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer). In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic. In embodiments, the second agent is a hormonal therapeutic agent. In embodiments, the second agent is a platinum-based compound. In embodiments, the second agent is tamoxifen. In embodiments, the second agent is trastuzumab. In embodiments, the second agent is cisplatin. In embodiments, the second agent is carboplatin. In embodiments, the second agent is an agent for treating leukemia. In embodiments, the second agent is an agent for treating breast cancer (e.g., triple negative breast cancer). In embodiments, the second agent is an agent for treating lung cancer. In embodiments, the second agent is an agent for treating non-small cell lung cancer. In embodiments, the second agent is an agent for treating a therapy resistant cancer. In embodiments, the second agent is an agent for reducing NFκB phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by NFκB phosphorylation. In embodiments, the second agent is an agent for reducing NFκB activity. In embodiments, the second agent is an agent for treating tamoxifen resistant cancer. In embodiments, the second agent is an agent for treating cisplatin
resistant cancer. In embodiments, the second agent is an agent for treating carboplatin resistant cancer. In embodiments, the second agent is an agent for treating trastuzumab resistant cancer. In embodiments, the second agent is an agent for treating hormonal therapy resistant cancer. In embodiments, the second agent is an agent for treating platinum-based compound resistant cancer. In embodiments, the second agent is an agent for treating a hyperproliferative disease (e.g. cancer or a non-malignant hyperproliferative disease). In embodiments, the second agent is an agent for treating a hamartomatous lesion. In embodiments, the second agent is an agent for treating angiomyolipoma. In embodiments, the second agent is an agent for treating lymphangioleiomyomatosis. In embodiments, the second agent is an agent for treating tuberous sclerosis complex. In embodiments, the second agent is an agent for treating a hamartia. In embodiments, the second agent is an agent for treating a hamartoma. In embodiments, the second agent is an agent for increasing the activity of a pathway including TSC1. In embodiments, the second agent is an agent for increasing TSC1 activity. In embodiments, the second agent is an agent for increasing the activity of a pathway including TSC2. In embodiments, the second agent is an agent for increasing TSC2 activity. In embodiments, the second agent is an agent for decreasing the activity of a pathway including mTOR. In embodiments, the second agent is an agent for decreasing mTOR activity. In embodiments, the second agent is an agent for decreasing the activity of a pathway including mTORC1. In embodiments, the second agent is an agent for decreasing mTORC1 activity.

[0192] In some embodiments, the compound is a compound described herein, including in an example, a table, a figure, or a claim. In some embodiments, the compound is a compound described in the Compounds section above.

IV. Methods of Treatment

[0193] In another aspect is provided a method of treating cancer in a patient in need of the treatment, the method including administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments) to the patient.

[0194] In embodiments, the cancer is breast cancer. In embodiments, the cancer is a therapy resistant breast cancer. In embodiments, the cancer is a hormonal therapy resistant breast cancer. In
embodiments, the cancer is tamoxifen resistant breast cancer. In embodiments, the cancer is trastuzumab (i.e. Herceptin™) resistant breast cancer. In embodiments, the cancer is breast cancer resistant to an aromatase inhibitor. In embodiments, the cancer is fulvestrant resistant breast cancer. In embodiments, the cancer is exemestane resistant breast cancer. In embodiments, the cancer is anastrozole resistant breast cancer. In embodiments, the cancer is aminoglutethimide resistant breast cancer. In embodiments, the cancer is testolactone resistant breast cancer. In embodiments, the cancer is letrozole resistant breast cancer. In embodiments, the cancer is vorozole resistant breast cancer. In embodiments, the cancer is formestane resistant breast cancer. In embodiments, the cancer is fadrozole resistant breast cancer. In embodiments, the cancer is metastatic breast cancer.

In embodiments, the cancer is ER positive breast cancer. In embodiments, the cancer is ER negative breast cancer. In embodiments, the cancer is breast cancer resistant to an anti-cancer agent. In embodiments, the cancer is breast cancer expressing a high level of HER2 (e.g. relative to a control such as a non-cancerous sample). In embodiments, the cancer is triple negative breast cancer. In embodiments, the cancer is a basal type breast cancer (e.g., having cytokeratin 5/6 and EGFR staining, having strong expression of cytokeratin 5/6). In embodiments, the triple negative breast cancer is a basal type breast cancer (e.g., having cytokeratin 5/6 and EGFR staining, having strong expression of cytokeratin 5/6). In embodiments, the triple negative breast cancer is secretory cell carcinoma. In embodiments, the triple negative breast cancer is adenoid cystic cancer type. In embodiments, the triple negative breast cancer is medullary cancer. In embodiments, the triple negative breast cancer is ductal carcinoma. In embodiments, the triple negative breast cancer is grade 3 invasive ductal carcinoma. In embodiments, the triple negative breast cancer is grade 3 invasive ductal carcinoma with no specific subtype. In embodiments, the triple negative breast cancer is metastatic cancer. In embodiments, the triple negative breast cancer includes a reduced level of activity of BRCA1 compared to control (e.g., non-cancer associated BRCA1 level of activity, average level of BRCA1 activity of non-cancerous cells) (e.g., reduced level of BRCA1 activity associated with BRCA1 mutation). In embodiments, the triple negative breast cancer includes a BRCA1 mutation compared to control (e.g., non-cancer associated BRCA1). In embodiments, the triple negative breast cancer is apocrine gland carcinoma. In embodiments, the triple negative breast cancer is squamous carcinoma. In embodiments, the triple negative breast cancer is inflammatory breast cancer.
In embodiments, the cancer is lung cancer. In embodiments, the cancer is non-small cell lung cancer (NSCLC). In embodiments, the cancer is a therapy resistant NSCLC. In embodiments, the cancer is oxaliplatin resistant NSCLC. In embodiments, the cancer is cisplatin resistant NSCLC. In embodiments, the cancer is NSCLC resistant to a platinum-based compound. In embodiments, the cancer is carboplatin resistant NSCLC. In embodiments, the cancer is lung cancer resistant to a platinum-based compound. In embodiments, the cancer is metastatic lung cancer. In embodiments, the cancer is metastatic NSCLC. In embodiments, the cancer is lung cancer resistant to an anti-cancer agent. In embodiments, the cancer is NSCLC resistant to an anti-cancer agent. In embodiments, the cancer is resistant to a taxane. In embodiments, the cancer is resistant to a hormonal therapy. In embodiments, the cancer is resistant to a platinum-based compound. In embodiments, the cancer is resistant to docetaxel.

In embodiments, the cancer is urinary bladder cancer. In embodiments, the cancer is a therapy resistant urinary bladder cancer. In embodiments, the cancer is prostate cancer. In embodiments, the cancer is a therapy resistant prostate cancer. In embodiments, the cancer is leukemia. In embodiments, the cancer is a therapy resistant leukemia. In embodiments, the cancer is lymphoma. In embodiments, the cancer is a therapy resistant lymphoma. In embodiments, the cancer is epidermoid carcinoma (i.e. squamous-cell carcinoma). In embodiments, the cancer is a therapy resistant epidermoid carcinoma (i.e. squamous-cell carcinoma). In embodiments, the cancer is fibrosarcoma. In embodiments, the cancer is a therapy resistant fibrosarcoma. In embodiments, the cancer is liver cancer (e.g. hepatocellular carcinoma). In embodiments, the cancer is a therapy resistant liver cancer (e.g. hepatocellular carcinoma). In embodiments, the cancer is kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma). In embodiments, the cancer is a therapy resistant kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma). In embodiments, the cancer is a hematopoietic cell cancer. In embodiments, the cancer is a therapy resistant hematopoietic cell cancer. In embodiments, the cancer is metastatic cancer. In embodiments, the cancer is resistant to an anti-cancer agent.

In another aspect is provided a method of treating a non-malignant hyperproliferative disease in a patient in need of the treatment, the method including administering a therapeutically
effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments) to the patient.

[0198] In embodiments, the non-malignant hyperproliferative disease is a hamartomatous lesion. In embodiments, the non-malignant hyperproliferative disease is angiomylipoma. In embodiments, the non-malignant hyperproliferative disease is lymphangioleiomyomatosis. In embodiments, the non-malignant hyperproliferative disease is tuberous sclerosis complex. In embodiments, the non-malignant hyperproliferative disease is a hamartia. In embodiments, the non-malignant hyperproliferative disease is a hamartoma.

[0199] In embodiments of the methods of treating a disease (e.g. cancer or a non-malignant hyperproliferative disease), the compound, or pharmaceutically acceptable salt thereof, is provided as a pharmaceutical composition (as described herein, including embodiments).

[0200] In embodiments, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent). In embodiments, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent), which is administered in a therapeutically effective amount. In embodiments, the second agent is an agent for treating cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer). In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic. In embodiments, the second agent is a hormonal therapeutic agent. In embodiments, the second agent is a platinum-based compound. In embodiments, the second agent is tamoxifen. In embodiments, the second agent is trastuzumab. In embodiments, the second agent is cisplatin. In embodiments, the second agent is carboplatin. In embodiments, the second agent is an agent for treating leukemia. In embodiments, the second agent is an agent for treating breast cancer. In embodiments, the second agent is an agent for treating lung cancer. In embodiments, the second agent is an agent for treating non-small cell lung cancer. In embodiments, the second agent is an agent for treating a therapy resistant cancer (e.g. a therapy resistant leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate
cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast
cancer, urinary bladder cancer, or prostate cancer). In embodiments, the second agent is an agent for
reducing NFκB phosphorylation. In embodiments, the second agent is an agent for inhibiting a
pathway activated by NFκB phosphorylation. In embodiments, the second agent is an agent for
reducing NFκB activity. In embodiments, the second agent is an agent for treating tamoxifen
resistant cancer. In embodiments, the second agent is an agent for treating cisplatin resistant cancer.
In embodiments, the second agent is an agent for treating carboplatin resistant cancer. In
embodiments, the second agent is an agent for treating trastuzumab resistant cancer. In
embodiments, the second agent is an agent for treating hormonal therapy resistant cancer. In
embodiments, the second agent is an agent for treating platinum-based compound resistant cancer.
In embodiments, the second agent is an agent for treating a hyperproliferative disease (e.g. cancer or
a non-malignant hyperproliferative disease). In embodiments, the second agent is an agent for
treating a hamartomatous lesion. In embodiments, the second agent is an agent for treating
angiomyolipoma. In embodiments, the second agent is an agent for treating
lymphangioleiomyomatosis. In embodiments, the second agent is an agent for treating tuberous
sclerosis complex. In embodiments, the second agent is an agent for treating a hamartia. In
embodiments, the second agent is an agent for treating a hamartoma. In embodiments, the second
agent is an agent for increasing the activity of a pathway including TSC1. In embodiments, the
second agent is an agent for increasing TSC1 activity. In embodiments, the second agent is an agent
for increasing the activity of a pathway including TSC2. In embodiments, the second agent is an
agent for increasing TSC2 activity. In embodiments, the second agent is an agent for decreasing the
activity of a pathway including mTOR. In embodiments, the second agent is an agent for decreasing
mTORC1 activity. In embodiments, the second agent is glembatumumab vedotin. In embodiments,
the second agent is capecitabine. In embodiments, the second agent is nab-paclitaxel (nanoparticle
albumin-bound paclitaxel). In embodiments, the second agent is sacituzumab govitecan. In
embodiments, the second agent is Vanticumab. In embodiments, the second agent is atezolizumab.
In embodiments, the second agent is gemcitabine. In embodiments, the second agent is metformin.
In embodiments, the second agent is LAS17. In embodiments, the second agent is an inhibitor of
glutathione-S-transferase Pi1. In embodiments, the second agent is a PARP inhibitor. In embodiments, the second agent is iniparib. In embodiments, the second agent is NK012. In embodiments, the second agent is irinotecan. In embodiments, the second agent is SN-38. In embodiments, the second agent is trastuzumab. In embodiments, the second agent is trastuzumab emtansine. In embodiments, the second agent is anastrozole. In embodiments, the second agent is exemestane. In embodiments, the second agent is fulvestrant. In embodiments, the second agent is goserelin. In embodiments, the second agent is letrozole. In embodiments, the second agent is leuprolide. In embodiments, the second agent is megestrol acetate. In embodiments, the second agent is tamoxifen. In embodiments, the second agent is toremifene. In embodiments, the second agent is a CDK4/6 inhibitor. In embodiments, the second agent is palbociclib. In embodiments, the second agent is everolimus. In embodiments, the second agent is cyclophosphamide. In embodiments, the second agent is docetaxel. In embodiments, the second agent is doxorubicin. In embodiments, the second agent is epirubicin. In embodiments, the second agent is methotrexate. In embodiments, the second agent is paclitaxel. In embodiments, the second agent is 5-fluorouracil. In embodiments, the second agent is capecitabine. In embodiments, the second agent is carboplatin. In embodiments, the second agent is cisplatin. In embodiments, the second agent is eribulin. In embodiments, the second agent is gemcitabine. In embodiments, the second agent is ixabepilone. In embodiments, the second agent is liposomal doxorubicin. In embodiments, the second agent is vinorelbine. In embodiments, the second agent is pertuzumab. In embodiments, the second agent is lapatinib.

[0201] In some embodiments, the compound is a compound described herein, including in an example, a table, a figure, or a claim. In some embodiments, the compound is a compound described in the Compounds section above. In embodiments, a therapeutically effective amount of the compound is administered in multiple sub-therapeutic doses over time.

V. Methods of Modulating a Target

[0202] In another aspect is provided a method of inhibiting cancer cell growth or survival including contacting the cancer cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).
In embodiments, the cancer cell is a stem cell. In embodiments, the cancer cell is a progenitor cell. In embodiments, the cancer cell is a cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) stem cell. In embodiments, the cancer cell is a cancer (e.g. leukemia, lung cancer, epidermoid carcinoma (i.e. squamous-cell carcinoma), fibrosarcoma, liver cancer (e.g. hepatocellular carcinoma), prostate cancer, kidney cancer (e.g. renal cell carcinoma or urothelial cell carcinoma), lymphoma, breast cancer, urinary bladder cancer, prostate cancer, or therapy resistant cancer) progenitor cell. In embodiments, the cancer cell is a lung cancer stem cell. In embodiments, the cancer cell is a lung cancer progenitor cell. In embodiments, the cancer cell is a breast cancer stem cell. In embodiments, the cancer cell is a breast cancer progenitor cell. In embodiments, the compound, or a pharmaceutically acceptable salt thereof, (as described herein, including embodiments) increases apoptosis in the cancer cell. In embodiments, the compound, or a pharmaceutically acceptable salt thereof, (as described herein, including embodiments) induces apoptosis in the cancer cell.

In another aspect is provided a method of modulating the level of activity of NF-κB in a cell including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

In embodiments of the methods of modulating NFκB, modulating is inhibiting the level of activity of NFκB. In embodiments of the methods of modulating NFκB, modulating is increasing the level of activity of NFκB. In embodiments of the methods of modulating NFκB, the compound, or pharmaceutically acceptable salt thereof, is provided as a pharmaceutical composition (as described herein, including embodiments). In embodiments of the method of modulating NFκB, the method includes contacting NFκB with a compound as described herein (including embodiments). In embodiments of the method of modulating NFκB, the method includes contacting a component of a pathway including NFκB with a compound as described herein (including embodiments). In embodiments of the methods of modulating NFκB, modulating is inhibiting the phosphorylation of NFκB. In embodiments of the methods of modulating NFκB, modulating is inhibiting a pathway activated by the phosphorylation of NFκB. In embodiments of the methods of modulating NFκB,
modulating is inhibiting a pathway including phosphorylated NFκB. In embodiments, the method
includes reducing the level of nuclear translocation of NFκB (e.g., compared to control, for example
a control is the method without administering a compound described herein). In embodiments, the
method includes reducing the level of IkBα phosphorylation (e.g., compared to control, for example
a control is the method without administering a compound described herein). In embodiments, the
method includes reducing the level of IkB Kinase activity (e.g., compared to control, for example a
control is the method without administering a compound described herein). In embodiments, the
method includes reducing the level of NFκB activity (e.g., compared to control, for example a
control is the method without administering a compound described herein).

[0206] In another aspect is provided a method of modulating the level of activity of TSC1 in a cell
including contacting the cell with an effective amount of a compound, or a pharmaceutically
acceptable salt thereof, as described herein (including embodiments).

[0207] In embodiments of the methods of modulating TSC1, modulating is inhibiting the level of
activity of TSC1. In embodiments of the methods of modulating TSC1, modulating is increasing the
level of activity of TSC1. In embodiments of the methods of modulating TSC1, modulating is
decreasing the level of activity of TSC1. In embodiments of the methods of modulating TSC1, the
compound, or pharmaceutically acceptable salt thereof, is provided as a pharmaceutical composition
(as described herein, including embodiments). In embodiments of the method of modulating TSC1,
the method includes contacting TSC1 with a compound as described herein (including
embodiments). In embodiments of the method of modulating TSC1, the method includes
modulating the level of activity or amount of a component in a pathway including TSC1.

[0208] In another aspect is provided a method of modulating the level of activity of TSC2 in a cell
including contacting the cell with an effective amount of a compound, or a pharmaceutically
acceptable salt thereof, as described herein (including embodiments).

[0209] In embodiments of the methods of modulating TSC2, modulating is inhibiting the level of
activity of TSC2. In embodiments of the methods of modulating TSC2, modulating is increasing the
level of activity of TSC2. In embodiments of the methods of modulating TSC2, modulating is
decreasing the level of activity of TSC2. In embodiments of the methods of modulating TSC2, the
compound, or pharmaceutically acceptable salt thereof, is provided as a pharmaceutical composition (as described herein, including embodiments). In embodiments of the method of modulating TSC2, the method includes contacting TSC2 with a compound as described herein (including embodiments). In embodiments of the method of modulating TSC2, the method includes modulating the level of activity or amount of a component in a pathway including TSC2.

[0210] In another aspect is provided a method of modulating the level of activity of mTOR in a cell including contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein (including embodiments).

[0211] In embodiments of the methods of modulating mTOR, modulating is inhibiting the level of activity of mTOR. In embodiments of the methods of modulating mTOR, modulating is increasing the level of activity of mTOR. In embodiments of the methods of modulating mTOR, the compound, or pharmaceutically acceptable salt thereof, is provided as a pharmaceutical composition (as described herein, including embodiments). In embodiments of the method of modulating mTOR, the method includes contacting mTOR with a compound as described herein (including embodiments). In embodiments of the method of modulating mTOR, the method includes modulating the level of activity or amount of a component in a pathway including mTOR. In embodiments of the methods of modulating mTOR, modulating is inhibiting the level of activity of mTORC1. In embodiments of the methods of modulating mTOR, modulating is increasing the level of activity of mTORC1. In embodiments of the methods of modulating mTOR, the compound, or pharmaceutically acceptable salt thereof, is provided as a pharmaceutical composition (as described herein, including embodiments). In embodiments of the method of modulating mTOR, the method includes contacting mTORC1 with a compound as described herein (including embodiments). In embodiments of the method of modulating mTOR, the method includes modulating the level of activity or amount of a component in a pathway including mTORC1.

[0212] In embodiments, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent). In embodiments, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent), which is administered in a therapeutically effective amount. In embodiments, the second
agent is a second agent as described herein, including in the method of treatment section above and including embodiments.

[0213] In some embodiments, the compound is a compound described herein, including in an example, a table, a figure, or a claim. In some embodiments, the compound is a compound described in the Compounds section above.

VI. ADDITIONAL EMBODIMENTS

[0214] Embodiment P1. A compound, or a pharmaceutically acceptable salt thereof, having the formula:

![Chemical structure](image)

\[(I)\]

wherein \( L^1 \) is a bond, substituted or unsubstituted \( C_1-C_4 \) alkylene, or substituted or unsubstituted 2 to 3 membered heteroalkylene; \( L^2 \) is a bond, substituted or unsubstituted heteroalkylene, \(-\text{NH}^-\), or \(-\text{O}^-\); \( R^1 \) is hydrogen, substituted or unsubstituted \( C_1-C_6 \) alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted \( C_1-C_6 \) cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl; \( R^2 \) is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0215] Embodiment P2. The compound of embodiment P1, or a pharmaceutically acceptable salt thereof, having the formula:

![Chemical structure](image)

\[(II)\]
[0216] Embodiment P3. The compound of one of embodiments P1 to P2, wherein $L^1$ is substituted or unsubstituted propylene.

[0217] Embodiment P4. The compound of one of embodiments P1 to P2, wherein $L^1$ is $\text{C}(\text{CH}_3)_2$–.

[0218] Embodiment P5. The compound of one of embodiments P1 to P2, wherein $L^1$ is substituted or unsubstituted methylene.

[0219] Embodiment P6. The compound of one of embodiments P1 to P5, wherein $L^2$ is $\text{O}(\text{CH}_2)_{z1}$– and $z1$ is an integer from 0 to 3.

[0220] Embodiment P7. The compound of one of embodiments P1 to P5, wherein $L^2$ is $\text{NH}(\text{CH}_2)_{z1}$– and $z1$ is an integer from 0 to 3.

[0221] Embodiment P8. The compound of one of embodiments P6 to P7, wherein $z1$ is 1.

[0222] Embodiment P9. The compound of one of embodiments P1 to P5, wherein $L^2$ is $\text{O}$–.

[0223] Embodiment P10. The compound of one of embodiments P1 to P9, wherein $R^1$ is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

[0224] Embodiment P11. The compound of one of embodiments P1 to P9, wherein $R^1$ is hydrogen.

[0225] Embodiment P12. The compound of one of embodiments P1 to P9, wherein $R^1$ is $-\text{CH}_3$.

[0226] Embodiment P13. The compound of one of embodiments P1 to P12, wherein $R^2$ is hydrogen.

[0227] Embodiment P14. The compound of one of embodiments P1 to P12, wherein $R^2$ is substituted or unsubstituted heteroaryl.

[0228] Embodiment P15. The compound of one of embodiments P1 to P12, wherein $R^2$ is substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.
[0229] Embodiment P16. The compound of one of embodiments P1 to P12, wherein $R^2$ is substituted or unsubstituted phenyl.

[0230] Embodiment P17. The compound of one of embodiments P1 to P12, having the formula:

![Chemical Structure]

(III);

wherein $R^3$ is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2$, $-SO_2CH_3$, $-SO_3H$, $-SO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent $R^3$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $z_2$ is an integer from 0 to 5.

[0231] Embodiment P18. The compound of embodiment P17, wherein $z_2$ is 1.

[0232] Embodiment P19. The compound of embodiment P17, wherein $z_2$ is 0.

[0233] Embodiment P20. The compound, or a pharmaceutically acceptable salt thereof, of embodiment P1, wherein the compound is:
[0234] Embodiment P21. The compound, or a pharmaceutically acceptable salt thereof, of embodiment P1, wherein the compound is:

[0235] Embodiment P22. The compound, or a pharmaceutically acceptable salt thereof, of embodiment P1, wherein the compound is:
[0236] Embodiment P23. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof, of one of embodiments P1 to P22.

[0237] Embodiment P24. A method of treating cancer in a patient in need of said treatment, said method comprising administering a therapeutically effective amount of a compound of one of embodiments P1 to P22, or a pharmaceutically acceptable salt thereof, to said patient.


[0239] Embodiment P26. A method of decreasing the level of activity of NF-κB or mTOR in a cell comprising contacting the cell with an effective amount of a compound of one of embodiments P1 to P22, or a pharmaceutically acceptable salt thereof.

[0240] Embodiment P27. A method of increasing the level of activity of TSC1 or TSC2 in a cell comprising contacting the cell with an effective amount of a compound of one of embodiments P1 to P22, or a pharmaceutically acceptable salt thereof.

[0241] Embodiment 1. A compound, or a pharmaceutically acceptable salt thereof, having the formula:

(I); wherein \( L^1 \) is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; \( L^2 \) is a bond, substituted or unsubstituted heteroalkylene, –NH–, or –O–; \( R^1 \) is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^2 \) is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
[0242] Embodiment 2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein \( L^1 \) is a bond, substituted or unsubstituted \( C_1-C_4 \) alkylene, or substituted or unsubstituted 2 to 3 membered heteroalkylene; \( L^2 \) is a bond, substituted or unsubstituted heteroalkylene, \(-\text{NH}-\), or \(-\text{O}-\); \( R^1 \) is hydrogen, substituted or unsubstituted \( C_1-C_6 \) alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted \( C_3-C_6 \) cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl; \( R^2 \) is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0243] Embodiment 3. The compound of one of embodiments 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

![Chemical Structure](II)

[0244] Embodiment 4. The compound of one of embodiments 1 to 3, wherein \( L^1 \) is a bond.

[0245] Embodiment 5. The compound of one of embodiments 1 to 3, wherein \( L^1 \) is unsubstituted methylene.

[0246] Embodiment 6. The compound of one of embodiments 1 to 3, wherein \( L^1 \) is substituted or unsubstituted propylene.

[0247] Embodiment 7. The compound of one of embodiments 1 to 3, wherein \( L^1 \) is \(-C(R^8)\); \( R^8 \) is independently oxo, halogen, \(-\text{CX}^8_3\), \(-\text{CHX}^8_2\), \(-\text{CH}_2\text{X}^8\), \(-\text{OCX}^8_3\), \(-\text{OCH}_2\text{X}^8\), \(-\text{OCHX}^8_2\), \(-\text{CN}\), \(-\text{OH}\), \(-\text{NH}_2\), \(-\text{COOH}\), \(-\text{CONH}_2\), \(-\text{SH}\), \(-\text{NHNH}_2\), \(-\text{ONH}_2\), \(-\text{NHC(O)NHNH}_2\), \(-\text{NHC(O)NH}_2\), \(-\text{NHC(O)H}\), \(-\text{NHC(O)OH}\), \(-\text{NHOH}\), \( R^9 \)-substituted or unsubstituted alkyl, \( R^9 \)-substituted or unsubstituted heteroalkyl, \( R^9 \)-substituted or unsubstituted cycloalkyl, \( R^9 \)-substituted or unsubstituted heterocycloalkyl, \( R^9 \)-substituted or unsubstituted aryl, or \( R^9 \)-substituted or unsubstituted heteroaryl; \( R^9 \) is independently oxo,
halogen, -CX\(^9\), -CHX\(^9\), -CH\(_2\)X\(^9\), -OCX\(^9\), -OCH\(_2\)X\(^9\), -OCHX\(^9\), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -SH, -NHNH\(_2\), -ONH\(_2\), -NH\(_2\)(O)NHNH\(_2\), -NH\(_2\)(O)NH\(_2\), -NH\(_2\)(O)H, -NH\(_2\)(O)OH, -NHOH, R\(^{10}\)-substituted or unsubstituted alkyl, R\(^{10}\)-substituted or unsubstituted heteroalkyl, R\(^{10}\)-substituted or unsubstituted cycloalkyl, R\(^{10}\)-substituted or unsubstituted heterocycloalkyl, unsubstituted alkyl, or unsubstituted aryl, or R\(^{10}\)-substituted or unsubstituted heteroaryl, R\(^{10}\) is independently oxo, halogen, -CX\(^{10}\), -CHX\(^{10}\), -CH\(_2\)X\(^{10}\), -OCX\(^{10}\), -OCH\(_2\)X\(^{10}\), -OCHX\(^{10}\), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -SH, -NHNH\(_2\), -ONH\(_2\), -NH\(_2\)(O)NHNH\(_2\), -NH\(_2\)(O)NH\(_2\), -NH\(_2\)(O)H, -NH\(_2\)(O)OH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl, and X\(^8\), X\(^9\), and X\(^{10}\) are independently –F, –Cl, –Br, or –I.

**[0248]** Embodiment 8. The compound of one of embodiments 1 to 3, wherein L\(^1\) is –C(R\(^8\))\(_2\)–; R\(^8\) is independently oxo, halogen, -CX\(^8\), -CHX\(^8\), -CH\(_2\)X\(^8\), -OCX\(^8\), -OCH\(_2\)X\(^8\), -OCHX\(^8\), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -SH, -NHNH\(_2\), -ONH\(_2\), -NH\(_2\)(O)NHNH\(_2\), -NH\(_2\)(O)NH\(_2\), -NH\(_2\)(O)H, -NH\(_2\)(O)OH, -NHOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and X\(^8\) is independently –F, –Cl, –Br, or –I.

**[0249]** Embodiment 9. The compound of one of embodiments 1 to 3, wherein L\(^1\) is –C(CH\(_3\))\(_2\)–.

**[0250]** Embodiment 10. The compound of one of embodiments 1 to 3, wherein L\(^1\) is substituted or unsubstituted methylene.

**[0251]** Embodiment 11. The compound of one of embodiments 1 to 10, wherein L\(^2\) is a bond, R\(^{15}\)-substituted or unsubstituted heteroalkylene, –NH–, or –O–; R\(^{15}\) is independently oxo, halogen, -CX\(^{15}\), -CHX\(^{15}\), -CH\(_2\)X\(^{15}\), -OCX\(^{15}\), -OCH\(_2\)X\(^{15}\), -OCHX\(^{15}\), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -SH, -NHNH\(_2\), -ONH\(_2\), -NH\(_2\)(O)NHNH\(_2\), -NH\(_2\)(O)NH\(_2\), -NH\(_2\)(O)H, -NH\(_2\)(O)OH, R\(^{16}\)-substituted or unsubstituted alkyl, R\(^{16}\)-substituted or unsubstituted heteroalkyl, R\(^{16}\)-substituted or unsubstituted cycloalkyl, R\(^{16}\)-substituted or unsubstituted heterocycloalkyl, R\(^{16}\)-substituted or unsubstituted aryl, or R\(^{16}\)-substituted or
unsubstituted heteroaryl; R\textsuperscript{16} is independently oxo, halogen, -CX\textsuperscript{16}, -CHX\textsuperscript{16}, -CH\textsubscript{2}X\textsuperscript{16}, -OCX\textsuperscript{16}, -OCH\textsubscript{2}X\textsuperscript{16}, -OCH\textsubscript{2}X\textsuperscript{16}, -CN, -OH, -NH\textsubscript{2}, -COOH, -C\textsubscript{ONH\textsubscript{2}}, -SH, -NH\textsubscript{2}, -ON\textsubscript{2}, -NHC(O)NH\textsubscript{2}, -NHC(O)NH\textsubscript{2}, -NHC(O)\textsubscript{H}, -NHC(O)\textsubscript{OH}, -NHOH, R\textsuperscript{17}-substituted or unsubstituted alkyl, R\textsuperscript{17}-substituted or unsubstituted heteroalkyl, R\textsuperscript{17}-substituted or unsubstituted cycloalkyl, R\textsuperscript{17}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{17}-substituted or unsubstituted aryl, or R\textsuperscript{17}-substituted or unsubstituted heteroaryl; R\textsuperscript{17} is independently oxo, halogen, -CX\textsuperscript{17}, -CHX\textsuperscript{17}, -CH\textsubscript{2}X\textsuperscript{17}, -OCX\textsuperscript{17}, -OCH\textsubscript{2}X\textsuperscript{17}, -OCH\textsubscript{2}X\textsuperscript{17}, -CN, -OH, -NH\textsubscript{2}, -COOH, -C\textsubscript{ONH\textsubscript{2}}, -SH, -NH\textsubscript{2}, -ON\textsubscript{2}, -NHC(O)NH\textsubscript{2}, -NHC(O)\textsubscript{H}, -NHC(O)\textsubscript{OH}, -NHOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and \textit{X}\textsuperscript{15}, \textit{X}\textsuperscript{16}, and \textit{X}\textsuperscript{17} are independently –F, –Cl, –Br, or –I.

[0252] Embodiment 12. The compound of one of embodiments 1 to 10, wherein L\textsuperscript{2} is a bond, R\textsuperscript{15}-substituted or unsubstituted heteroalkylene, –NH–, or –O–; R\textsuperscript{15} is independently oxo, halogen, -CX\textsuperscript{15}, -CHX\textsuperscript{15}, -CH\textsubscript{2}X\textsuperscript{15}, -OCX\textsuperscript{15}, -OCH\textsubscript{2}X\textsuperscript{15}, -OCH\textsubscript{2}X\textsuperscript{15}, -CN, -OH, -NH\textsubscript{2}, -COOH, -C\textsubscript{ONH\textsubscript{2}}, -SH, -NH\textsubscript{2}, -ON\textsubscript{2}, -NHC(O)NH\textsubscript{2}, -NHC(O)\textsubscript{H}, -NHC(O)\textsubscript{OH}, -NHOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and \textit{X}\textsuperscript{15} is independently –F, –Cl, –Br, or –I.

[0253] Embodiment 13. The compound of one of embodiments 1 to 10, wherein L\textsuperscript{2} is –O(CH\textsubscript{2})\textsubscript{z}, and \textit{z} is an integer from 0 to 3.

[0254] Embodiment 14. The compound of one of embodiments 1 to 10, wherein L\textsuperscript{2} is –NH(CH\textsubscript{2})\textsubscript{z}, and \textit{z} is an integer from 0 to 3.

[0255] Embodiment 15. The compound of one of embodiments 13 to 14, wherein \textit{z} is 1.

[0256] Embodiment 16. The compound of one of embodiments 1 to 10, wherein L\textsuperscript{2} is –O(CH\textsubscript{2})–.

[0257] Embodiment 17. The compound of one of embodiments 1 to 10, wherein L\textsuperscript{2} is –O–.
[0258] Embodiment 18. The compound of one of embodiments 1 to 17, wherein R^1 is independently hydrogen, -CX^1, -CN, -COOH, -CONH₂, -CHX^1, -CH₂X^1, R^1-substituted or unsubstituted C₁-C₆ alkyl, R^2-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^4-substituted or unsubstituted C₃-C₆ cycloalkyl, R^5-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^4-substituted or unsubstituted phenyl, or R^4-substituted or unsubstituted 5 to 6 membered heteroaryl; R^4 is independently halogen, oxo, -CX^4, -CHX^4, -CH₂X^4, -OCX^4, -OCHX^4, -OCH₂X^4, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(CH₃), -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=O(NH)NH₂, -NHC=O(NH₂), -NHSO₂H, -NHC=O(H), -NHC(O)OH, -NHOH, R^5-substituted or unsubstituted C₁-C₆ alkyl, R^5-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^5-substituted or unsubstituted C₃-C₆ cycloalkyl, R^5-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^5-substituted or unsubstituted phenyl, or R^5-substituted or unsubstituted 5 to 6 membered heteroaryl, R^5 is independently halogen, oxo, -CX^5, -CHX^5, -CH₂X^5, -OCX^5, -OCHX^5, -OCH₂X^5, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(CH₃), -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=O(NH)NH₂, -NHC=O(NH₂), -NHSO₂H, -NHC=O(H), -NHC(O)OH, -NHOH, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl; and X¹, X², and X⁵ are independently –F, -Cl, -Br, or -I.

[0259] Embodiment 19. The compound of one of embodiments 1 to 17, wherein R¹ is substituted or unsubstituted C₁-C₄ alkyl.

[0260] Embodiment 20. The compound of one of embodiments 1 to 17, wherein R¹ is unsubstituted C₁-C₄ alkyl.

[0261] Embodiment 21. The compound of one of embodiments 1 to 17, wherein R¹ is hydrogen.

[0262] Embodiment 22. The compound of one of embodiments 1 to 17, wherein R¹ is –CH₃.

[0263] Embodiment 23. The compound of one of embodiments 1 to 22, wherein R² is hydrogen, –OH, R³-substituted or unsubstituted cycloalkyl, R³-substituted or unsubstituted 106
heterocycloalkyl, R^1-substituted or unsubstituted aryl, or R^3-substituted or unsubstituted heteroaryl; R^3 is independently halogen, oxo, -CX^3, -CHX^3, -CH2X^3, -OCX^3, -OCHX^3, -OCH2X^3, -CN, -S(O)CH3, -OH, -NH2, -COOH, -CONH2, -NO2, -C(O)CH3, -CH2CH3, -CH2CH2OH, -SH, -SO3H, -SO4H, -SO2NH2, -SO2CH3, -NHNH2, -ONH2, -NHC=(O)NHNH2, -NHC=(O)NH2, -NHSO3H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH3, R^6-substituted or unsubstituted alkyl, R^6-substituted or unsubstituted heteroaryl, R^6-substituted or unsubstituted cycloalkyl, R^6-substituted or unsubstituted heterocycloalkyl, R^6-substituted or unsubstituted aryl, or R^6-substituted or unsubstituted heteroaryl; two adjacent R^3 substituents may optionally be joined to form an R^6-substituted or unsubstituted heterocycloalkyl, R^6-substituted or unsubstituted alkyl, or R^6-substituted or unsubstituted heteroaryl; R^6 is independently halogen, oxo, -CX^6, -CHX^6, -CH2X^6, -OCX^6, -OCHX^6, -OCH2X^6, -CN, -S(O)CH3, -OH, -NH2, -COOH, -CONH2, -NO2, -C(O)CH3, -CH2CH3, -CH2CH2OH, -SH, -SO3H, -SO4H, -SO2NH2, -SO2CH3, -NHNH2, -ONH2, -NHC=(O)NHNH2, -NHC=(O)NH2, -NHSO3H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH3, R^7-substituted or unsubstituted alkyl, R^7-substituted or unsubstituted heteroaryl, R^7-substituted or unsubstituted cycloalkyl, R^7-substituted or unsubstituted heterocycloalkyl, R^7-substituted or unsubstituted aryl, or R^7-substituted or unsubstituted heteroaryl; R^7 is independently halogen, oxo, -CX^7, -CHX^7, -CH2X^7, -OCX^7, -OCHX^7, -OCH2X^7, -CN, -S(O)CH3, -OH, -NH2, -COOH, -CONH2, -NO2, -C(O)CH3, -CH2CH3, -CH2CH2OH, -SH, -SO3H, -SO4H, -SO2NH2, -SO2CH3, -NHNH2, -ONH2, -NHC=(O)NHNH2, -NHC=(O)NH2, -NHSO3H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCH3, R^8-substituted or unsubstituted alkyl, or R^8-substituted or unsubstituted heteroaryl; and X^3, X^6, and X^7 are independently -F, -Cl, -Br, or -I.

[0264] Embodiment 24. The compound of one of embodiments 1 to 22, wherein R^2 is hydrogen, -OH, R^3-substituted or unsubstituted C4-C6 cycloalkyl, R^3-substituted or unsubstituted 4 to 6 membered heterocycloalkyl, R^3-substituted or unsubstituted phenyl, or R^3-substituted or unsubstituted 5 to 6 membered heteroaryl; R^3 is independently halogen, oxo, -CX^3, -CHX^3, -CH2X^3, -OCX^3, -OCHX^3, -OCH2X^3, -CN, -S(O)CH3, -OH, -NH2, -COOH, -CONH2, -NO2, -C(O)CH3, -CH2CH3, -CH2CH2OH, -SH, -SO3H, -SO4H, -SO2NH2, -SO2CH3, -NHNH2.
-ONH₂, -NHC=(O)NHNNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, R⁶-substituted or unsubstituted C₁-C₆ alkyl, R⁶-substituted or unsubstituted 2 to 6 membered heteroalkyl, R⁶-substituted or unsubstituted C₃-C₆ cycloalkyl, R⁶-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R⁶-substituted or unsubstituted phenyl, or R⁶-substituted or unsubstituted 5 to 6 membered heteroaryl; R⁶ is halogen, oxo, -CX⁶³, -CHX⁶², -CH₂X⁶, -OCX⁶³, -OCHX⁶², -OCH₂X⁶, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₂H, -SO₃H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, R⁷-substituted or unsubstituted C₁-C₆ alkyl, R⁷-substituted or unsubstituted 2 to 6 membered heteroalkyl, R⁷-substituted or unsubstituted C₃-C₆ cycloalkyl, R⁷-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R⁷-substituted or unsubstituted phenyl, or R⁷-substituted or unsubstituted 5 to 6 membered heteroaryl; R⁷ is independently halogen, oxo, -CX⁷³, -CHX⁷², -CH₂X⁷, -OCX⁷³, -OCHX⁷², -OCH₂X⁷, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₂H, -SO₃H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl; and X³, X⁶, and X⁷ are independently -F, -Cl, -Br, or -I.

[0265] Embodiment 25. The compound of one of embodiments 1 to 22, wherein R² is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0266] Embodiment 26. The compound of one of embodiments 1 to 22, wherein R² is hydrogen.

[0267] Embodiment 27. The compound of one of embodiments 1 to 22, wherein R² is substituted or unsubstituted 5 to 6 membered heteroaryl.

[0268] Embodiment 28. The compound of one of embodiments 1 to 22, wherein R² is substituted or unsubstituted phenyl.

[0269] Embodiment 29. The compound of one of embodiments 1 to 22, wherein R² is unsubstituted phenyl.
[0270] Embodiment 30. The compound of one of embodiments 1 to 22, having the formula:

(III), wherein \( R^3 \) is independently halogen, \(-\text{CF}_3,\)
\(-\text{CCl}_3,\ -\text{CBr}_3,\ -\text{CI}_3,\ -\text{CN},\ -\text{OH},\ -\text{NH}_2,\ -\text{COOH},\ -\text{CONH}_2,\ -\text{NO}_2,\ -\text{SH},\ -\text{SO}_2,\ -\text{SO}_2\text{CH}_3,\ -\text{SO}_3\text{H},\ -\text{SO}_3\text{H}_2,\ -\text{SO}_2\text{NH}_2,\ -\text{NHNH}_2,\ -\text{ONH}_2,\ -\text{NHC(O)NH}_2\), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent \( R^3 \) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( z2 \) is an integer from 0 to 5.

[0271] Embodiment 31. The compound of embodiment 30, wherein \( z2 \) is 1.

[0272] Embodiment 32. The compound of embodiment 30, wherein \( z2 \) is 0.

[0273] Embodiment 33. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0274] Embodiment 34. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:
Embodiment 35. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

Embodiment 36. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

Embodiment 37. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

Embodiment 38. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:
[0279] Embodiment 39. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0280] Embodiment 40. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0281] Embodiment 41. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0282] Embodiment 42. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:
[0283] Embodiment 43. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0284] Embodiment 44. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0285] Embodiment 45. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0286] Embodiment 46. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:
[0287] Embodiment 47. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0288] Embodiment 48. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0289] Embodiment 49. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0290] Embodiment 50. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:
[0291] Embodiment 51. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0292] Embodiment 52. The compound of one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, having the formula:

[0293] Embodiment 53. The compound, or a pharmaceutically acceptable salt thereof, of embodiment 1, wherein the compound is:
5 [0294] Embodiment 54. The compound, or a pharmaceutically acceptable salt thereof, of embodiment 1, wherein the compound is:

(JD211), (JD212),

(JD213), (JD214),

(JD215), or

(JD216).

10 [0295] Embodiment 55. The compound, or a pharmaceutically acceptable salt thereof, of embodiment 1, wherein the compound is:
[0296] Embodiment 56. The compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 1 to 55, wherein the compound is not

[0297] Embodiment 57. The compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 1 to 55, wherein the compound is not

[0298] Embodiment 58. The compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 1 to 55, wherein the compound is not

[0299] Embodiment 59. The compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 1 to 55, wherein the compound is not
[0300]  Embodiment 60.  The compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 1 to 55, wherein the compound is not

[0301]  Embodiment 61.  The compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 1 to 55, wherein the compound is not

[0302]  Embodiment 62.  A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof, of one of embodiments 1 to 61.

[0303]  Embodiment 63.  A method of treating cancer in a patient in need of said treatment, said method comprising administering a therapeutically effective amount of a compound of one of embodiments 1 to 61, or a pharmaceutically acceptable salt thereof, to said patient.

[0304]  Embodiment 64.  The method of embodiment 63 wherein the cancer is lung cancer.

[0305]  Embodiment 65.  The method of embodiment 63 wherein the cancer is non-small cell lung cancer.

[0306]  Embodiment 66.  The method of embodiment 63 wherein the cancer is breast cancer.
[0307] Embodiment 67. The method of embodiment 63 wherein the cancer is triple negative breast cancer.

[0308] Embodiment 68. The method of embodiment 63 wherein the cancer is resistant to an anti-cancer agent.

[0309] Embodiment 69. The method of embodiment 63 further comprising administering a second agent.

[0310] Embodiment 70. The method of embodiment 69, wherein the second agent is an anti-cancer agent.

[0311] Embodiment 71. The method of one of embodiments 69 to 70, wherein the second agent is glembatumumab vedotin, capecitabine, nab-paclitaxel, sacituzumab govitecan, vanticumab, atezolizumab, gemcitabine, metformin, iniparib, irinotecan, trastuzumab, trastuzumab emtansine, anastrozole, exemestane, fulvestrant, goserelin, letrozole, leuprolide, megestrol acetate, tamoxifen, toremifene, palbociclib, everolimus, cyclophosphamide, docetaxel, doxorubicin, epirubicin, methotrexate, paclitaxel, 5-fluorouracil, capecitabine, carboplatin, cisplatin, eribulin, ixabepilone, liposomal doxorubicin, vinorelbine, pertuzumab, lapatinib, erlotinib, gefitinib, cetuximab, panitumumab, afatinib, cisplatin, carboplatin, or nedaplatin.

[0312] Embodiment 72. A method of decreasing the level of activity of NF-κB or mTOR in a cell comprising contacting the cell with an effective amount of a compound of one of embodiments 1 to 61, or a pharmaceutically acceptable salt thereof.

[0313] Embodiment 73. A method of increasing the level of activity of TSC1 or TSC2 in a cell comprising contacting the cell with an effective amount of a compound of one of embodiments 1 to 61, or a pharmaceutically acceptable salt thereof.

VII. EXAMPLES

[0314] The following examples are offered to illustrate, but not to limit the claimed invention.

[0315] Lung cancer is the leading cause of cancer death in men and women worldwide. The poor prognosis of advanced non-small cell lung cancer (NSCLC) is due, in part, to emergence of tumor resistance to chemotherapy. Recent data indicate that human tumors, including NSCLC, contain a
small subset of cancer stem/progenitor cells (CSC) responsible for drug resistance and tumor maintenance. If such minute subsets of CSC drive tumor formation and drug resistance, therapies targeting the bulk tumor mass but not CSC will fail. Applicants confirm identification of subpopulations of chemotherapy-resistant human NSCLC cells with enrichment for CSC biomarkers and exhibiting significant CSC activity. Applicants identified CD133+/ALDH+ tumor stem/progenitor cells from human lung cancer cells in vitro using established Aldefluor assays in combination with labeled anti-CD133 antibodies. Estrogen, a known risk factor for lung cancer progression, stimulated a modest increase in the numbers of CSC. In contrast to control CD133- /ALDH- tumor cell subsets, CSC subpopulations grew as tumor spheres and maintained self-renewal capacity in vitro and exhibited a greater tumorigenic capability than non-CSC subsets in vivo, properties indicative of CSC. Furthermore, resistance of CSC-like cells to cisplatin (a standard chemotherapy for NSCLC treatment) was fully reversed by treatment with parthenolide (PTL), a naturally-occurring sesquiterpene lactone compound with strong antitumor activity in leukemia and prostate cancer, while sparing normal cells.

[0316] Applicants have developed a set of novel analogues of parthenolide which have improved antitumor properties.

[0317] Novel parthenolide derivatives for treatment of NSCLC are being tested in a panel of cell line models of lung cancer. In addition, novel parthenolide derivatives are being tested for their toxicity on normal cells such as blood vessels cells (human umbilical vein endothelial cells) and lung cells (human bronquial epithelial cells). Analogues of the present invention may be used alone or in combination with standard chemotherapy treatments currently used in the clinic, such as cisplatin, carboplatin and taxanes. Analogues of the present invention may be used in the treatment

A. General Experimental Detail for Chemical Synthesis of Parthenolide Analogues

[0318] Dichloromethane and methanol were distilled from calcium hydride under an argon atmosphere. Diethyl ether was distilled from benzoquinone ketyl radical under an argon atmosphere. All other solvents or reagents were purified according to literature procedures. High Resolution Mass Spectrometry was obtained on a Waters LCT Premier XE Time of Flight LC-MS. $^1$H NMR, $^{13}$C NMR spectra were obtained on AV-300, ARX-400, ARX-500 or Avance-500 spectrometers. The chemical shifts are reported in parts per million (ppm, δ). The coupling
constants are reported in Hertz (Hz) and the resonance patterns are reported with the following notations: br (broad), s (singlet), d (double), t (triplet), q (quartet) and m (multiplet). Thin-layer chromatography (TLC) was carried out using precoated silica gel sheets (Merck 60 F254). Visual detection was performed with ultraviolet light (short wave and long wave), p-anisaldehyde stain, and potassium permanganate stain. Flash chromatography was performed using SilicaFlash™ P60 (60 A, 40-63 mm) silica gel from SiliCycle Inc. with compressed air.

[0319] The parthenolide analogues were synthesized according to the following chemical synthesis scheme:

JD200 (PTL)

JD212 R = Me, R' = H
JD213 R = H, R' = Me
JD216 R = R' = H

JD215 R = Me, R' = H
JD214 R = H, R' = Me
JD211 R = R' = H
The chemical compounds are illustrated in FIG. 1.

(3R,3aS,10bS,E)-6,9a-dimethyl-2-oxo-2,3,3a,4,5,8,9,9a,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-3-yl)methyl)glycine, JD211. To a solution of JD216 (13 mg, 0.031 mmol) in EtOAc/MeOH (1.0 Ml/1.0 mL) was added 5% Pd/C (2.0 mg). Argon was passed over the mixture for several minutes and then the argon was replaced with hydrogen and the mixture was stirred vigorously for 15 min. The mixture was filtered through a thick pad of Celite and was purified by flash chromatography on silica gel (Hexane/EtOAc = 2/1) to obtain the desired product, JD211. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 5.16 (d, \(J = 9.7\) Hz, 1H), 4.11 (t, \(J = 9.0\) Hz, 1H), 3.64 (s, 2H), 3.19 (dd, \(J = 20.6, 13.1\) Hz, 2H), 2.91 (d, \(J = 4.0\) Hz, 1H), 2.78 (t, \(J = 9.9\) Hz, 1H), 2.38 – 2.25 (m, 2H), 1.82 (dd, \(J = 13.9, 6.6\) Hz, 1H), 1.78 – 1.66 (m, 1H), 1.63 (s, 3H), 1.33 (s, 1H), 1.24 – 1.20 (m, 1H), 1.19 (s, 3H), 1.09 (td, \(J = 12.8, 5.7\) Hz, 1H). \(^1\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 176.07,
169.05, 134.44, 124.49, 82.25, 65.16, 61.29, 48.88, 45.82, 45.08, 44.82, 36.09, 29.77, 28.58, 23.64, 16.80, 16.62. HR-MS (ESI) Calcd for [C_{12}H_{24}NO_3 + H]^+ 324.1811, found 324.1807.

[0322] Benzyl 2-(((3R,3aS,10bS,E)-6,9a-dimethyl-2-oxo-2,3,3a,4,5,8,9,9a,10a,10b-decahydrooxir-enol[2',3':9,10]cycloeca[1,2-b]furan-3-yl)methyl)amino)-2-methylpropanoate, JD212. To a stirred solution of parthenolide (25 mg, 0.1 mmol) and Et,N (0.279 mL, 2.0 mmol) in t-BuOH (1.0 mL) was added benzyl 2-amino-2-methylpropanoate hydrochloride (69 mg, 0.3 mmol). The reaction was stirred at 21 °C until the consumption of starting material was demonstrated by TLC. The reaction mixture was extracted with ethyl acetate (3 × 15 mL), washed with water and brine, and dried over MgSO_4. After removal of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel (Hexane/EtOAc = 15/1) to obtain the desired product, JD212. ^1^H NMR (500 MHz, CDCl_3) δ 7.42 – 7.32 (m, 5H), 5.31 (d, J = 11.8 Hz, 1H), 5.20 (d, J = 11.9 Hz, 1H), 5.15 – 5.07 (m, 1H), 4.02 (t, J = 7.6 Hz, 1H), 1.78 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H), 1.29 (s, 3H). ^13^C NMR (126 MHz, CDCl_3) δ 177.20, 170.60, 134.49, 134.27, 129.09, 128.94, 128.91, 125.28, 83.92, 68.69, 65.62, 62.49, 61.90, 48.00, 42.91, 40.84, 36.45, 29.09, 24.74, 24.08, 19.69, 17.16, 16.78. HR-MS (ESI) Calcd for [C_{26}H_{35}NO_3 + H]^+ 442.2593, found 442.2589.

[0323] Benzyl N-(((3R,3aS,10bS,E)-6,9a-dimethyl-2-oxo-2,3,3a,4,5,8,9,9a,10a,10b-decahydrooxire-no[2',3':9,10]cycloeca[1,2-b]furan-3-yl)methyl)-N-methylglycinate, JD213. To a stirred solution of parthenolide (25 mg, 0.1 mmol) and Et,N (0.279 mL, 2.0 mmol) in t-BuOH (1.0 mL) was added benzyl methylglycinate hydrochloride (65 mg, 0.3 mmol). The reaction was stirred at 21 °C until the consumption of starting material was demonstrated by TLC. The reaction mixture was extracted with ethyl acetate (3 × 15 mL), washed with water and brine, and dried over MgSO_4. After removal of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel (Hexane/EtOAc = 10/1) to obtain the desired product, JD213. ^1^H NMR (500 MHz, CDCl_3) δ 7.36 (d, J = 3.5 Hz, 5H), 5.15 (m, 3H), 3.83 (t, J = 9.1 Hz, 1H), 3.49 (t, J = 15.2 Hz, 2H), 3.10 – 2.93 (m, 2H), 2.71 (d, J = 8.9 Hz, 1H), 1.68 (s, 3H), 1.63 (dd, J = 17.6, 8.8 Hz, 1H), 1.28 (s, 3H), 1.20 (d, J = 5.9 Hz, 1H). ^13^C NMR (126 MHz, CDCl_3) δ 176.29, 170.16, 135.49, 134.59, 128.57, 128.33, 124.94, 82.33, 66.36, 61.49, 58.56, 54.35, 47.36, 46.90, 43.05.
40.98, 36.57, 29.67, 24.02, 17.14, 16.88. HR-MS (ESI) Calcd for [C$_{25}$H$_{33}$NO$_5$ + H]$^+$ 428.2437, found 428.2430.

[0324] N-((3R,3aS,10bS,E)-6,9a-Dimethyl-2-oxo-2,3,3a,4,5,8,9,9a,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-3-yl)methyl)-N-methylglycine, JD214. To a solution of JD213 (12 mg, 0.028 mmol) in EtOAc/MeOH (1.0 Ml/1.0 mL) was added 5% Pd/C (2.0 mg). Argon was passed over the mixture for several minutes and then the argon was replaced with hydrogen and the mixture was stirred vigorously for 15 min. The mixture was filtered through a thick pad of Celite and was purified by flash chromatography on silica gel (Hexane/EtOAc = 2/1) to obtain the desired product, JD214. HR-MS (ESI) Calcd for [C$_{18}$H$_{27}$NO$_5$ + H]$^+$ 338.1971, found 338.1971.

[0325] 2-(((3R,3aS,10bS,E)-6,9a-Dimethyl-2-oxo-2,3,3a,4,5,8,9,9a,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-3-yl)methyl)amino)-2-methylpropanoic acid, JD215. To a solution of JD212 (12 mg, 0.027 mmol) in EtOAc/MeOH (1.0 Ml/1.0 mL) was added 5% Pd/C (2.0 mg). Argon was passed over the mixture for several minutes and then the argon was replaced with hydrogen and the mixture was stirred vigorously for 15 min. The mixture was filtered through a thick pad of Celite and was purified by flash chromatography on silica gel (Hexane/EtOAc = 3/1) to obtain the desired product, JD215. HR-MS (ESI) Calcd for [C$_{19}$H$_{29}$NO$_5$ + H]$^+$ 352.2124, found 352.2120.

[0326] Benzyl ((3R,3aS,10bS,E)-6,9a-dimethyl-2-oxo-2,3,3a,4,5,8,9,9a,10a,10b-decahydrooxire-no[2',3':9,10]cyclodeca[1,2-b]furan-3-yl)methyl)glycinate, JD216. To a stirred solution of parthenolide (25 mg, 0.1 mmol) and Et$_3$N (0.279 mL, 2.0 mmol) in t-BuOH (1.0 mL) was added benzyl glycinate hydrochloride (60 mg, 0.3 mmol). The reaction was stirred at 21 °C until the consumption of starting material was demonstrated by TLC. The reaction mixture was extracted with ethyl acetate (3 × 15 mL), washed with water and brine, and dried over MgSO$_4$. After removal of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel (Hexane/EtOAc = 10/1) to obtain the desired product, JD216. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35 (m, 5H), 5.17 (m, 3H), 3.84 (t, J = 9.1 Hz, 1H), 3.49 (s, 2H), 3.03 (dd, J = 12.4, 3.8 Hz, 1H), 2.86 (dd, J = 12.4, 6.0 Hz, 1H), 2.73 (d, J = 9.0 Hz, 1H), 1.88 (dd, J = 15.0, 6.3 Hz, 1H), 1.69 (s,
Parthenolide analogues JD211-JD216 were tested for antitumor activity using triple-negative breast cancer cells (MDA-MB-231) in vitro. Doses ranged from 0-50 micromolar and tumor cell proliferation was assessed using established methods. Antitumor effects and particularly JD213, JD214, JD215 and JD216 were greater than that observed with dimethylamino-parthenolide (DMAPT), as seen in FIG. 2. This was most notable at lower compound dose at 10 micromolar. These findings indicate that novel compounds such as JD213, JD214, JD215 and JD216 are more promising candidates for anticancer therapy then DMAPT because these cancers are more sensitive to compounds other than DMAPT.

Table 1. Selected parthenolide analogues inhibit proliferation of MDA-MB-231 triple-negative breast cancer cells. Data corresponds to FIG. 5.

<table>
<thead>
<tr>
<th>ID</th>
<th>Cell proliferation (% control) initial</th>
<th>Cell proliferation (% control) as a function of parthenolide analog dose (10 uM.)</th>
<th>Cell proliferation (% control) as a function of parthenolide analog dose (50 uM.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JD200</td>
<td>100</td>
<td>81.0</td>
<td>3.3</td>
</tr>
<tr>
<td>JD201</td>
<td>100</td>
<td>105.5</td>
<td>15.2</td>
</tr>
<tr>
<td>JD202</td>
<td>100</td>
<td>68.8</td>
<td>38.3</td>
</tr>
<tr>
<td>JD203</td>
<td>100</td>
<td>86.4</td>
<td>32.4</td>
</tr>
<tr>
<td>JD211</td>
<td>100</td>
<td>106.0</td>
<td>105.8</td>
</tr>
<tr>
<td>JD212</td>
<td>100</td>
<td>103.4</td>
<td>100.8</td>
</tr>
<tr>
<td>JD213</td>
<td>100</td>
<td>26.7</td>
<td>0.4</td>
</tr>
<tr>
<td>JD214</td>
<td>100</td>
<td>40.0</td>
<td>16.6</td>
</tr>
<tr>
<td>JD215</td>
<td>100</td>
<td>59.5</td>
<td>0</td>
</tr>
<tr>
<td>JD216</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.
REFERENCES


WHAT IS CLAIMED IS:

1. A compound, or a pharmaceutically acceptable salt thereof, having the formula:

![Chemical structure image]

wherein $L^1$ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

$L^2$ is a bond, substituted or unsubstituted heteroalkylene, $-$NH$-$, or $-$O$-$;

$R^1$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

$R^2$ is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof,

wherein $L^1$ is a bond, substituted or unsubstituted C$_1$-C$_3$ alkylene, or substituted or unsubstituted 2 to 3 membered heteroalkylene;

$L^2$ is a bond, substituted or unsubstituted heteroalkylene, $-$NH$-$, or $-$O$-$;

$R^1$ is hydrogen, substituted or unsubstituted C$_1$-C$_6$ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C$_3$-C$_6$ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl;

$R^2$ is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

3. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:
4. The compound of one of claims 1 to 2, wherein \( L^1 \) is a bond.

5. The compound of one of claims 1 to 2, wherein \( L^1 \) is unsubstituted methylene.

6. The compound of one of claims 1 to 2, wherein \( L^1 \) is substituted or unsubstituted propylene.

7. The compound of one of claims 1 to 2, wherein \( L^1 \) is \(-C(\text{R}^8)_2-\);

\( \text{R}^8 \) is independently oxo,

halogen, \(-\text{CX}^8 \), \(-\text{CHX}^8 \), \(-\text{CH}_2 \text{X}^8 \), \(-\text{OCX}^8 \), \(-\text{OCH}_2 \text{X}^8 \), \(-\text{OCHX}^8 \), \(-\text{CN} \), \(-\text{OH} \), \(-\text{NH}_2 \), \(-\text{COOH} \), \(-\text{CONH}_2 \)

\(-\text{SH} \), \(-\text{NHNH}_2 \), \(-\text{ONH}_2 \), \(-\text{NHC(O)NHNH}_2 \), \(-\text{NHC(O)NH}_2 \), \(-\text{NHC(O)H} \), \(-\text{NHC(O)OH} \), \(-\text{NOH} \)

\( \text{R}^9 \)-substituted or unsubstituted alkyl, \( \text{R}^9 \)-substituted or unsubstituted heteroalkyl, \( \text{R}^9 \)-substituted or unsubstituted cycloalkyl, \( \text{R}^9 \)-substituted or unsubstituted heterocycloalkyl, \( \text{R}^9 \)-substituted or unsubstituted aryl, or \( \text{R}^9 \)-substituted or unsubstituted heteroaryl;

\( \text{R}^9 \) is independently oxo,

halogen, \(-\text{CX}^9 \), \(-\text{CHX}^9 \), \(-\text{CH}_2 \text{X}^9 \), \(-\text{OCX}^9 \), \(-\text{OCH}_2 \text{X}^9 \), \(-\text{OCHX}^9 \), \(-\text{CN} \), \(-\text{OH} \), \(-\text{NH}_2 \), \(-\text{COOH} \), \(-\text{CONH}_2 \)

\(-\text{SH} \), \(-\text{NHNH}_2 \), \(-\text{ONH}_2 \), \(-\text{NHC(O)NHNH}_2 \), \(-\text{NHC(O)NH}_2 \), \(-\text{NHC(O)H} \), \(-\text{NHC(O)OH} \), \(-\text{NOH} \)

\( \text{R}^{10} \)-substituted or unsubstituted alkyl, \( \text{R}^{10} \)-substituted or unsubstituted heteroalkyl, \( \text{R}^{10} \)-substituted or unsubstituted cycloalkyl, \( \text{R}^{10} \)-substituted or unsubstituted heterocycloalkyl, \( \text{R}^{10} \)-substituted or unsubstituted aryl, or \( \text{R}^{10} \)-substituted or unsubstituted heteroaryl;

\( \text{R}^{10} \) is independently oxo,

halogen, \(-\text{CX}^{10} \), \(-\text{CHX}^{10} \), \(-\text{CH}_2 \text{X}^{10} \), \(-\text{OCX}^{10} \), \(-\text{OCH}_2 \text{X}^{10} \), \(-\text{OCHX}^{10} \), \(-\text{CN} \), \(-\text{OH} \), \(-\text{NH}_2 \), \(-\text{COOH} \), \(-\text{C}

\(-\text{ONH}_2 \), \(-\text{SH} \), \(-\text{NHNH}_2 \), \(-\text{ONH}_2 \), \(-\text{NHC(O)NHNH}_2 \)

\(-\text{NHC(O)NH}_2 \), \(-\text{NHC(O)H} \), \(-\text{NHC(O)OH} \), \(-\text{NOH} \), \(-\text{NH}_2 \), \(-\text{COOH} \), \(-\text{C}

\( X^8, X^9, \) and \( X^{10} \) are independently \(-\text{F} \), \(-\text{Cl} \), \(-\text{Br} \), or \(-\text{I} \).
8. The compound of one of claims 1 to 2, wherein L¹ is –C(R⁸)₂–;

   R⁸ is independently oxo,

   halogen, -CX⁸, -CHX⁸, -CH₂X⁸, -OCX⁸, -OCH₂X⁸, -OCHX⁸, -CN, -OH, -NH₂, -COOH, -CONH₂

   -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₃, -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH,

   unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted

   heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and

   X⁸ is independently –F, -Cl, -Br, or -I.

9. The compound of one of claims 1 to 2, wherein L¹ is –C(CH₃)₂–.

10. The compound of one of claims 1 to 2, wherein L¹ is substituted or

    unsubstituted methylene.

11. The compound of one of claims 1 to 2, wherein L² is a bond, R¹⁵-substituted

    or unsubstituted heteroalkylene,–NH–, or –O–;

    R¹⁵ is independently oxo,

    halogen, -CX¹⁵, -CHX¹⁵, -CH₂X¹⁵, -OCX¹⁵, -OCH₂X¹⁵, -OCHX¹⁵, -CN, -OH, -NH₂, -COOH, -C

    ONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,

    -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, R¹⁶-substituted or unsubstituted alkyl, R¹⁶-

    substituted or unsubstituted heteroalkyl, R¹⁶-substituted or unsubstituted cycloalkyl, R¹⁶-substituted

    or unsubstituted heterocycloalkyl, R¹⁶-substituted or unsubstituted aryl, or R¹⁶-substituted or

    unsubstituted heteroaryl;

    R¹⁶ is independently oxo,

    halogen, -CX¹⁶, -CHX¹⁶, -CH₂X¹⁶, -OCX¹⁶, -OCH₂X¹⁶, -OCHX¹⁶, -CN, -OH, -NH₂, -COOH, -C

    ONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,

    -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, R¹⁷-substituted or unsubstituted alkyl, R¹⁷-

    substituted or unsubstituted heteroalkyl, R¹⁷-substituted or unsubstituted cycloalkyl, R¹⁷-substituted

    or unsubstituted heterocycloalkyl, R¹⁷-substituted or unsubstituted aryl, or R¹⁷-substituted or

    unsubstituted heteroaryl;

    R¹⁷ is independently oxo,

    halogen, -CX¹⁷, -CHX¹⁷, -CH₂X¹⁷, -OCX¹⁷, -OCH₂X¹⁷, -OCHX¹⁷, -CN, -OH, -NH₂, -COOH, -C

    ONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
20 -NHC(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and
21
22
23

\[ X^{15}, X^{16}, \text{and } X^{17} \text{ are independently } -F, -Cl, -Br, \text{ or } -I. \]

12. The compound of one of claims 1 to 2, wherein \( L^2 \) is a bond, \( R^{15} \)-substituted or unsubstituted heteroalkylene, \( -\text{NH}, \) or \( -\text{O}^-; \)
3
4 \( R^{15} \) is independently oxo,

5 halogen, \(-\text{CX}^{15}_3, -\text{CHX}^{15}_2, -\text{CH}_2\text{X}^{15}_2, -\text{OCX}^{15}_3, -\text{OCH}_2\text{X}^{15}_2, -\text{CN}, -\text{OH}, -\text{NH}_2, -\text{COOH}, -\text{C} \)
6 \( \text{ONH}_2, -\text{SH}, -\text{NHNH}_2, -\text{ONH}_2, -\text{NHC(O)NHNH}_2, \)
7 \(-\text{NHC(O)NH}_2, -\text{NHC(O)H}, -\text{NHC(O)OH}, -\text{NHOH}, \) unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and
9 \( X^{15} \) is independently \( -F, -Cl, -Br, \) or \( -I. \)
13. The compound of one of claims 1 to 2, wherein \( L^2 \) is \( -\text{O(CH}_2)_z\text{H}^- \) and \( z \) is an integer from 0 to 3.
14. The compound of one of claims 1 to 2, wherein \( L^2 \) is \( -\text{NH(CH}_2)_z\text{H}^- \) and \( z \) is an integer from 0 to 3.
15. The compound of claim 13, wherein \( z \) is 1.
16. The compound of one of claims 1 to 2, wherein \( L^2 \) is \( -\text{O(CH}_2)_z^- \).
17. The compound of one of claims 1 to 2, wherein \( L^2 \) is \( -\text{O}^-.
18. The compound of one of claims 1 to 2, wherein \( R^1 \) is independently hydrogen, \(-\text{CX}^{13}_3, -\text{CN}, -\text{COOH}, -\text{CONH}_2, -\text{CHX}^{12}_2, -\text{CH}_2\text{X}^{12}_1, \) \( R^3 \)-substituted or unsubstituted \( C_1-C_6 \) alkyl, \( R^3 \)-substituted or unsubstituted 2 to 6 membered heteroalkyl, \( R^3 \)-substituted or unsubstituted \( C_3-C_6 \) cycloalkyl, \( R^4 \)-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, \( R^4 \)-substituted or unsubstituted phenyl, or \( R^4 \)-substituted or unsubstituted 5 to 6 membered heteroaryl;
6 \( R^4 \) is independently halogen, oxo, \(-\text{CX}^{13}_3, -\text{CHX}^{12}_2, -\text{CH}_2\text{X}^{12}_1, -\text{OCX}^{13}_3, -\text{OCH}_2\text{X}^{13}_2, -\text{OCH}_2\text{X}^{12}_1, -\text{CN}, -\text{S(O)CH}_3, -\text{OH}, -\text{NH}_2, -\text{COOH}, -\text{CONH}_2, -\text{NO}_2, -\text{C(O)CH}_3, -\text{CH}_2\text{CH}_3, -\)}
CH₂CH₂OH, -SH, -SO₂H, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₂, -NHNH₂, -ONH₂, -NHC=O(NH)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=O(H), -NHC(O)OH, -NOH, R²-substituted or unsubstituted C₁-C₆ alkyl, R³-substituted or unsubstituted 2 to 6 membered heteroalkyl, R⁵-substituted or unsubstituted C₃-C₆ cycloalkyl, R⁵-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R⁵-substituted or unsubstituted phenyl, or R⁵-substituted or unsubstituted 5 to 6 membered heteroaryl;

R² is independently halogen, oxo, -CX₃, -CHX₂, -CH₂X, -OCX₃, -OCHX₃, -OCH₂X₂, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NOH, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl; and X¹, X⁴, and X⁵ are independently -F, -Cl, -Br, or -I.

19. The compound of one of claims 1 to 2, wherein R¹ is substituted or unsubstituted C₁-C₄ alkyl.

20. The compound of one of claims 1 to 2, wherein R¹ is unsubstituted C₁-C₄ alkyl.

21. The compound of one of claims 1 to 2, wherein R¹ is hydrogen.

22. The compound of one of claims 1 to 2, wherein R¹ is -CH₃.

23. The compound of one of claims 1 to 2, wherein R² is hydrogen, -OH, R³-substituted or unsubstituted cycloalkyl, R³-substituted or unsubstituted heterocycloalkyl, R³-substituted or unsubstituted aryl, or R³-substituted or unsubstituted heteroaryl;

R³ is independently halogen, oxo, -CX₃, -CHX₂, -CH₂X, -OCX₃, -OCHX₃, -OCH₂X₂, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NOH, -OCH₃, R⁶-substituted or unsubstituted alkyl, R⁶-substituted or unsubstituted heteroalkyl, R⁶-substituted or unsubstituted
cycloalkyl, R^6-substituted or unsubstituted heterocycloalkyl, R^6-substituted or unsubstituted aryl, or
R^6-substituted or unsubstituted heteroaryl;

two adjacent R^3 substituents may optionally be joined to form an R^6-substituted or
unsubstituted cycloalkyl, R^6-substituted or unsubstituted heterocycloalkyl, R^6-substituted or
unsubstituted aryl, or R^6-substituted or unsubstituted heteroaryl;

R^6 is independently halogen, oxo, –CX^6^3, –CHX^6^2, –CH_2X^6^, –OCX^6^3, –OCHX^6^2, –
OCH_2X^6^, –CN, –S(O)CH_3, –OH, –NH_2, –COOH, –CONH_2, –NO_2, –C(O)CH_3, –CH_2CH_3,
–CH_2CH_2OH, –SH, –SO_2H, –SO_3H, –SO_2NH_2, –SO_2CH_3, –NHNH_2, –ONH_2, –NHC=(O)NHNH_2,
–NHC=(O)NH_2, –NHSO_2H, –NHC=(O)H, –NHC(O)OH, –NHOH, –OCH_3, R^7-substituted or
unsubstituted alkyl, R^7-substituted or unsubstituted heteroalkyl, R^7-substituted or unsubstituted
cycloalkyl, R^7-substituted or unsubstituted heterocycloalkyl, R^7-substituted or unsubstituted aryl, or
R^7-substituted or unsubstituted heteroaryl;

R^7 is independently halogen, oxo, –CX^7^3, –CHX^7^2, –CH_2X^7^, –OCX^7^3, –OCHX^7^2, –
OCH_2X^7^, –CN, –S(O)CH_3, –OH, –NH_2, –COOH, –CONH_2, –NO_2, –C(O)CH_3, –CH_2CH_3,
–CH_2CH_2OH, –SH, –SO_2H, –SO_3H, –SO_2NH_2, –SO_2CH_3, –NHNH_2, –ONH_2, –NHC=(O)NHNH_2,
–NHC=(O)NH_2, –NHSO_2H, –NHC=(O)H, –NHC(O)OH, –NHOH, –OCH_3, unsubstituted alkyl,
unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted
aryl, or unsubstituted heteroaryl; and

X^3, X^6, and X^7 are independently –F, -Cl, -Br, or –I.

24. The compound of one of claims 1 to 2, wherein R^2 is hydrogen, –OH, R^3-
substituted or unsubstituted C_4–C_6 cycloalkyl, R^3-substituted or unsubstituted 4 to 6 membered
heterocycloalkyl, R^3-substituted or unsubstituted phenyl, or R^3-substituted or unsubstituted 5 to 6
membered heteroaryl;

R^3 is independently halogen, oxo, –CX^3^3, –CHX^3^2, –CH_2X^3^, –OCX^3^3, –OCHX^3^2, –
OCH_2X^3^, –CN, –S(O)CH_3, –OH, –NH_2, –COOH, –CONH_2, –NO_2, –C(O)CH_3, –CH_2CH_3,
–CH_2CH_2OH, –SH, –SO_2H, –SO_3H, –SO_2NH_2, –SO_2CH_3, –NHNH_2, –ONH_2, –NHC=(O)NHNH_2,
–NHC=(O)NH_2, –NHSO_2H, –NHC=(O)H, –NHC(O)OH, –NHOH, R^6-substituted or unsubstituted
C_1–C_6 alkyl, R^6-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^6-substituted or
unsubstituted C_3–C_6 cycloalkyl, R^6-substituted or unsubstituted 3 to 6 membered heterocycloalkyl,
R⁶-substituted or unsubstituted phenyl, or R⁶-substituted or unsubstituted 5 to 6 membered heteroaryl;

R⁶ is halogen, oxo, -CX³⁶, -CHX³⁶, -CH₂X³⁶, -OCX³⁶, -OCHX³⁶, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -CH₂CH₂OH, -SH, -SO₃H, -SO₂H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₃H, -NHC=(O)H, -NHC(O)OH, -NHOH, R⁷-substituted or unsubstituted C₁-C₆ alkyl, R⁷-substituted or unsubstituted 2 to 6 membered heteroalkyl, R⁷-substituted or unsubstituted C₃-C₆ cycloalkyl, R⁷-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R⁷-substituted or unsubstituted phenyl, or R⁷-substituted or unsubstituted 5 to 6 membered heteroaryl;

R⁷ is independently halogen, oxo, -CX³⁶, -CHX³⁶, -CH₂X³⁶, -OCX³⁶, -OCHX³⁶, -OCH₂X³⁶, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH₂CH₃, -SH, -SO₃H, -SO₂H, -SO₂NH₂, -SO₂CH₃, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₃H, -NHC=(O)H, -NHC(O)OH, -NHOH, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl; and

X³, X⁶, and X⁷ are independently -F, -Cl, -Br, or -I.

25. The compound of one of claims 1 to 2, wherein R² is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

26. The compound of one of claims 1 to 2, wherein R² is hydrogen.

27. The compound of one of claims 1 to 2, wherein R² is substituted or unsubstituted 5 to 6 membered heteroaryl.

28. The compound of one of claims 1 to 2, wherein R² is substituted or unsubstituted phenyl.

29. The compound of one of claims 1 to 2, wherein R² is unsubstituted phenyl.

30. The compound of one of claims 1 to 2, having the formula:
wherein R\(^3\) is independently halogen, \(-\text{CF}_3, -\text{CCL}_3, -\text{CBr}_3, -\text{CI}_3, -\text{CN}, -\text{OH}, -\text{NH}_2, -\text{COOH}, -\text{CONH}_2, -\text{NO}_2, -\text{SH}, -\text{SO}_2, -\text{SO}_2\text{CH}_3, -\text{SO}_3\text{H}, -\text{SO}_4\text{H}, -\text{SO}_2\text{NH}_2, -\text{NHNH}_2, -\text{ONH}_2,\)

-\text{NHC(O)NH}_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

two adjacent R\(^3\) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z\(^2\) is an integer from 0 to 5.

31. The compound of claim 30, wherein z\(^2\) is 1.

32. The compound of claim 30, wherein z\(^2\) is 0.

33. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

34. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:
35. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

36. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

37. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

38. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:
39. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

40. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

41. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

42. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:
43. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

44. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

45. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

46. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:
47. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

48. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

49. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

50. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:
51. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

52. The compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, having the formula:

53. The compound, or a pharmaceutically acceptable salt thereof, of claim 1, wherein the compound is:
54. The compound, or a pharmaceutically acceptable salt thereof, of claim 1, wherein the compound is:

55. The compound, or a pharmaceutically acceptable salt thereof, of claim 1, wherein the compound is:
56. The compound, or a pharmaceutically acceptable salt thereof, of one of claims 1 to 2, wherein the compound is not

57. The compound, or a pharmaceutically acceptable salt thereof, of one of claims 1 to 2, wherein the compound is not

58. The compound, or a pharmaceutically acceptable salt thereof, of one of claims 1 to 2, wherein the compound is not

59. The compound, or a pharmaceutically acceptable salt thereof, of one of claims 1 to 2, wherein the compound is not

60. The compound, or a pharmaceutically acceptable salt thereof, of one of claims 1 to 2, wherein the compound is not
61. The compound, or a pharmaceutically acceptable salt thereof, of one of claims 1 to 2, wherein the compound is not

62. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof, of one of claims 1 to 2.

63. A method of treating cancer in a patient in need of said treatment, said method comprising administering a therapeutically effective amount of a compound of one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, to said patient.

64. The method of claim 63 wherein the cancer is lung cancer.

65. The method of claim 63 wherein the cancer is non-small cell lung cancer.

66. The method of claim 63 wherein the cancer is breast cancer.

67. The method of claim 63 wherein the cancer is triple negative breast cancer.

68. The method of claim 63 wherein the cancer is resistant to an anti-cancer agent.

69. The method of claim 63 further comprising administering a second agent.

70. The method of claim 69, wherein the second agent is an anti-cancer agent.

71. The method of one of claims 69 to 70, wherein the second agent is glembatumumab vedotin, capecitabine, nab-paclitaxel, sacituzumab govetecan, vantictumab,
atezolizumab, gemcitabine, metformin, iniparib, irinotecan, trastuzumab, trastuzumab emtansine,
anastrozole, exemestane, fulvestrant, goserelin, letrozole, leuprolide, megestrol acetate, tamoxifen,
toremifene, palbociclib, everolimus, cyclophosphamide, docetaxel, doxorubicin, epirubicin,
methotrexate, paclitaxel, 5-fluorouracil, capecitabine, carboplatin, cisplatin, eribulin, ixabepilone,
liposomal doxorubicin, vinorelbine, pertuzumab, lapatinib, erlotinib, gefitinib, cetuximab,
panitumumab, afatinib, cisplatin, carboplatin, or nedaplatin.

72. A method of decreasing the level of activity of NF-κB or mTOR in a cell
comprising contacting the cell with an effective amount of a compound of one of claims 1 to 2, or a
pharmaceutically acceptable salt thereof.

73. A method of increasing the level of activity of TSC1 or TSC2 in a cell
comprising contacting the cell with an effective amount of a compound of one of claims 1 to 2, or a
pharmaceutically acceptable salt thereof.
FIG. 6

[Bar graph showing cell proliferation (% control) for HUVEC and TNBC]
A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/33; A61K 31/343; A61K 31/365; C07D 303/02; C07D 307/77; C07D 307/93 (2017.01)
CPC - A61K 31/33; A61K 31/343; A61K 31/365; C07D 303/02; C07D 307/77; C07D 307/93 (2016.11)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/33; A61K 31/343; A61K 31/365; C07D 303/02; C07D 307/77; C07D 307/93 (2017.01)
CPC - A61K 31/33; A61K 31/343; A61K 31/365; C07D 303/02; C07D 307/77; C07D 307/93 (2016.11)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/185: 5114/449: 5114/668; IPC(8) - A61K 31/33; A61K 31/343; A61K 31/365; C07D 303/02; C07D 307/77; C07D 307/93 (2017.01) CPC - A61K 31/33; A61K 31/343; A61K 31/365; C07D 303/02; C07D 307/77; C07D 307/93 (2016.11) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, STN, PubChem, Google Patents, Google Scholar

Search terms used: Parthenolide derivative formamide treat cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>PUBCHEM, Substance Record for SID 103582279 Create Date: 2010-12-22. [retrieved on 02 November 2016]. Retrieved from the Internet: <a href="https://pubchem.ncbi.nlm.nih.gov/substance/103582279%3E">https://pubchem.ncbi.nlm.nih.gov/substance/103582279&gt;</a> entire document</td>
<td>1-3, 11, 12, 18, 21, 23, 24, 26, 56-70, 72, 73</td>
</tr>
</tbody>
</table>

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to explain the prior invention (as specifically stated)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Document member of the same patent family

Date of the actual completion of the international search
10 January 2017

Date of mailing of the international search report
16 FEB 2017

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 571-272-8300

Authorized officer
Blaine R. Copenhaver
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 71
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1-4, 11, 12, 18, 21, 23, 24, 26, 56-70, 72, and 73 have been analyzed subject to the restriction that the claims read on a compound or a pharmaceutically acceptable salt thereof having the formula (I), wherein the compound of formula (I) is a compound of formula (II): wherein L1 is a bond; L2 is a bond; R1 is hydrogen; and R2 is hydrogen.

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, 11, 12, 18, 21, 23, 24, 26, 56-70, 72, 73

Remark on Protest
☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-70, 72, and 73 are drawn to compounds, or a pharmaceutically acceptable salt thereof having the formula (I), pharmaceutical compositions thereof, and methods thereof.

The first invention of Group I+ is restricted to a compound or a pharmaceutically acceptable salt thereof having the formula (I), wherein the compound of formula (I) is a compound of formula (II): wherein L1 is a bond; L2 is a bond; R1 is hydrogen; and R2 is hydrogen; pharmaceutical compositions thereof; and methods thereof. It is believed that claims 1-4, 11, 12, 18, 21, 23, 24, 26, 56-70, 72, and 73 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound or a pharmaceutically acceptable salt thereof having the formula (I), wherein the compound of formula (I) is a compound of formula (II): wherein L1 is unsubstituted heteroalkylene; L2 is –NH--; R1 is hydrogen; and R2 is hydrogen; pharmaceutical compositions thereof; and methods thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the “+” group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, L1, and L2.

The Groups I+ share the technical features of a compound, or a pharmaceutically acceptable salt thereof, having the core structure of formula (I); a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof; a method of treating cancer in a patient in need of said treatment, said method comprising administering a therapeutically effective amount of a compound; a method of decreasing the level of activity of NF-KB or mTOR in a cell comprising contacting the cell with an effective amount of a compound; and a method of increasing the level of activity of TSC1 or TSC2 in a cell comprising contacting the cell with an effective amount of a compound. However, these shared technical features do not represent a contribution over the prior art.

Specifically, Substance Record for SID 103582279 to PubChem teaches a compound having the core structure of formula (I) (Pg. 3; see shown structure...).

Additionally, US 2015/0031725 A1 to The Regents of the University of California teaches a paotenedol derivative having the core structure of formula (I) (Para. [0167]; see first shown structure...); a pharmaceutical composition (Abstract; Claims 1, 9, and 10; Para. [0016]) comprising a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof (Abstract; Claims 1, 9, and 10; Para. [0016]); a method of treating cancer in a patient in need of said treatment (Claim 11; Paras. [0017] and [0019]), said method comprising administering a therapeutically effective amount of a compound; a method of decreasing the level of activity of NF-KB in a cell comprising contacting the cell with an effective amount of a compound (Claim 19; Para. [0020]); and a method of increasing the level of activity of TSC1 in a cell comprising contacting the cell with an effective amount of a compound (Claim 20; Para. [0021])

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.