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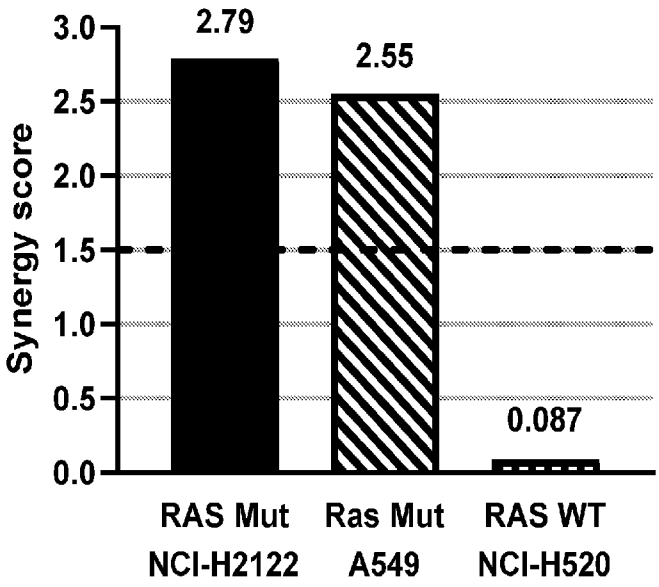
(54) Title: SUBSTITUTED 4-PIPERIDINYL-QUINAZOLINES, 4-PIPERIDINYL-PYRIMIDINE-2-AMINES, AND RELATED COMPOUNDS AND THEIR USE IN TREATING MEDICAL CONDITIONS

Figure 1.



(57) Abstract: The invention provides substituted 4-piperidinyl-quinazolines, 4-piperidinyl-pyrimidine-2-amines, and related compounds, pharmaceutical compositions, their use for inhibiting ERK5 activity, and their use in the treatment of medical disorders, such as cancer.

[Continued on next page]

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SUBSTITUTED 4-PIPERIDINYL-QUINAZOLINES, 4-PIPERIDINYL-PYRIMIDINE-2-AMINES, AND RELATED COMPOUNDS AND THEIR USE IN TREATING MEDICAL CONDITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 63/074,769, filed September 4, 2020; United States Provisional Patent Application serial number 63/074,918, filed September 4, 2020; United States Provisional Patent Application serial number 63/156,544, filed March 4, 2021; and United States Provisional Patent Application serial number 63/156,588, filed March 4, 2021; the contents of each of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention provides substituted 4-piperidinyl-quinazolines, 4-piperidinyl-pyrimidine-2-amines, and related compounds, pharmaceutical compositions, their use for inhibiting ERK5 activity, and their use in the treatment of medical disorders, such as cancer.

BACKGROUND

[0003] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Solid tumors, including breast cancer, lung cancer, and pancreatic cancer remain prevalent among the world population. Current treatment options for these cancers are not effective for all patients and/or can have substantial adverse side effects. New therapies are needed to address this unmet need in cancer therapy.

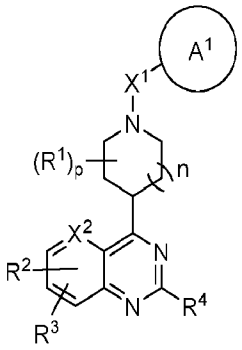
[0004] Extracellular-signal-regulated kinase 5 (ERK5), also known as mitogen-activated protein kinase 7 (MAPK7) and Big MAPK1 (BMK1), has been reported to impact cell survival, proliferation, migration, and differentiation. The mechanism of ERK5's effects are believed to include translocation to the nucleus and enhancing gene transcription, by phosphorylating transcription factors and/or interacting with transcription factors through the transactivation domain. Evidence suggests that ERK5 may be involved in the onset and progression of multiple cancers, and that inhibition of ERK5 activity may provide a therapeutic benefit for cancer. Use

of certain ERK5 inhibitor compounds for treating cancer has been described in, for example, international patent application WO 2019/170543, the contents of which are herein incorporated by reference in its entirety.

[0005] New compounds having inhibitory activity toward ERK5 are therefore needed as therapeutic agents for the treatment of medical disorders, such as cancer. The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

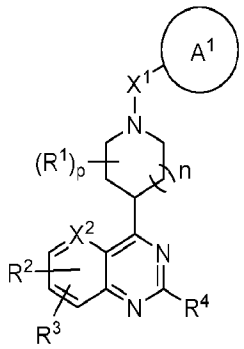
[0006] The invention provides substituted 4-piperidinyl-quinazolines and related compounds, pharmaceutical compositions, their use for inhibiting ERK5 activity, and their use in the treatment of medical disorders, such as cancer. In particular, one aspect of the invention provides a collection of substituted 4-piperidinyl-quinazolines and related compounds, such as a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description in Section I. Further description of additional collections of substituted 4-piperidinyl-quinazolines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

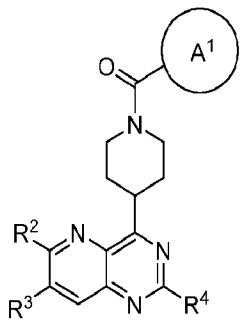
[0007] Another aspect of the invention provides a collection of substituted 4-piperidinyl-quinazolines and related compounds, such as a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description in Section I. Further description of additional collections of substituted 4-piperidinyl-quinazolines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0008] Another aspect of the invention provides a collection of substituted 4-piperidinyl-pyrido[3,2-*d*]pyrimidines and related compounds, such as a compound represented by Formula III:



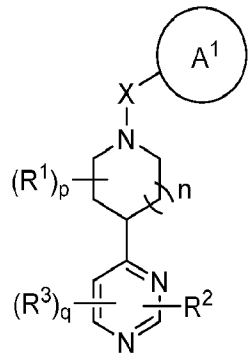
(III)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description in Section I. Further description of additional collections of substituted 4-piperidinyl-pyrido[3,2-*d*]pyrimidines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0009] Another aspect of the invention provides a method of treating a disorder mediated by ERK5 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I, II, or III in Section I, to a subject in need thereof to treat the disorder, as further described in the detailed description.

[0010] Another aspect of the invention provides a method of inhibiting ERK5 activity. The method comprises contacting ERK5 with an effective amount of a compound described herein, such as a compound of Formula I, II, or III in Section I, to inhibit ERK5 activity, as further described in the detailed description.

[0011] The invention provides substituted 4-piperidinyl-pyrimidine-2-amines and related compounds, pharmaceutical compositions, their use for inhibiting ERK5 activity, and their use in the treatment of medical disorders, such as cancer. In particular, one aspect of the invention provides a collection of substituted 4-piperidinyl-pyrimidine-2-amines and related compounds, such as a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description in Section I-A. Further description of additional collections of substituted 4-piperidinyl-pyrimidine-2-amines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0012] Another aspect of the invention provides a method of treating a disorder mediated by ERK5 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I in Section I-A, to a subject in need thereof to treat the disorder, as further described in the detailed description.

[0013] Another aspect of the invention provides a method of inhibiting ERK5 activity. The method comprises contacting ERK5 with an effective amount of a compound described herein, such as a compound of Formula I in Section I-A, to inhibit ERK5 activity, as further described in the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **Figure 1** depicts results of the 3D cancer cell culture assay described in Example 12.

[0015] **Figure 2** depicts results of the mouse xenograft tumor growth assay with a pancreatic cancer cell line, as described in Example 13.

[0016] **Figure 3** depicts results of the mouse xenograft tumor growth assay with a lung cancer cell line, as described in Example 13.

DETAILED DESCRIPTION

[0017] The invention provides substituted 4-piperidinyl-quinazolines, 4-piperidinyl-pyrimidine-2-amines, and related compounds, pharmaceutical compositions, their use for inhibiting ERK5 activity, and their use in the treatment of medical disorders, such as cancer. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Handbook of experimental immunology" (D.M. Weir & C.C. Blackwell, eds.); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0018] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

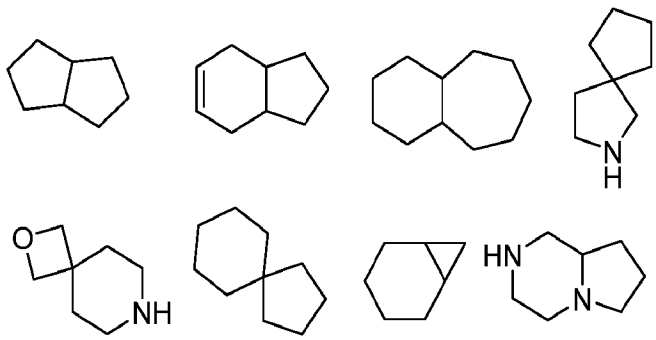
Definitions

[0019] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "-O-alkyl" etc. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

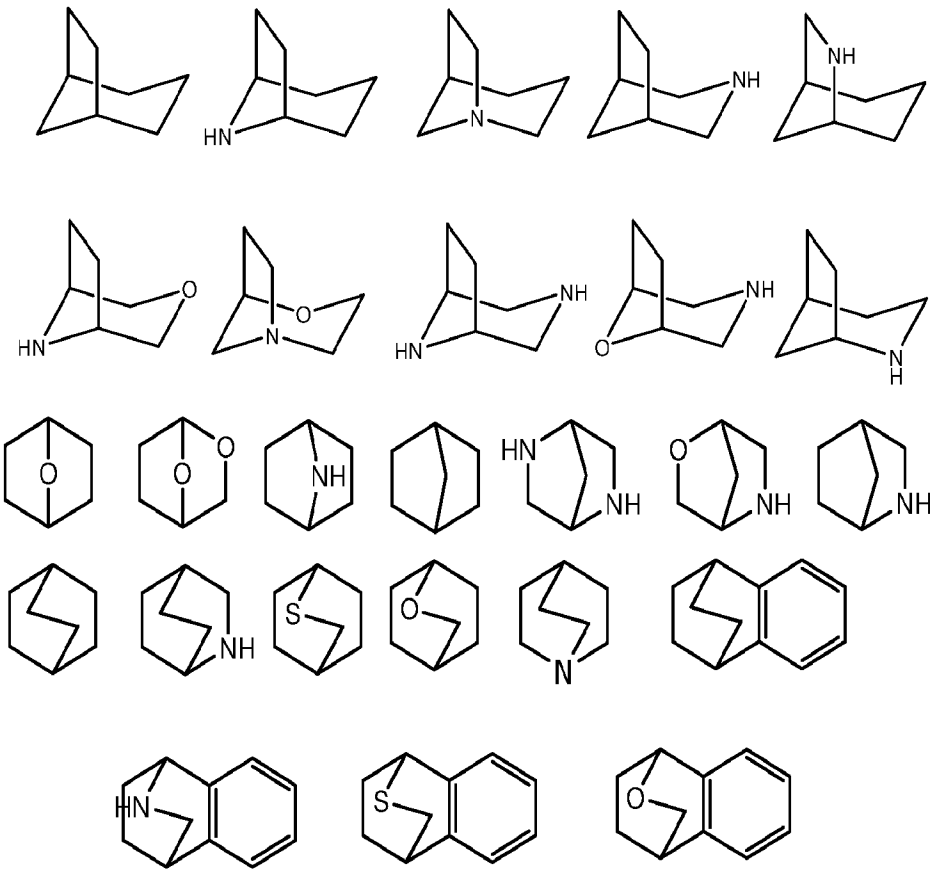
[0020] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "cycloaliphatic"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0021] As used herein, the term "bicyclic ring" or "bicyclic ring system" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used

herein, the term "heterobicyclic" is a subset of "bicyclic" that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



[0022] Exemplary bridged bicyclics include:



[0023] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0024] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[0025] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0026] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

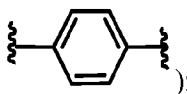
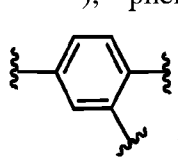
[0027] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0028] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0029] The term "-(C_0 alkylene)-" refers to a bond. Accordingly, the term "-(C_{0-3} alkylene)-" encompasses a bond (i.e., C_0) and a -(C_{1-3} alkylene)- group.

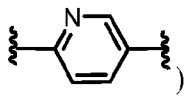
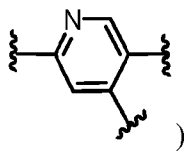
[0030] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0031] The term "halogen" means F, Cl, Br, or I.

[0032] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. The term "phenylene" refers to a multivalent phenyl group having the appropriate number of open valences to account for groups attached to it. For example, "phenylene" is a bivalent phenyl group when it has two groups attached to it (e.g., ); "phenylene" is a trivalent phenyl group when it has three groups attached to it (e.g., ). The term "arylene" refers to a bivalent aryl group.

[0033] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6,

or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where unless otherwise specified, the radical or point of attachment is on the heteroaromatic ring or on one of the rings to which the heteroaromatic ring is fused. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0034] The term "heteroarylene" refers to a multivalent heteroaryl group having the appropriate number of open valences to account for groups attached to it. For example, "heteroarylene" is a bivalent heteroaryl group when it has two groups attached to it; "heteroarylene" is a trivalent heteroaryl group when it has three groups attached to it. The term "pyridinylene" refers to a multivalent pyridine radical having the appropriate number of open valences to account for groups attached to it. For example, "pyridinylene" is a bivalent pyridine radical when it has two groups attached to it (e.g., ); "pyridinylene" is a trivalent pyridine radical when it has three groups attached to it (e.g., ).

[0035] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic

or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0036] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono– or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. The term “oxo-heterocyclyl” refers to a heterocyclyl substituted by an oxo group. The term “heterocyclylene” refers to a multivalent heterocyclyl group having the appropriate number of open valences to account for groups attached to it. For example, “heterocyclylene” is a bivalent heterocyclyl group when it has two groups attached to it; “heterocyclylene” is a trivalent heterocyclyl group when it has three groups attached to it. The term “piperidinylene” refers to a multivalent piperidinyl group having the appropriate number of open valences to account for groups attached to it.

[0037] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0038] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not,

means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0039] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; –CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, SC(S)SR°; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; –SC(S)SR°, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)(NR^\circ)R^\circ$; $-S(O)_2N=C(NR^\circ_2)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene)O–$N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene)C(O)O–$N(R^\circ)_2$.

[0040] Each R° is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono–

or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted by a divalent substituent on a saturated carbon atom of R° selected from =O and =S; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, $-(CH_2)_{0-2}R^{\bullet}$, $-(haloR^{\bullet})$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-O(haloR^{\bullet})$, –CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^{\bullet}$, or $-SSR^{\bullet}$.

[0041] Each $R^{\bullet}$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^{\bullet}$ is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, or a divalent substituent bound to vicinal substitutable carbons of an "optionally substituted" group is $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0042] When R^* is C_{1-6} aliphatic, R^* is optionally substituted with halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, -OH, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^{\bullet}$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0043] An optional substituent on a substitutable nitrogen is independently $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring

having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $R^{\dagger}$ is C_{1-6} aliphatic, $R^{\dagger}$ is optionally substituted with halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), -OH, $-OR^{\bullet}$, -O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^{\bullet}$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0044] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0045] Further, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al.*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and*

Use. (2002) Zurich: Wiley-VCH; S. Berge *et al.*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al.*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

[0046] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0047] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0048] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Alternatively, a particular enantiomer of a

compound of the present invention may be prepared by asymmetric synthesis. Still further, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxylic acid) diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers.

[0049] Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. Chiral center(s) in a compound of the present invention can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. Further, to the extent a compound described herein may exist as a atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

[0050] Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0051] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0052] The term "alkyl" refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} alkyl, C_1-C_{10} alkyl, and C_1-C_6 alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0053] The term "cycloalkyl" refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein,

e.g., as "C_3-C_6 cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl. The term "cycloalkylene" refers to a bivalent cycloalkyl group.

[0054] The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. Exemplary haloalkyl groups include -CH_2F, -CHF_2, -CF_3, -CH_2CF_3, -CF_2CF_3, and the like. The term "haloalkylene" refers to a bivalent haloalkyl group.

[0055] The term "hydroxyalkyl" refers to an alkyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkyl groups include -CH_2CH_2OH, -$C(H)(OH)CH_3$, -$CH_2C(H)(OH)CH_2CH_2OH$, and the like.

[0056] The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

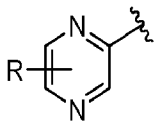
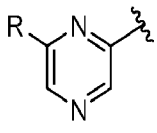
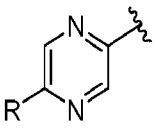
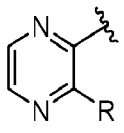
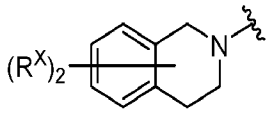
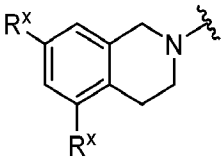
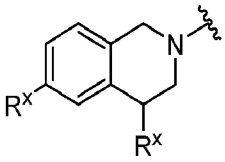
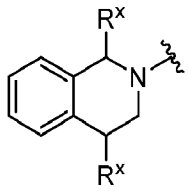
[0057] The term "carbocyclylene" refers to a multivalent carbocyclyl group having the appropriate number of open valences to account for groups attached to it. For example, "carbocyclylene" is a bivalent carbocyclyl group when it has two groups attached to it; "carbocyclylene" is a trivalent carbocyclyl group when it has three groups attached to it.

[0058] The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term "haloalkoxyl" refers to an alkoxyl group that is substituted with at least one halogen. Exemplary haloalkoxyl groups include -OCH_2F, -$OCHF_2$, -OCF_3, -OCH_2CF_3, -OCF_2CF_3, and the like. The term "hydroxyalkoxyl" refers to an alkoxyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkoxyl groups include -OCH_2CH_2OH, -$OCH_2C(H)(OH)CH_2CH_2OH$, and the like. The term "alkoxylene" refers to a bivalent alkoxyl group.

[0059] The term "oxo" is art-recognized and refers to a "=O" substituent. For example, a cyclopentane susbsituted with an oxo group is cyclopentanone.

[0060] The symbol "$\sim\!\!\sim$" indicates a point of attachment.

[0061] When a chemical structure containing a ring is depicted with a substituent having a bond that crosses a ring bond, the substituent may be attached at any available position on the

ring. For example, the chemical structure  encompasses  ,  , and  . In the context of a polycyclic fused ring, when a chemical structure containing a polycyclic fused ring is depicted with one or more substituent(s) having a bond that crosses multiple rings, the one or more substituent(s) may be independently attached to any of the rings crossed by the bond. To illustrate, the chemical structure  encompasses, for example,  ,  , and  .

[0062] When any substituent or variable occurs more than one time in any constituent or the compound of the invention, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

[0063] One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

[0064] As used herein, the terms "subject" and "patient" are used interchangeably and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and, most preferably, includes humans.

[0065] The term "IC_{50}" is art-recognized and refers to the concentration of a compound that is required to achieve 50% inhibition of the target. The potency of an inhibitor is usually defined by its IC_{50} value. The lower the IC_{50} value the greater the potency of the antagonist and the lower the concentration that is required to inhibit the maximum biological response. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less than about 100 μM, less than about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0066] As used herein, the terms "inhibitor" or "ERK5 inhibitor" or "ERK5 antagonist" are defined as a compound that binds to and/or inhibits ERK5 with measurable affinity. In some embodiments, inhibition in the presence of the inhibitor is observed in a dose-dependent manner. In some embodiments, the measured signal (*e.g.*, signaling activity or biological activity) is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% lower than the signal measured with a negative control under comparable conditions.

[0067] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change or inhibition in ERK5 activity between a sample comprising a compound of the present invention, or composition thereof, and ERK5, and an equivalent sample comprising ERK5, in the absence of said compound, or composition thereof.

[0068] As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory, or preventative result). An effective amount can be administered in one or more administrations, applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0069] As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof. In some embodiments, treatment can be administered after one or more symptoms have developed. In other

embodiments, treatment can be administered in the absence of symptoms. For example, treatment can be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment can also be continued after symptoms have resolved, for example, to prevent or delay their recurrence.

[0070] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0071] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, s*ee e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0072] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0073] In addition, when a compound of the invention contains both a basic moiety (such as, but not limited to, a pyridine or imidazole) and an acidic moiety (such as, but not limited to, a carboxylic acid) zwitterions ("inner salts") may be formed. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts. Such salts of the compounds of the invention may be formed, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0074] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited

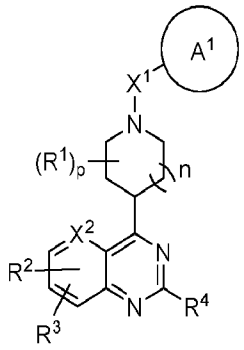
components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0075] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

I. Substituted 4-Piperidinyl-quinazolines and Related Compounds

[0076] The invention provides substituted 4-piperidinyl-quinazolines and related compounds. The compounds may be used in the pharmaceutical compositions and therapeutic methods described herein. Exemplary compounds are described in the following sections, along with exemplary procedures for making the compounds.

[0077] One aspect of the invention provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond;

R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and halo;

R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-;

X^2 is N or $C(R^2)$;

A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3

heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

n is 1 or 2; and

m and p are each independently 0, 1, 2, or 3;

provided that if p is 0 and X^1 is -C(O)-, then n is 2.

[0078] The definitions of variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0079] In certain embodiments, the compound is a compound of Formula I.

[0080] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond.

[0081] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0082] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4}

haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0083] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$. In certain embodiments, two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond.

[0084] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, or -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0085] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0086] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is -CH_2OH. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is -OCF_3. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkoxyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain

embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro. In certain embodiments, R^1 represents independently for each occurrence -$N(R^5)(R^6)$.

[0087] In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.

[0088] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0089] As defined generally above, R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0090] In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen or halo. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0091] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence halo. In certain embodiments, R^2 is fluoro. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each

occurrence C_{1-4} haloalkyl. In certain embodiments, R^2 is trifluoromethyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^2 is $-CH_2OH$. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0092] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0093] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0094] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and halo.

[0095] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0096] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and

halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo.

[0097] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0098] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0099] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4}

alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, or a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is piperazinyl or piperazin-2-onyl, each of which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl or 1-methylpiperazin-2-on-4-yl.

[0100] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0101] In certain embodiments, R^3 is a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from

nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen; wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen; wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazin-2-onyl, each of which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 1-methylpiperazin-2-on-4-yl.

[0102] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl.

[0103] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is -OCF_3. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is C_{1-4} haloalkyl. In certain embodiments, R^3 is trifluoromethyl. In certain embodiments, R^3 is C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is -CH_2OH.

[0104] In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0105] As defined generally above, R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halo. In certain embodiments, R^4

is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is C_{1-4} haloalkyl. In certain embodiments, R^4 is trifluoromethyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0106] As defined generally above, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0107] In certain embodiments, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{3-5} cycloalkyl.

[0108] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0109] In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0110] As defined generally above, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0111] In certain embodiments, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^6 represents independently for each

occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{3-5} cycloalkyl.

[0112] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0113] In certain embodiments, R^6 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0114] In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{3-5} cycloalkyl.

[0115] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and

sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0116] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl); or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0117] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0118] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently

selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0119] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -N(R^5)(R^6), C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -N(R^5)(R^6). In certain embodiments, R^7 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence –OCF_3 or –NH_2.

[0120] In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence -N(R^5)(R^6), hydroxyl, halo, or cyano. In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence -N(R^5)(R^6), or halo. In certain embodiments, one occurrence of R^7 is C_{1-4} haloalkoxyl, C_{1-4} haloalkyl, -S-(C_{1-4} haloalkyl), or -O-(C_{3-4} cycloalkyl), and any further occurrences of R^7 are –NH_2.

[0121] In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, –SCF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2, –F, or –Cl. In certain

embodiments, one occurrence of R^7 is $-OCF_3$, $-CF_3$, or -O-(cyclopropyl), and any further occurrences of R^7 are independently $-NH_2$, –F, or –Cl. In certain embodiments, one occurrence of R^7 is $-OCF_3$, $-CF_3$, or -O-(cyclopropyl), and any further occurrences of R^7 are independently $-NH_2$.

[0122] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, $-S(O)_2-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0123] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-O-(C_{0-4}$ alkylene)$-(C_{3-6}$ cycloalkyl), $-N(R^5)(R^6)$, hydroxyl, halo, cyano, $-S-(C_{1-6}$ haloalkyl), or $-S-(C_{1-6}$ alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-O-(C_{0-4}$ alkylene)$-(C_{3-6}$ cycloalkyl), or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence $-N(R^5)(R^6)$, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence $-S-(C_{1-6}$ haloalkyl) or $-S-(C_{1-6}$ alkyl).

[0124] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 represents independently for

each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0125] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0126] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $-OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{1-4} alkylene)-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence $-N(R^5)(R^6)$. In certain embodiments, R^7 is $-NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{2-6} alkenyl. In certain embodiments, R^7 represents independently for each occurrence C_{2-6} alkynyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl). In certain embodiments, R^7 is $-S-CF_3$. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence $-S(O)_2-(C_{1-6}$ alkyl).

[0127] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^7 is phenyl. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0128] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0129] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0130] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

[0131] As defined generally above, X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-. In certain embodiments, X^1 is -C(O)-. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-. In certain embodiments, X^1 is -

S(O)-. In certain embodiments, X^1 is $-S(O)_2-$. In certain embodiments, X^1 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

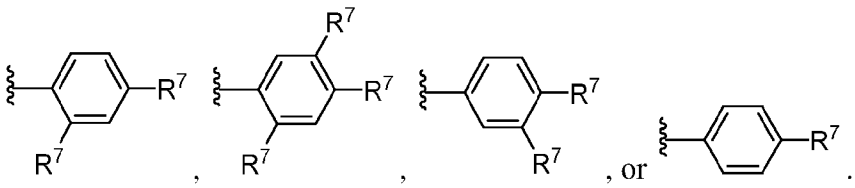
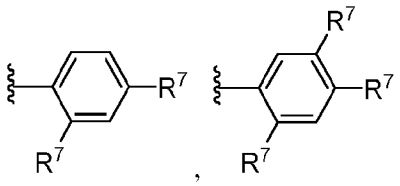
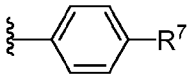
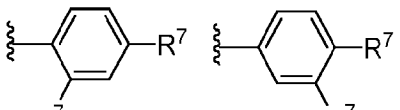
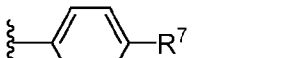
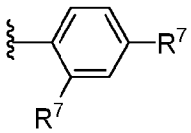
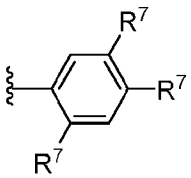
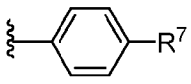
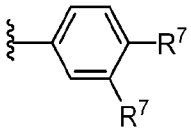
[0132] As defined generally above, X^2 is N or $C(R^2)$. In certain embodiments, X^2 is N. In certain embodiments, X^2 is $C(R^2)$. In certain embodiments, X^2 is C(H). In certain embodiments, X^2 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

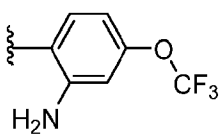
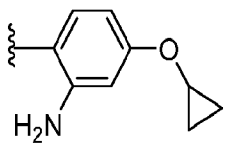
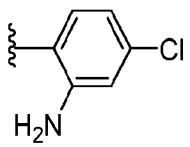
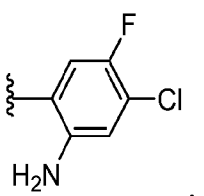
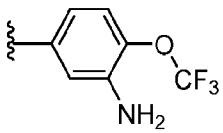
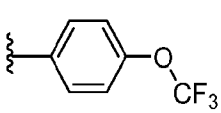
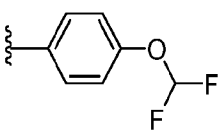
[0133] As defined generally above, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

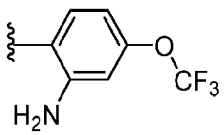
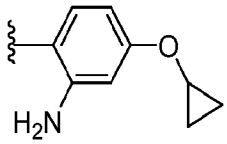
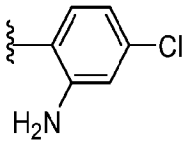
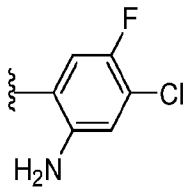
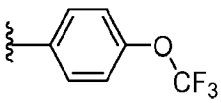
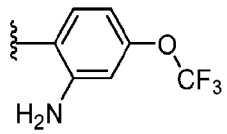
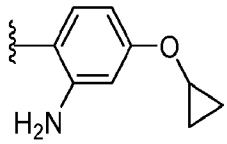
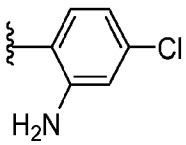
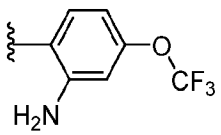
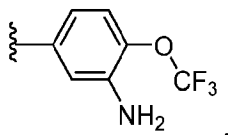
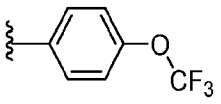
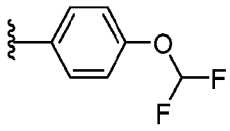
[0134] In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

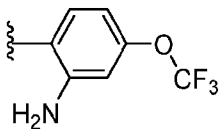
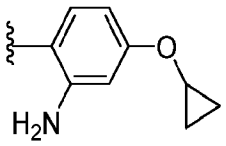
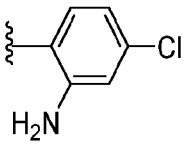
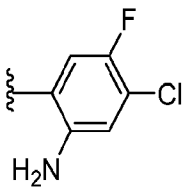
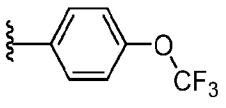
[0135] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain

embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

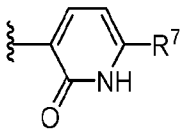
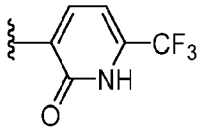
[0136] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, A^1 is  , , , or . In certain embodiments, A^1 is  , , or  . In certain embodiments, A^1 is  , , or  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

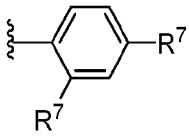
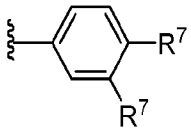
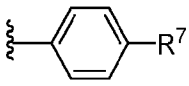
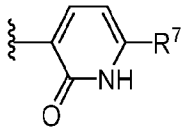
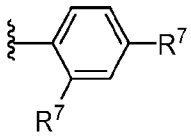
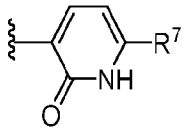
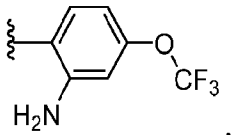
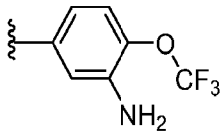
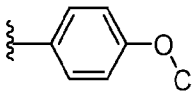
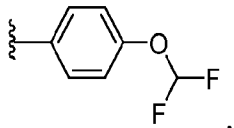
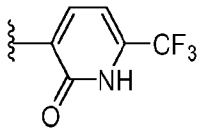
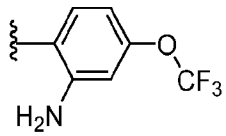
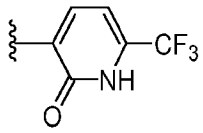
[0137] In certain embodiments, A^1 is  ,  ,  ,  ,  ,  , or  . In certain

embodiments, A^1 is  ,  ,  ,  , or  . In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  ,  ,  , or  .

[0138] In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0139] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is

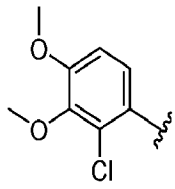
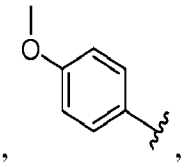
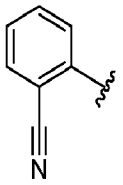
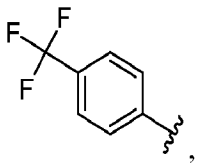
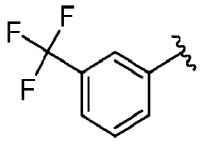
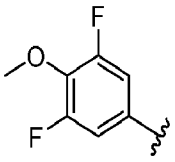
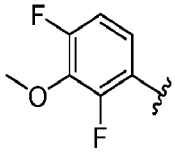
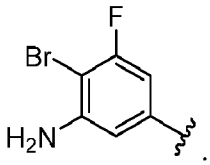
a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

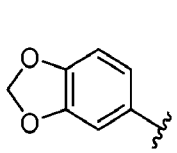
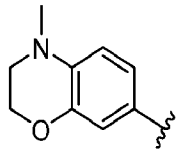
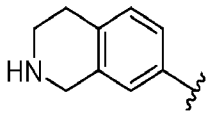
[0140] In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  or  . In certain embodiments, A^1 is  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is or  .

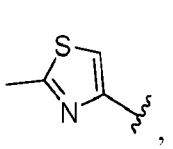
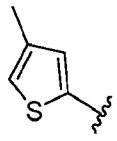
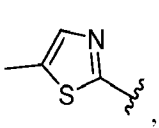
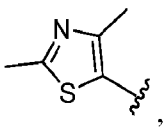
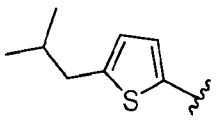
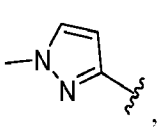
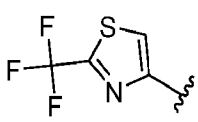
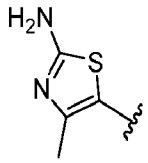
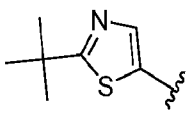
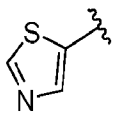
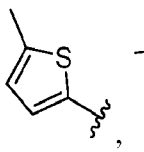
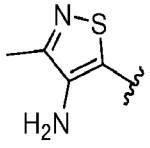
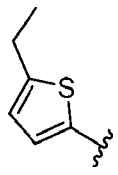
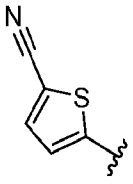
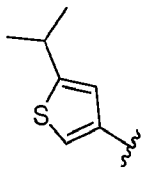
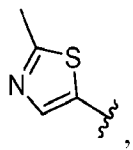
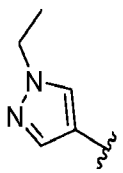
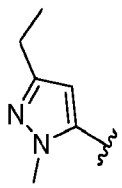
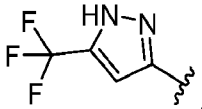
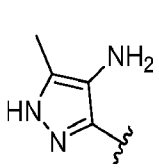
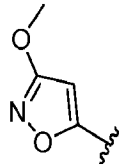
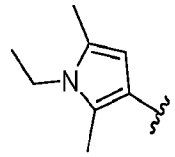
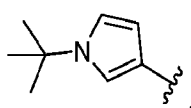
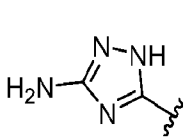
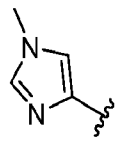
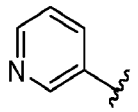
[0141] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

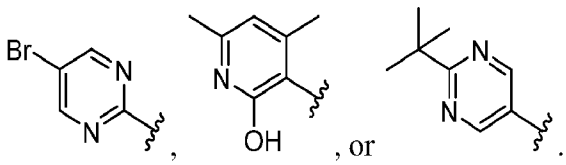
[0142] In certain embodiments, A^1 is naphthyl substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3

heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

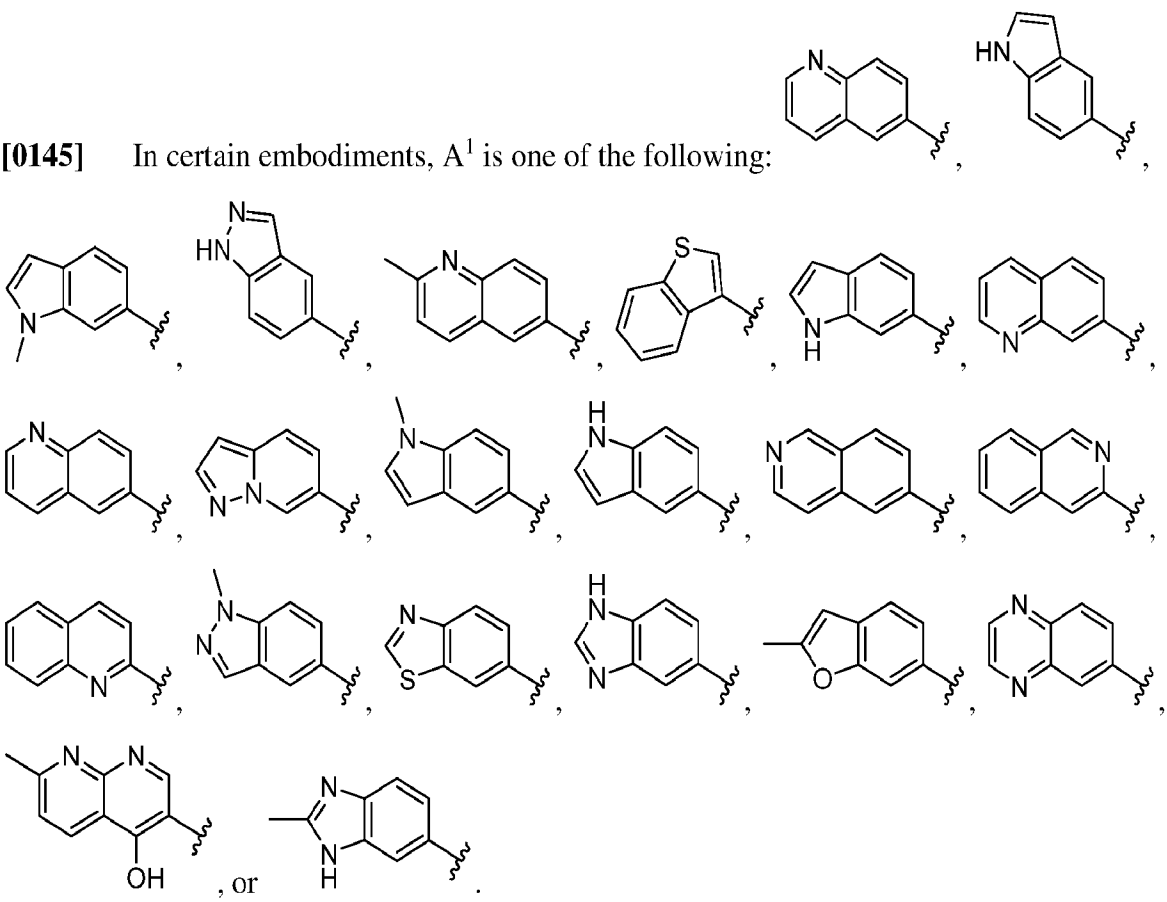
[0143] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  , or  .

In certain embodiments, A^1 is one of the following:  ,  , or  .

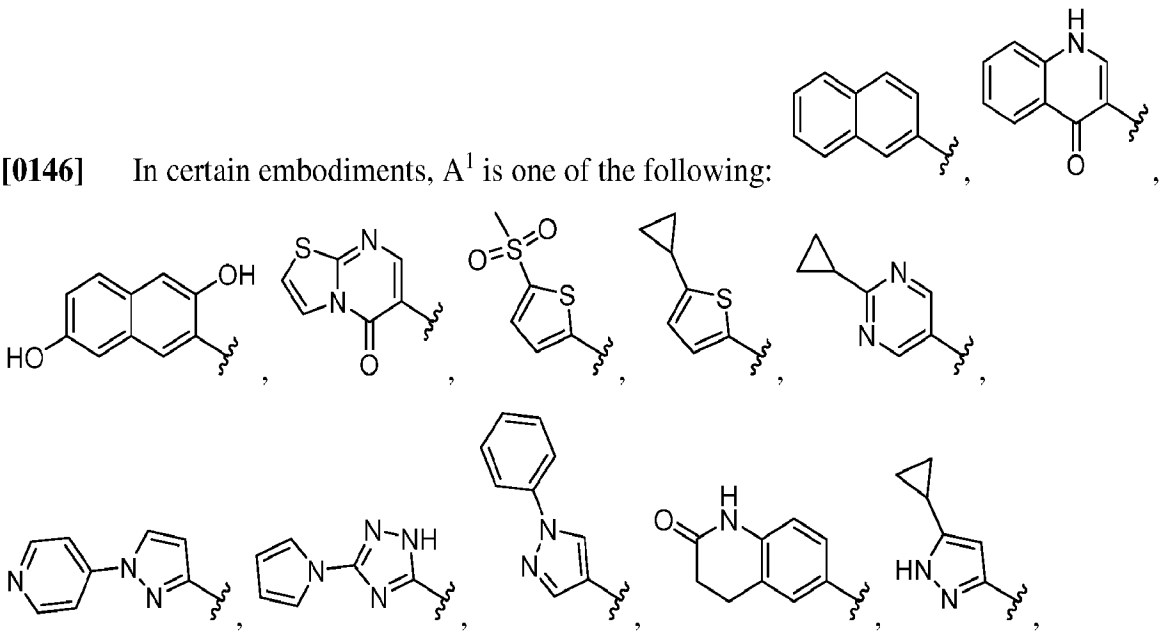
[0144] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , . In certain embodiments, A^1 is one of the following:  ,

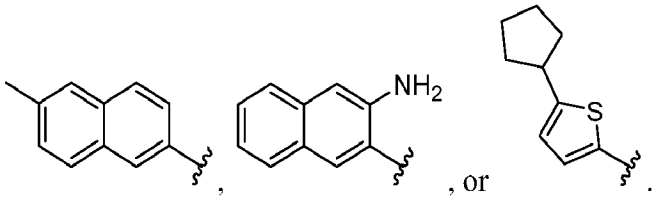


[0145] In certain embodiments, A^1 is one of the following:



[0146] In certain embodiments, A^1 is one of the following:





, , or .

[0147] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Tables 1, 1-A, and 5, below.

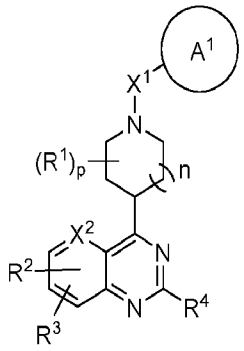
[0148] As defined generally above, n is 1 or 2; provided that if p is 0, and X^1 is -C(O)-, then n is 2. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is selected from the values represented in the compounds in Tables 1, 1-A, and 5, below.

[0149] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Tables 1, 1-A, and 5, below.

[0150] As defined generally above, p is 0, 1, 2, or 3. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 0 or 1. In certain embodiments, p is 1 or 2. In certain embodiments, p is 2 or 3. In certain embodiments, p is 0, 1, or 2. In certain embodiments, p is 1, 2, or 3. In certain embodiments, p is selected from the values represented in the compounds in Tables 1, 1-A, and 5, below.

[0151] The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

[0152] One aspect of the invention provides a compound represented by Formula I-1:



(I-1)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring;

R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered

saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-;

X^2 is N or $C(R^2)$;

A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

n is 1 or 2;

m is 0, 1, 2, or 3; and

p is 0, 1, or 2;

provided that if p is 0 and X^1 is -C(O)-, then n is 2.

[0153] The definitions of variables in Formula I-1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0154] In certain embodiments, the compound is a compound of Formula I-1.

[0155] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4}

hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0156] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.

[0157] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$. In certain embodiments, two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0158] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, or -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0159] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0160] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain

embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkoxyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro. In certain embodiments, R^1 represents independently for each occurrence $-N(R^5)(R^6)$.

[0161] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0162] As defined generally above, R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0163] In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen or halo. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0164] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence halo. In certain embodiments, R^2 is fluoro. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^2 is trifluoromethyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^2 is $-CH_2OH$. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0165] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0166] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0167] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0168] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0169] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0170] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2

substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0171] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl.

[0172] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is C_{1-4} haloalkyl. In certain embodiments, R^3 is trifluoromethyl. In certain embodiments, R^3 is C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is $-CH_2OH$.

[0173] In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0174] As defined generally above, R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halo. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is C_{1-4} haloalkyl. In certain embodiments, R^4 is trifluoromethyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0175] As defined generally above, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0176] In certain embodiments, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{3-5} cycloalkyl.

[0177] In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0178] As defined generally above, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0179] In certain embodiments, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{3-5} cycloalkyl.

[0180] In certain embodiments, R^6 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0181] As defined generally above, R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0182] In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{3-5} cycloalkyl.

[0183] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0184] In certain embodiments, R^5 and R^6 are selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0185] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, $-S(O)_2-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0186] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6}

haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0187] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -$N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^5)(R^6)$. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$, $–NH_2$, $–CF_3$, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$ or $–NH_2$.

[0188] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0189] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence -$N(R^5)(R^6)$, halo, or cyano.

[0190] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl,

or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0191] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0192] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $-OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence $-N(R^5)(R^6)$. In certain embodiments, R^7 is $-NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 represents independently for each occurrence $-S(O)_2-(C_{1-6}$ alkyl).

[0193] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^7 is phenyl. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered saturated or partially

unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0194] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0195] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0196] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

[0197] As defined generally above, X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-. In certain embodiments, X^1 is -C(O)-. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-. In certain embodiments, X^1 is -S(O)-. In certain embodiments, X^1 is -$S(O)_2$-. In certain embodiments, X^1 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

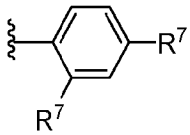
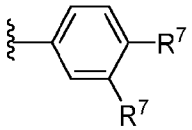
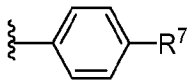
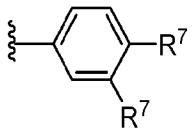
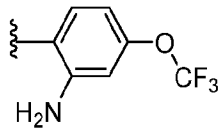
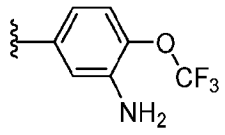
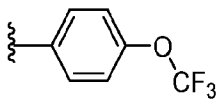
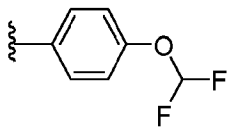
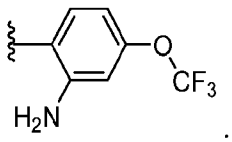
[0198] As defined generally above, X^2 is N or $C(R^2)$. In certain embodiments, X^2 is N. In certain embodiments, X^2 is $C(R^2)$. In certain embodiments, X^2 is C(H). In certain embodiments, X^2 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

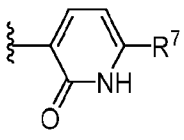
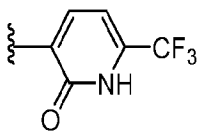
[0199] As defined generally above, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

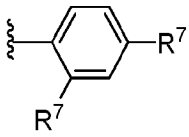
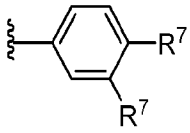
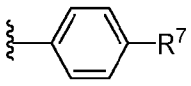
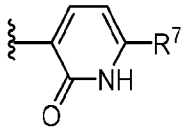
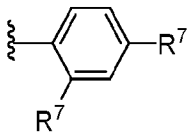
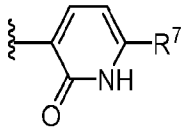
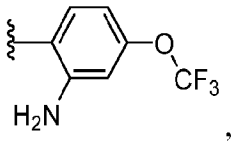
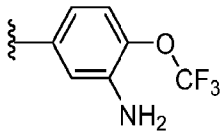
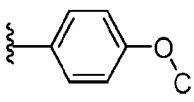
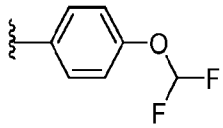
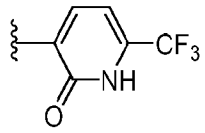
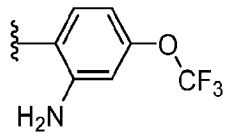
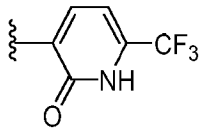
[0200] In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0201] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms

independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

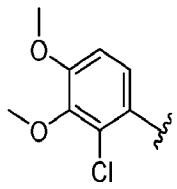
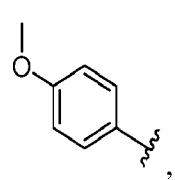
[0202] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  .

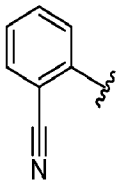
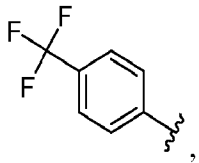
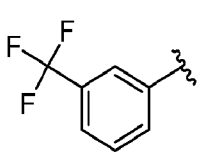
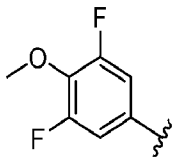
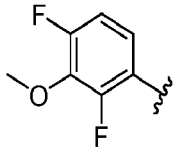
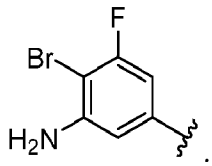
[0203] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

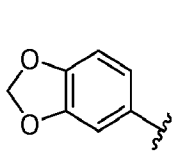
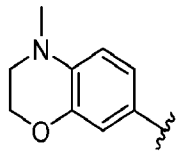
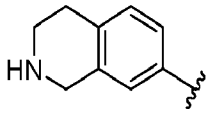
[0204] In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  or  . In certain embodiments, A^1 is  ,  ,  ,  ,  , or  or  .

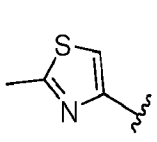
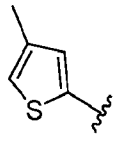
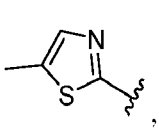
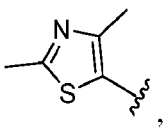
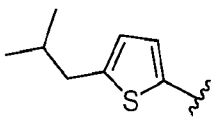
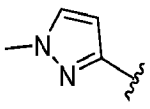
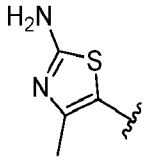
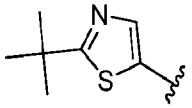
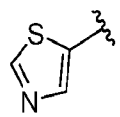
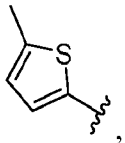
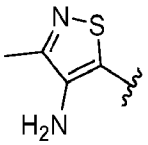
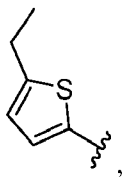
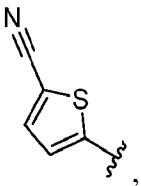
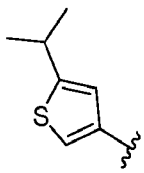
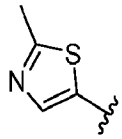
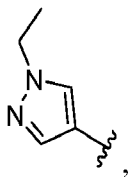
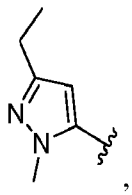
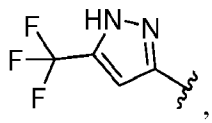
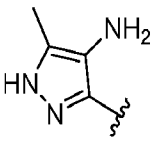
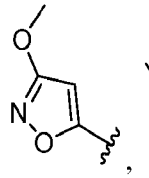
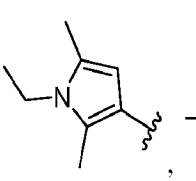
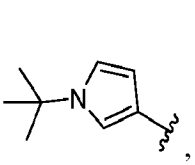
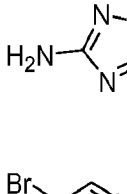
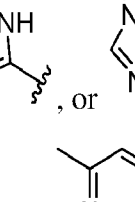
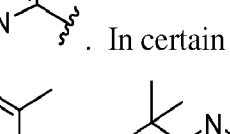
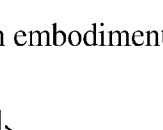
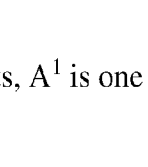
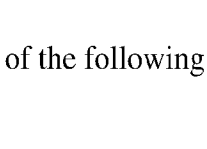
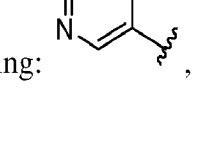
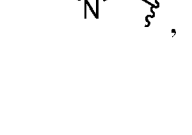
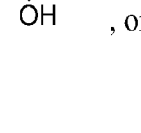
[0205] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

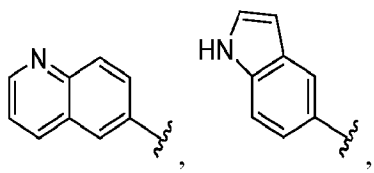
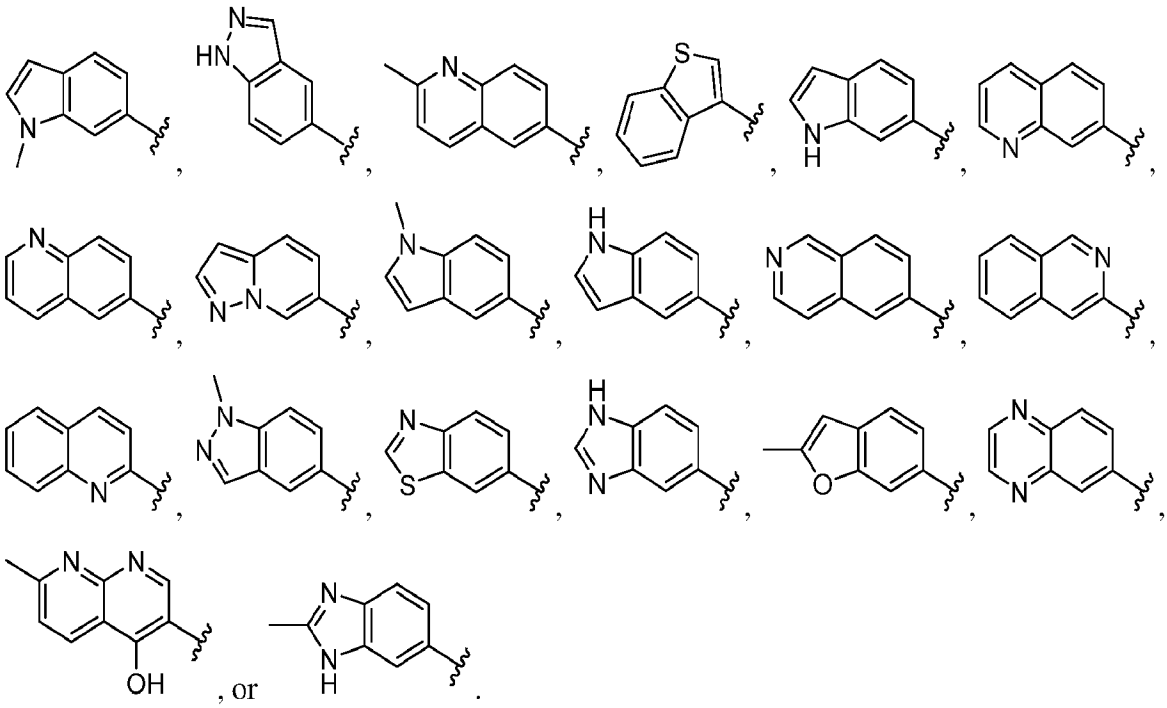
[0206] In certain embodiments, A^1 is naphthyl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

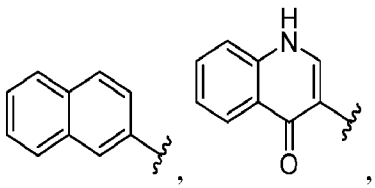
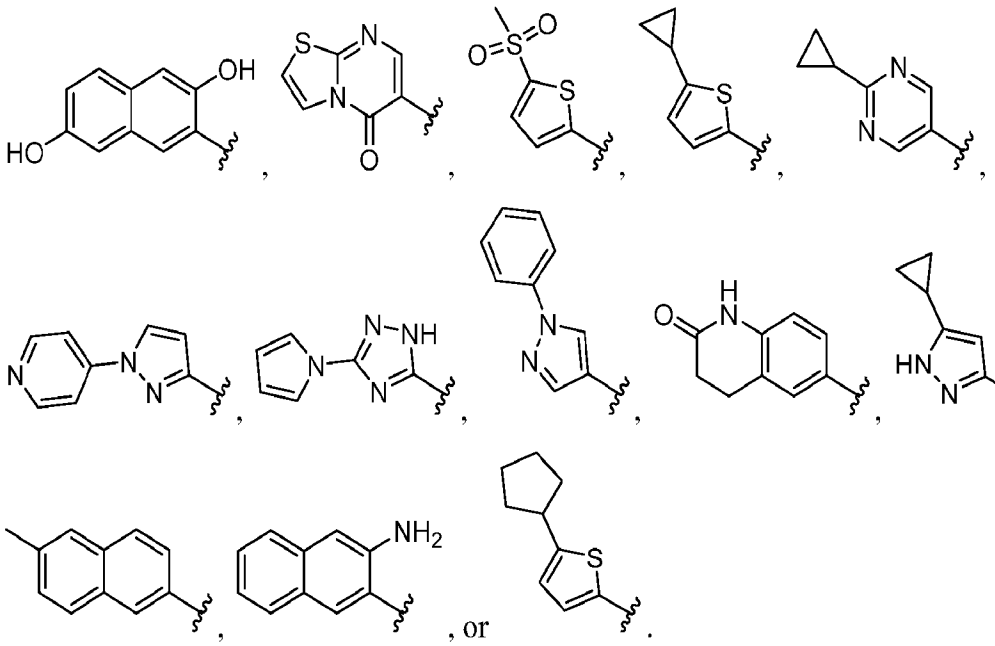
[0207] In certain embodiments, A^1 is one of the following:  ,  ,






, or  .

In certain embodiments, A^1 is one of the following:  ,  , or  .

[0208] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , . In certain embodiments, A^1 is one of the following: , , or .

[0209] In certain embodiments, A^1 is one of the following:  ,  , or .

[0210] In certain embodiments, A^1 is one of the following:  ,  , , or .

[0211] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Tables 1 and 5, below.

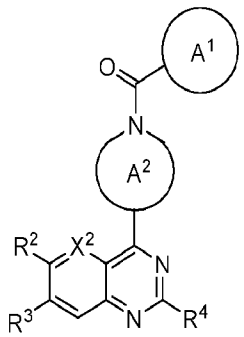
[0212] As defined generally above, n is 1 or 2; provided that if p is 0, and X^1 is -C(O)-, then n is 2. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is selected from the values represented in the compounds in Tables 1 and 5, below.

[0213] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Tables 1 and 5, below.

[0214] As defined generally above, p is 0, 1, or 2; provided that if p is 0, and X^1 is -C(O)-, then n is 2. In certain embodiments, p is 0, and n is 2. In certain embodiments, p is 0, X^1 is -C(O)-, and n is 2. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 0 or 1; provided that if p is 0, and X^1 is -C(O)-, then n is 2. In certain embodiments, p is 1 or 2. In certain embodiments, p is selected from the values represented in the compounds in Tables 1 and 5, below.

[0215] The description above describes multiple embodiments relating to compounds of Formula I-1. The patent application specifically contemplates all combinations of the embodiments.

[0216] Another aspect of the invention provides a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

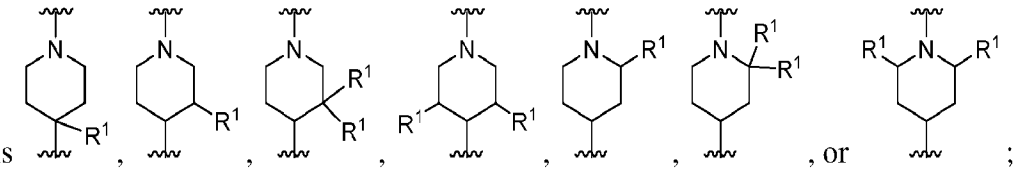
R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

X^2 is N or $C(R^2)$;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

A^2 is  ;

wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1; and

m is 0, 1, 2, or 3.

[0217] The definitions of variables in Formula I-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0218] In certain embodiments, the compound is a compound of Formula I-A.

[0219] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0220] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0221] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$.

[0222] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Table 1, below.

[0223] As defined generally above, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents

independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0224] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0225] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0226] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table 1, below.

[0227] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0228] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0229] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6

membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0230] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl.

[0231] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Table 1, below.

[0232] As defined generally above, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Table 1, below.

[0233] As defined generally above, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Table 1, below.

[0234] As defined generally above, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each

occurrence C_{1-4} alkyl. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Table 1, below.

[0235] As defined generally above, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl.

[0236] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are selected from the groups depicted in the compounds in Table 1, below.

[0237] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0238] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0239] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, or C_{1-6} alkyl. In certain embodiments, R^7 represents

independently for each occurrence C_{1-6} haloalkoxyl, -$N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^5)(R^6)$. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$, $–NH_2$, $–CF_3$, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$ or $–NH_2$.

[0240] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence -$N(R^5)(R^6)$, halo, or cyano.

[0241] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl.

[0242] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $–OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence -$N(R^5)(R^6)$. In certain embodiments, R^7 is $–NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano.

[0243] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

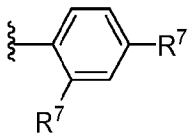
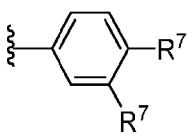
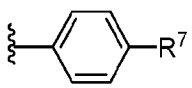
[0244] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl.

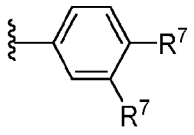
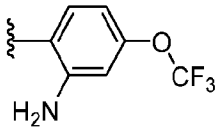
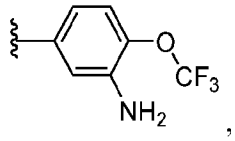
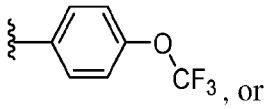
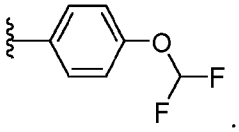
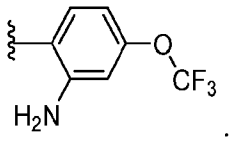
[0245] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Table 1, below.

[0246] As defined generally above, X^2 is N or $C(R^2)$. In certain embodiments, X^2 is N. In certain embodiments, X^2 is $C(R^2)$. In certain embodiments, X^2 is C(H). In certain embodiments, X^2 is selected from the groups depicted in the compounds in Table 1, below.

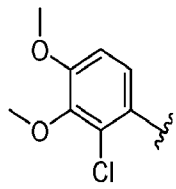
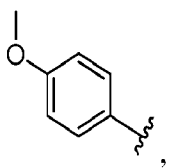
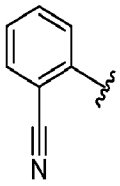
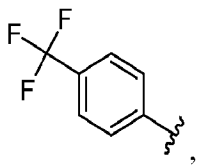
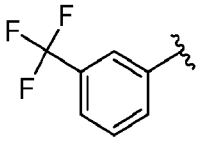
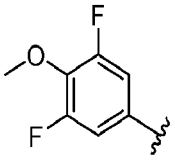
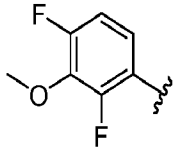
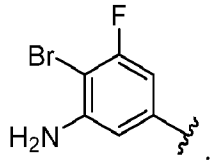
[0247] As defined generally above, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

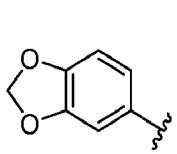
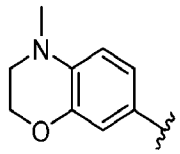
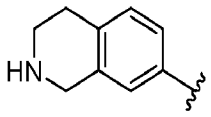
[0248] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

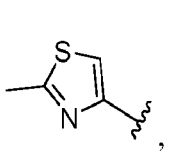
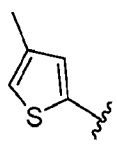
[0249] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, A^1 is  ,  , or  . In certain embodiments,

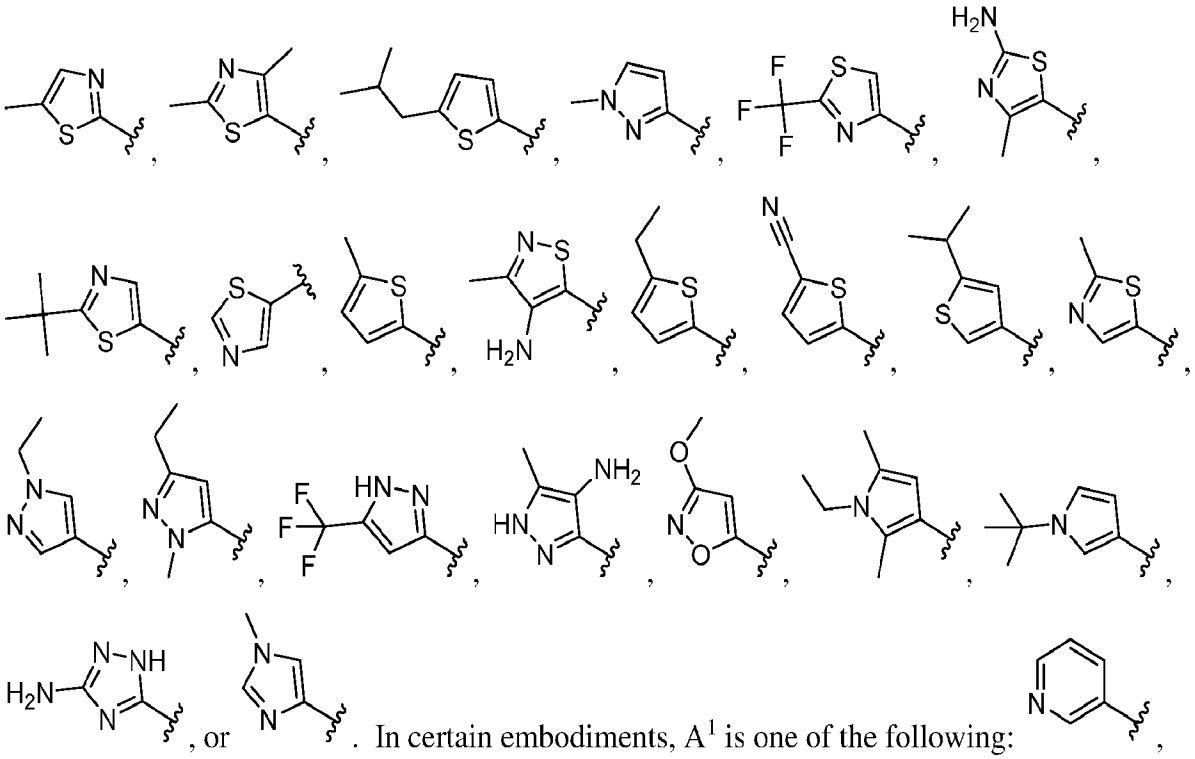
A^1 is  . In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  .

[0250] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

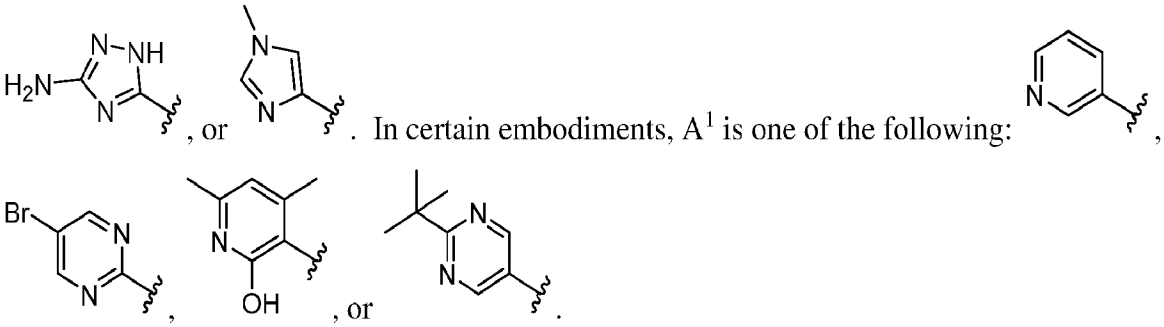
[0251] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  , or  .

In certain embodiments, A^1 is one of the following:  ,  , or  .

[0252] In certain embodiments, A^1 is one of the following:  ,  ,

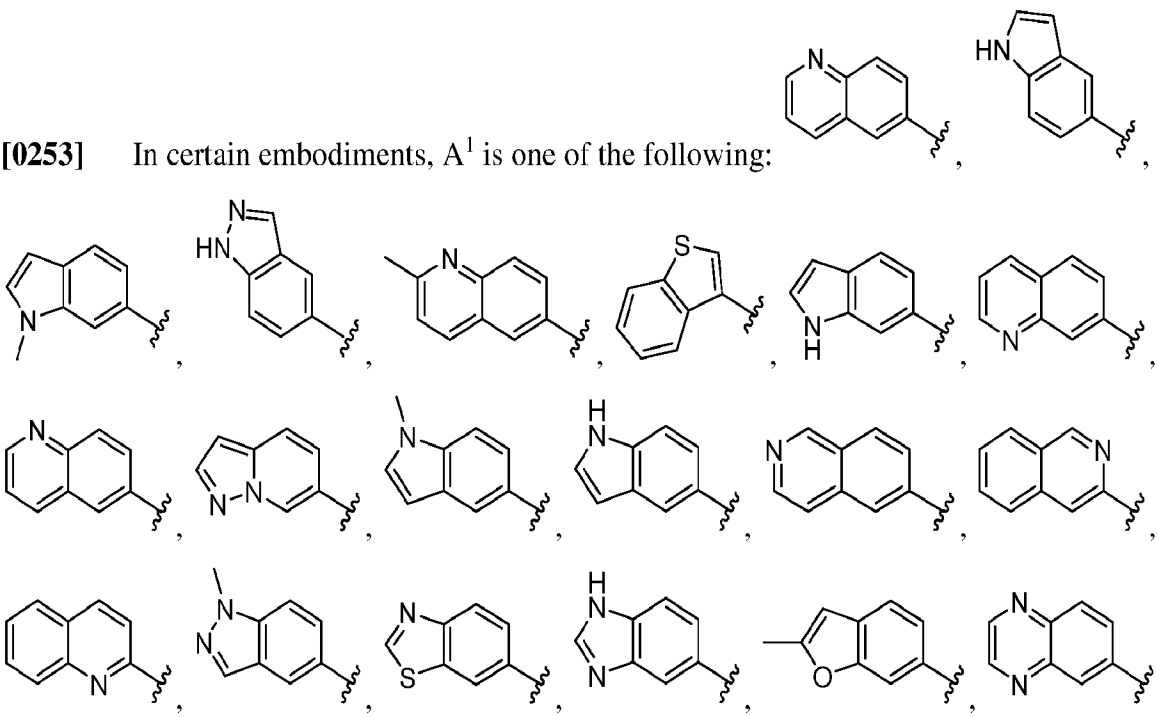


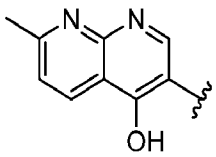
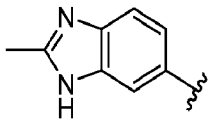
, or . In certain embodiments, A^1 is one of the following:



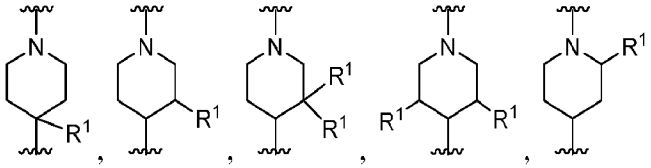
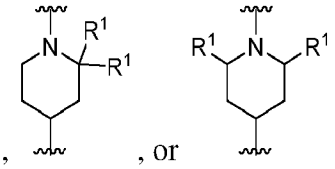
, or .

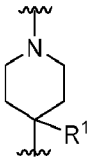
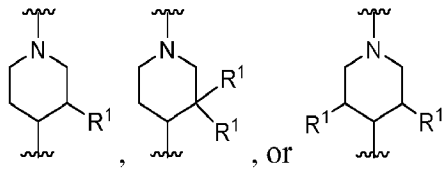
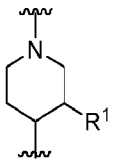
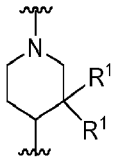
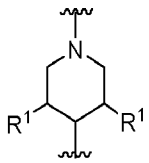
[0253] In certain embodiments, A^1 is one of the following:

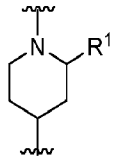
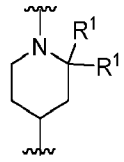
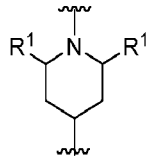
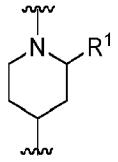
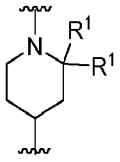
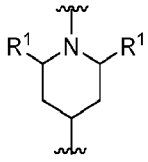



, or 
.

[0254] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Table 1, below.

[0255] As defined generally above, A^2 is 
, 
; wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

[0256] In certain embodiments, A^2 is 
wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is 
wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is 
wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is 
wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is 
wherein the piperidinylene nitrogen atom is attached

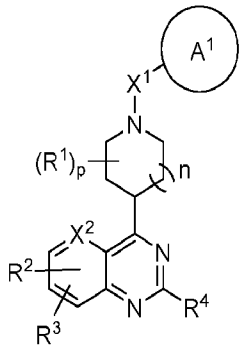
to -C(O)-A^1. In certain embodiments, A^2 is  ,  , or  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

[0257] In certain embodiments, A^2 is selected from the values represented in the compounds in Table 1, below.

[0258] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Table 1, below.

[0259] The description above describes multiple embodiments relating to compounds of Formula I-A. The patent application specifically contemplates all combinations of the embodiments.

[0260] Another aspect of the invention provides a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond;

R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and halo;

R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-;

X^2 is N or C(R^2);

A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7; and when X^1 is -S(O)- or -$S(O)_2$-, A^1 is additionally selected from phenyl, and a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

n is 1 or 2; and

m and p are each independently 0, 1, 2, or 3.

[0261] The definitions of variables in Formula II above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0262] In certain embodiments, the compound is a compound of Formula II.

[0263] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond.

[0264] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0265] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0266] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$. In certain embodiments, two occurrences of

R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond.

[0267] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, or -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0268] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0269] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is -CH_2OH. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is -OCF_3. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkoxyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro. In certain embodiments, R^1 represents independently for each occurrence -$N(R^5)(R^6)$.

[0270] In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken

together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.

[0271] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0272] As defined generally above, R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0273] In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen or halo. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0274] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence halo. In certain embodiments, R^2 is fluoro. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^2 is trifluoromethyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^2 is $-CH_2OH$. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0275] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0276] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0277] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo.

[0278] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0279] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo.

[0280] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0281] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0282] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, or a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is piperazinyl or piperazin-2-onyl, each of which is substituted

with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl or 1-methylpiperazin-2-on-4-yl.

[0283] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0284] In certain embodiments, R^3 is a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4}

alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and halo. In certain embodiments, R^3 is a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazin-2-onyl, each of which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 1-methylpiperazin-2-on-4-yl.

[0285] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl.

[0286] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is -OCF_3. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is C_{1-4} haloalkyl. In certain embodiments, R^3 is trifluoromethyl. In certain embodiments, R^3 is C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is -CH_2OH.

[0287] In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0288] As defined generally above, R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halo. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is C_{1-4} haloalkyl. In certain embodiments, R^4 is trifluoromethyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0289] As defined generally above, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In

certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0290] In certain embodiments, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{3-5} cycloalkyl.

[0291] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0292] In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0293] As defined generally above, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0294] In certain embodiments, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{3-5} cycloalkyl.

[0295] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain

embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0296] In certain embodiments, R^6 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0297] In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{3-5} cycloalkyl.

[0298] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -S(O)$_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0299] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl); or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected

from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0300] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S(O)$_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0301] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0302] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -

O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -N(R^5)(R^6), C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -N(R^5)(R^6). In certain embodiments, R^7 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence –OCF_3 or –NH_2.

[0303] In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence -N(R^5)(R^6), hydroxyl, halo, or cyano. In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence -N(R^5)(R^6), or halo. In certain embodiments, one occurrence of R^7 is C_{1-4} haloalkoxyl, C_{1-4} haloalkyl, -S-(C_{1-4} haloalkyl), or -O-(C_{3-4} cycloalkyl), and any further occurrences of R^7 are –NH_2.

[0304] In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, –SCF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2, –F, or –Cl. In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2, –F, or –Cl. In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2.

[0305] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S(O)$_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6

membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0306] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl) or -S-(C_{1-6} alkyl).

[0307] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0308] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain

embodiments, R^7 represents independently for each occurrence phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0309] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $-OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{1-4} alkylene)-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6). In certain embodiments, R^7 is $-NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{2-6} alkenyl. In certain embodiments, R^7 represents independently for each occurrence C_{2-6} alkynyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl). In certain embodiments, R^7 is -S-CF_3. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence -$S(O)_2$-(C_{1-6} alkyl).

[0310] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^7 is phenyl. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0311] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0312] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0313] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0314] As defined generally above, X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-. In certain embodiments, X^1 is -C(O)-. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-. In certain embodiments, X^1 is -S(O)-. In certain embodiments, X^1 is -$S(O)_2$-. In certain embodiments, X^1 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0315] As defined generally above, X^2 is N or C(R^2). In certain embodiments, X^2 is N. In certain embodiments, X^2 is C(R^2). In certain embodiments, X^2 is C(H). In certain embodiments, X^2 is selected from the groups depicted in the compounds in Tables 2, 2-A, 3, and 4, below.

[0316] As defined generally above, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen,

and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7; and when X^1 is -S(O)- or -$S(O)_2$-, A^1 is additionally selected from phenyl and a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0317] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7.

[0318] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0319] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3

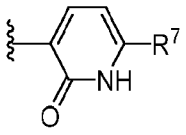
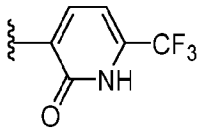
heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0320] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

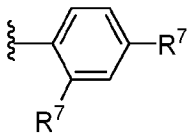
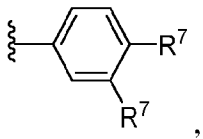
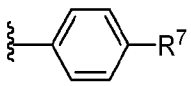
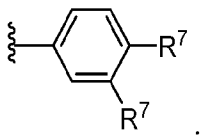
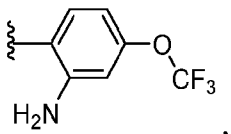
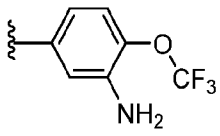
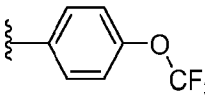
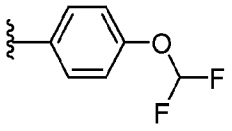
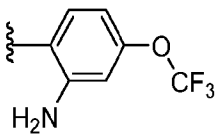
[0321] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

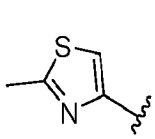
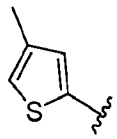
[0322] In certain embodiments, A^1 is naphthyl substituted with m occurrences of R^7.

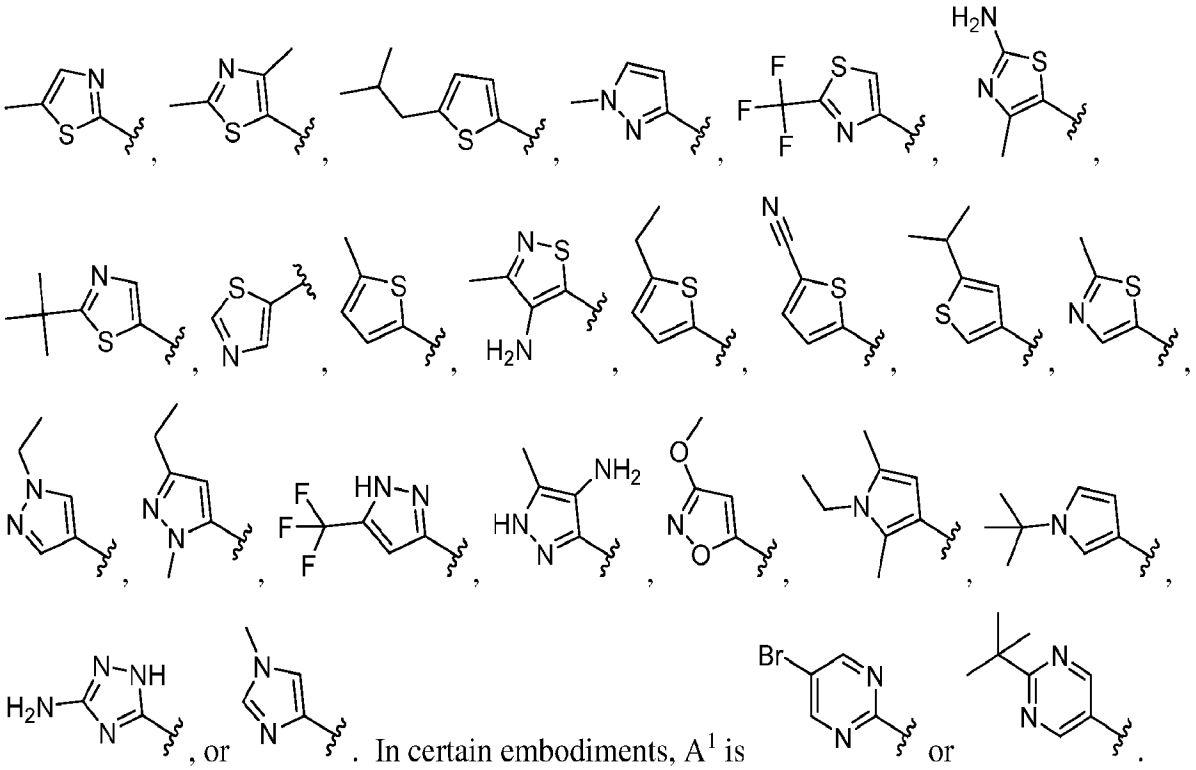
[0323] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms

independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0324] In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is phenyl or a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; wherein said heteroaryl is substituted with m occurrences of R^7.

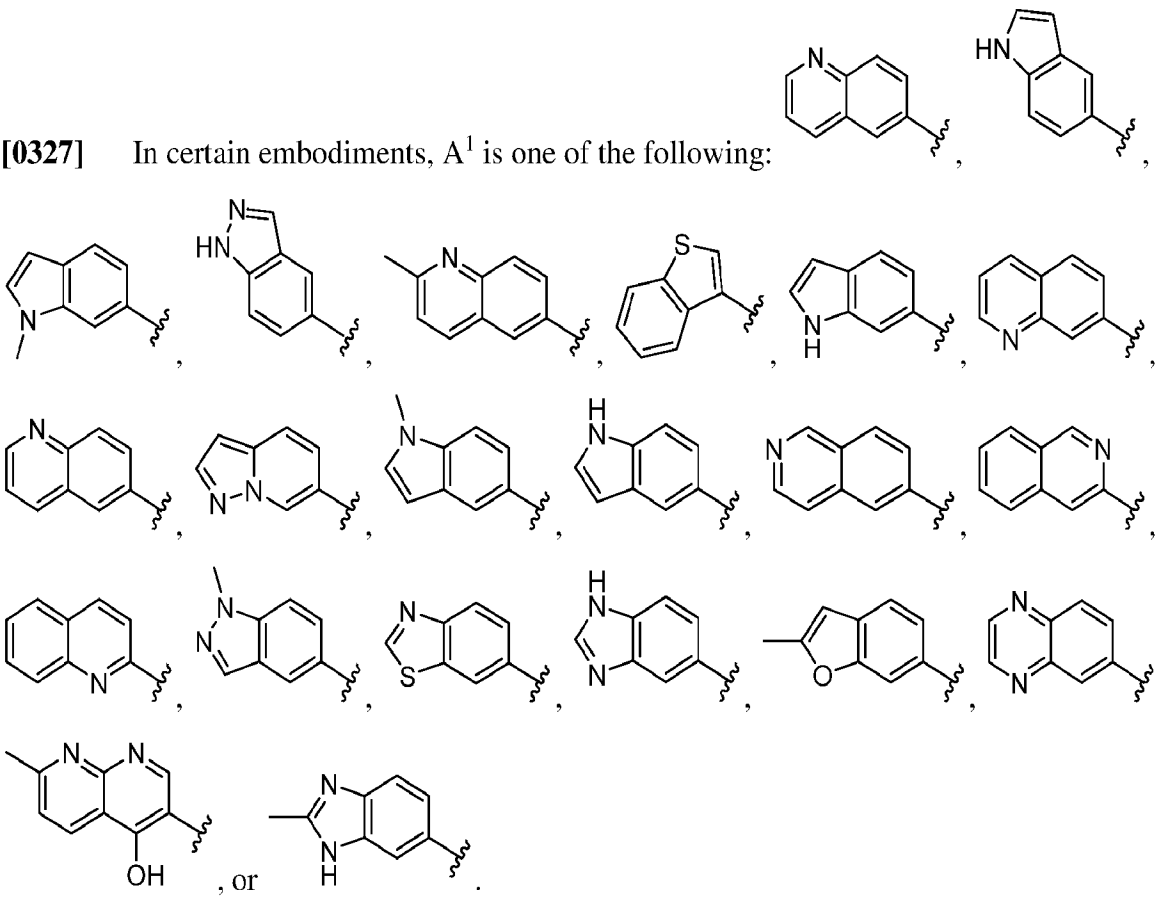
[0325] In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  ,  , or  . In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  . In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  ,  ,  , or  . In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  .

[0326] In certain embodiments, A^1 is one of the following:  ,  ,

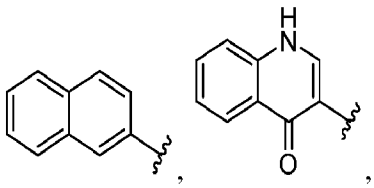
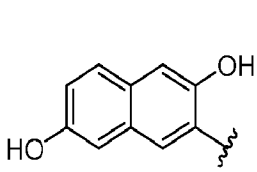
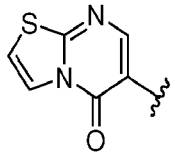


, or . In certain embodiments, A^1 is or .

[0327] In certain embodiments, A^1 is one of the following:



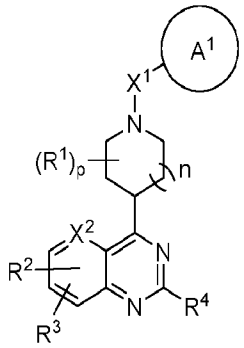
, or .

[0328] In certain embodiments, A^1 is one of the following:  ,  ,  ,

certain embodiments, p is selected from the values represented in the compounds in Tables 2, 2-A, 3, and 4, below.

[0333] The description above describes multiple embodiments relating to compounds of Formula II. The patent application specifically contemplates all combinations of the embodiments.

[0334] Another aspect of the invention provides a compound represented by Formula II-1:



(II-1)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring;

R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-;

X^2 is N or $C(R^2)$;

A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7; and when X^1 is -S(O)- or -$S(O)_2$-, A^1 is additionally selected from phenyl, and a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

n is 1 or 2;

m is 0, 1, 2, or 3; and

p is 0, 1, or 2.

[0335] The definitions of variables in Formula II-1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0336] In certain embodiments, the compound is a compound of Formula II-1.

[0337] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0338] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or -$N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.

[0339] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or -$N(R^5)(R^6)$. In certain embodiments, two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0340] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, or -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0341] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0342] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkoxyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro. In certain embodiments, R^1 represents independently for each occurrence $-N(R^5)(R^6)$.

[0343] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0344] As defined generally above, R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0345] In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen or halo. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0346] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence halo. In certain embodiments, R^2 is fluoro. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain

embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^2 is trifluoromethyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^2 is $-CH_2OH$. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0347] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0348] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0349] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0350] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0351] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered

saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0352] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0353] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl.

[0354] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is C_{1-4} haloalkyl. In certain embodiments, R^3 is trifluoromethyl. In certain embodiments, R^3 is C_{1-4} hydroxyalkyl. In certain embodiments, R^3 is $-CH_2OH$.

[0355] In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0356] As defined generally above, R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halo. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is C_{1-4} haloalkyl.

In certain embodiments, R^4 is trifluoromethyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0357] As defined generally above, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0358] In certain embodiments, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{3-5} cycloalkyl.

[0359] In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0360] As defined generally above, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0361] In certain embodiments, R^6 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^6 represents independently for each occurrence C_{3-5} cycloalkyl.

[0362] In certain embodiments, R^6 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0363] As defined generally above, R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0364] In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{3-5} cycloalkyl.

[0365] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0366] In certain embodiments, R^5 and R^6 are selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0367] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, $-S(O)_2-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and

sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0368] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0369] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -$N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^5)(R^6)$. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$, $–NH_2$, $–CF_3$, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$ or $–NH_2$.

[0370] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0371] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence -$N(R^5)(R^6)$, halo, or cyano.

[0372] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0373] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0374] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $–OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence -$N(R^5)(R^6)$. In certain embodiments, R^7 is $–NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents

independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 represents independently for each occurrence $-S(O)_2-(C_{1-6}$ alkyl).

[0375] In certain embodiments, R^7 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^7 is phenyl. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^7 represents independently for each occurrence a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0376] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0377] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0378] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0379] As defined generally above, X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-. In certain embodiments, X^1 is -C(O)-. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-. In certain embodiments, X^1 is -S(O)-. In certain embodiments, X^1 is -$S(O)_2$-. In certain embodiments, X^1 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0380] As defined generally above, X^2 is N or $C(R^2)$. In certain embodiments, X^2 is N. In certain embodiments, X^2 is $C(R^2)$. In certain embodiments, X^2 is C(H). In certain embodiments, X^2 is selected from the groups depicted in the compounds in Tables 2, 3, and 4, below.

[0381] As defined generally above, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7; and when X^1 is -S(O)- or -$S(O)_2$-, A^1 is additionally selected from phenyl and a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0382] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7.

[0383] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

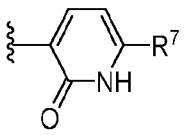
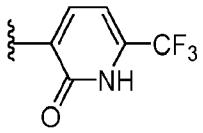
[0384] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0385] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

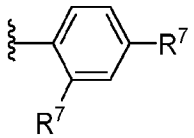
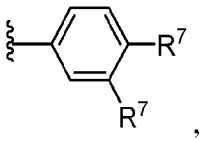
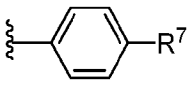
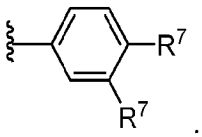
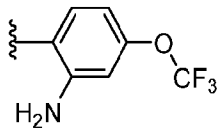
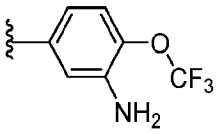
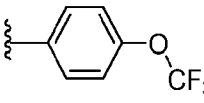
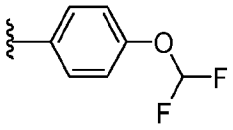
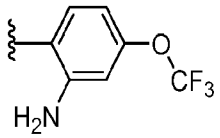
[0386] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-

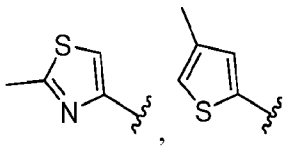
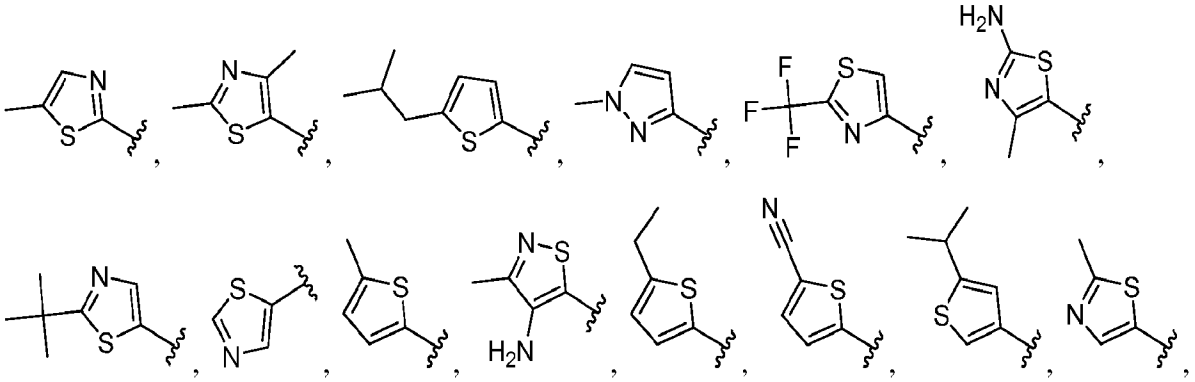
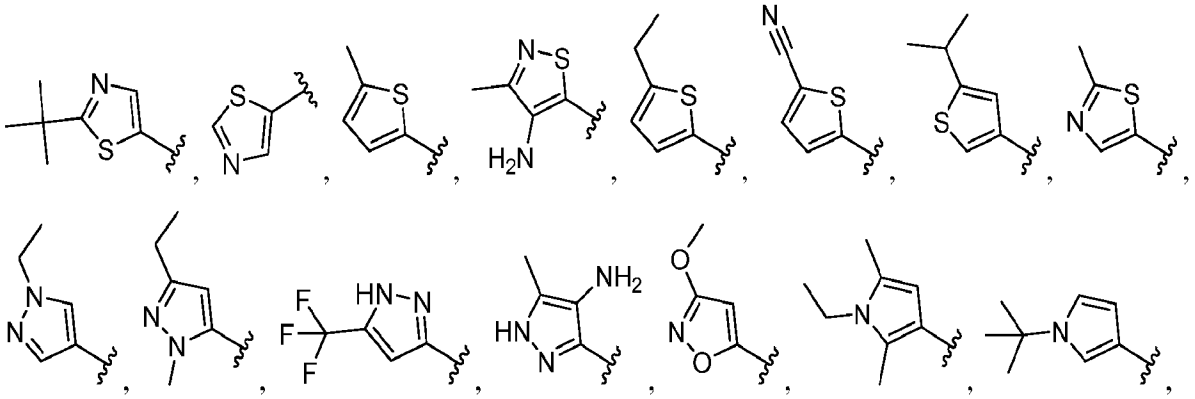
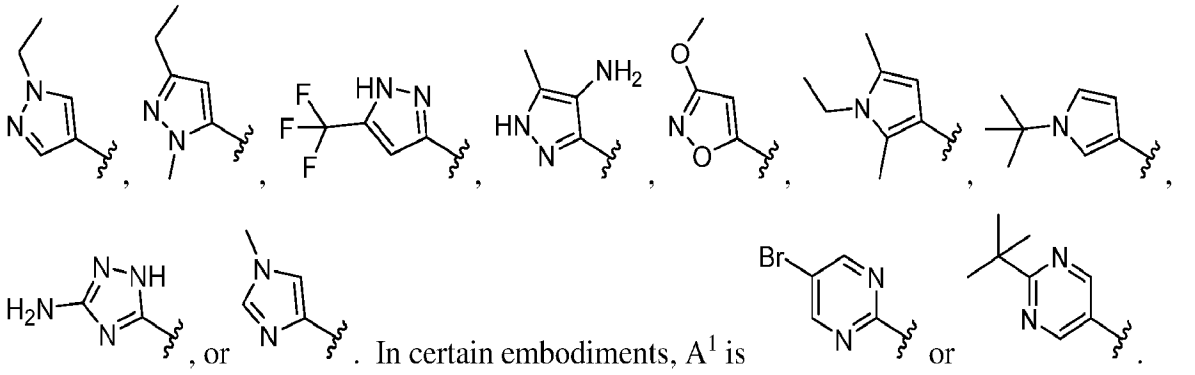
heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

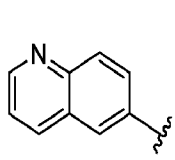
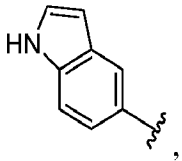
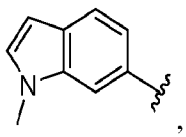
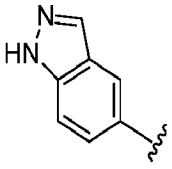
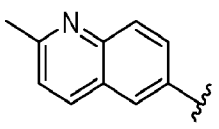
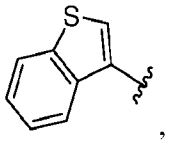
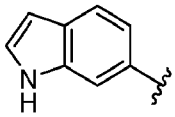
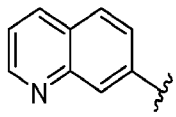
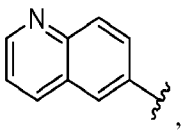
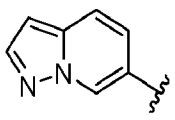
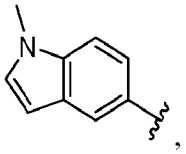
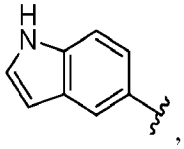
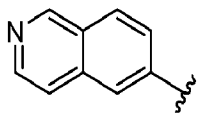
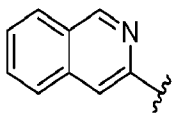
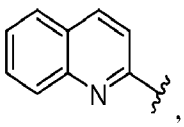
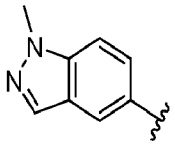
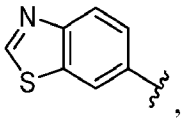
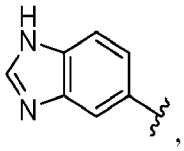
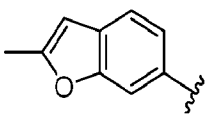
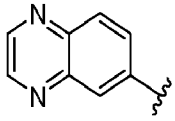
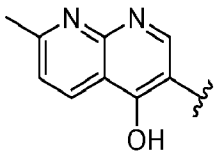
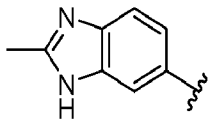
[0387] In certain embodiments, A^1 is naphthyl substituted with m occurrences of R^7.

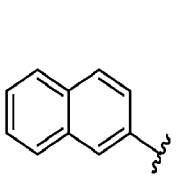
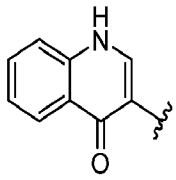
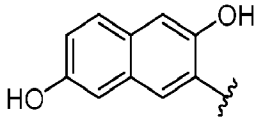
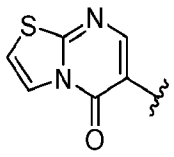
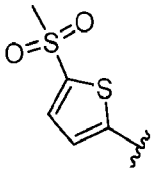
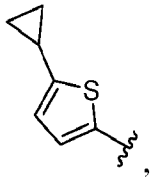
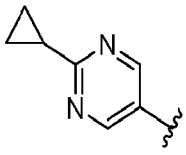
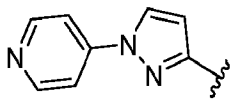
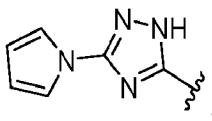
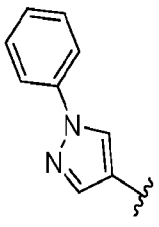
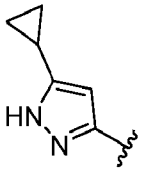
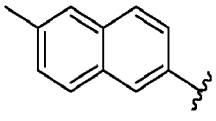
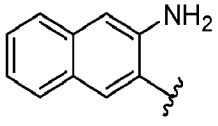
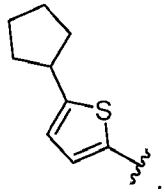
[0388] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0389] In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is phenyl or a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; wherein said heteroaryl is substituted with m occurrences of R^7.

[0390] In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  ,  , or  . In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  . In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  ,  ,  , or  . In certain embodiments, X^1 is -S(O)- or -$S(O)_2$-, and A^1 is  .

[0391] In certain embodiments, A^1 is one of the following:  ,  ,  ,  , , or . In certain embodiments, A^1 is or .

[0392] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

[0393] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

[0394] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Table 2, below.

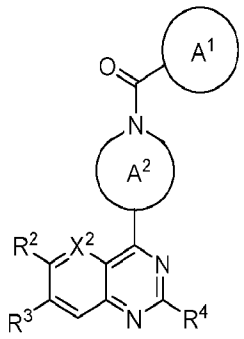
[0395] As defined generally above, n is 1 or 2. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is selected from the values represented in the compounds in Tables 2, 3, and 4, below.

[0396] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Tables 2, 3, and 4, below.

[0397] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. n certain embodiments, p is 0 or 1. In certain embodiments, p is 1 or 2. In certain embodiments, p is selected from the values represented in the compounds in Tables 2, 3, and 4, below.

[0398] The description above describes multiple embodiments relating to compounds of Formula II-1. The patent application specifically contemplates all combinations of the embodiments.

[0399] Another aspect of the invention provides a compound represented by Formula II-A:



(II-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

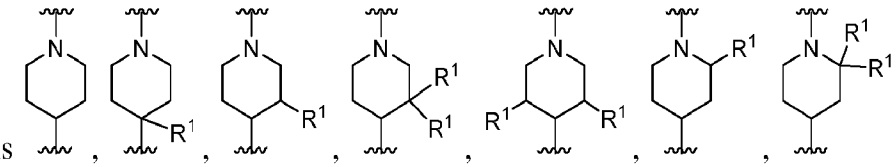
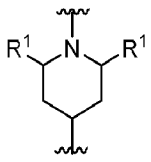
R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

X^2 is N or C(R^2);

A^1 is 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

A^2 is  , or  ; wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1; and

m is 0, 1, 2, or 3.

[0400] The definitions of variables in Formula II-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0401] In certain embodiments, the compound is a compound of Formula II-A.

[0402] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0403] In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0404] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0405] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain

embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$.

[0406] As defined generally above, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0407] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0408] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0409] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0410] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents

independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0411] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0412] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl.

[0413] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl.

[0414] As defined generally above, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl.

[0415] As defined generally above, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl.

[0416] As defined generally above, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain

embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl.

[0417] In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl.

[0418] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0419] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0420] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0421] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), C_{1-6} alkyl, or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -N(R^5)(R^6), C_{1-6} haloalkyl, halo, or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -N(R^5)(R^6), or phenyl. In certain embodiments, R^7 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, chloro, or phenyl. In certain embodiments, R^7 represents independently for each occurrence –OCF_3, –NH_2, or phenyl.

[0422] In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or phenyl. In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), C_{1-6} alkyl, or phenyl. In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or phenyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or phenyl.

[0423] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each

occurrence C_{1-6} haloalkoxyl, -$N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^5)(R^6)$. In certain embodiments, R^7 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence –OCF_3 or –NH_2.

[0424] In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence -$N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, one occurrence of R^7 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^7 represent independently for each occurrence -$N(R^5)(R^6)$, or halo. In certain embodiments, one occurrence of R^7 is C_{1-4} haloalkoxyl, C_{1-4} haloalkyl, -S-(C_{1-4} haloalkyl), or -O-(C_{3-4} cycloalkyl), and any further occurrences of R^7 are –NH_2.

[0425] In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, –SCF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2, –F, or –Cl. In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2, –F, or –Cl. In certain embodiments, one occurrence of R^7 is –OCF_3, –CF_3, or -O-(cyclopropyl), and any further occurrences of R^7 are independently –NH_2.

[0426] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -$N(R^5)(R^6)$, hydroxyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or

hydroxyl. In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl) or -S-(C_{1-6} alkyl).

[0427] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl.

[0428] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $-OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{1-4} alkylene)-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6). In certain embodiments, R^7 is $-NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl). In certain embodiments, R^7 is -S-CF_3. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} alkyl). In certain embodiments, R^7 is phenyl.

[0429] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0430] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2

heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

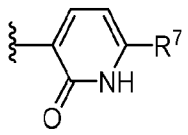
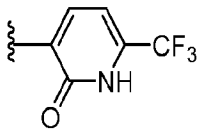
[0431] As defined generally above, X^2 is N or $C(R^2)$. In certain embodiments, X^2 is N. In certain embodiments, X^2 is $C(R^2)$. In certain embodiments, X^2 is C(H).

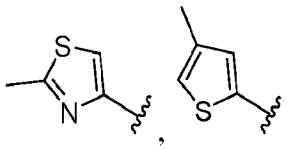
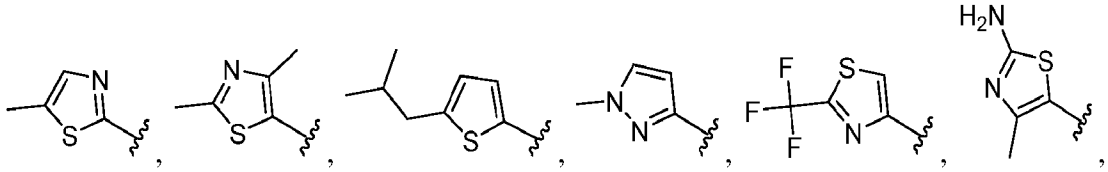
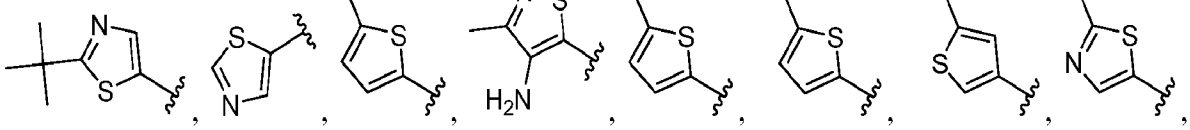
[0432] As defined generally above, A^1 is 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

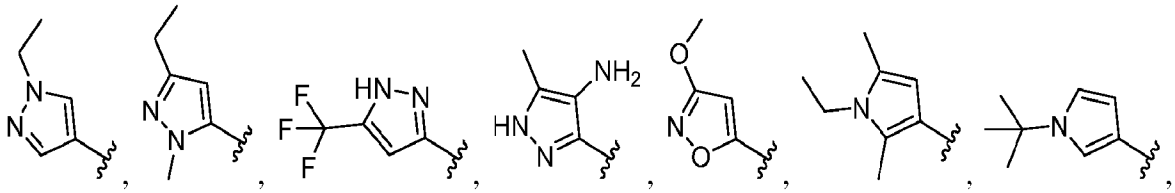
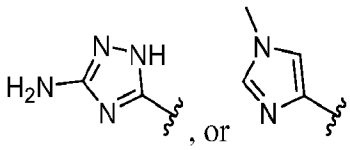
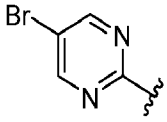
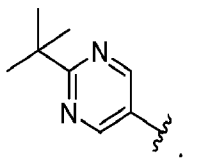
[0433] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0434] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic

heteroaryl having 2 or 3 nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

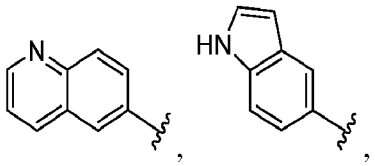
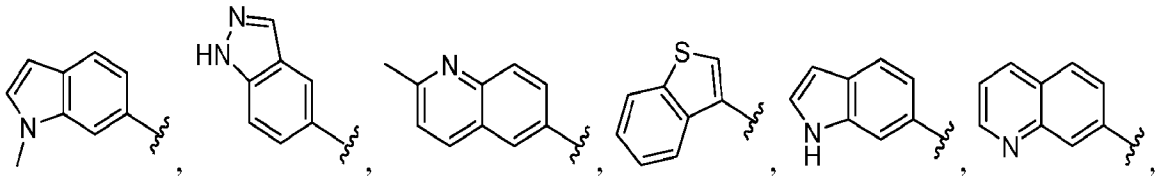
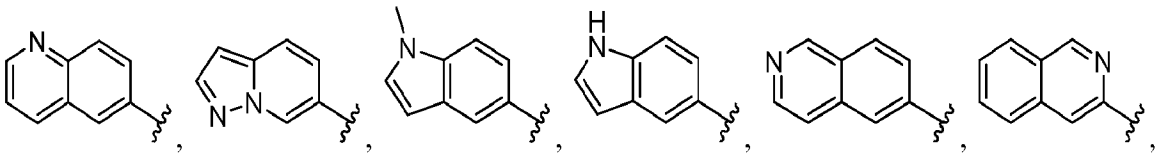
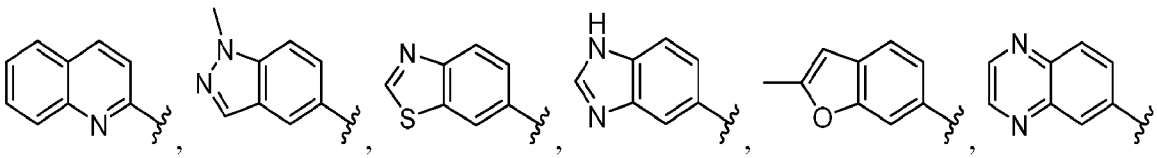
[0435] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0436] In certain embodiments, A^1 is one of the following:  ,  ,  .

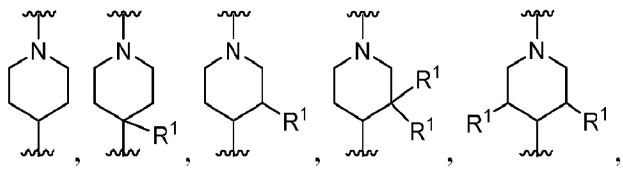
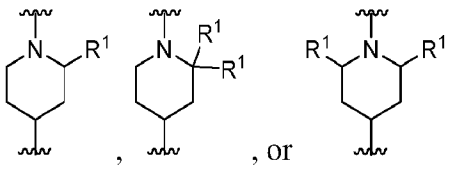
, or . In certain embodiments, A^1 is or .

[0437] In certain embodiments, A^1 is one of the following:

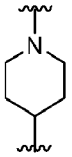
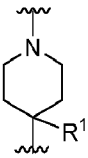
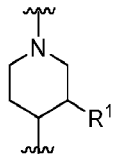
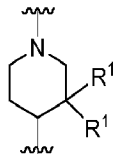
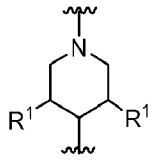
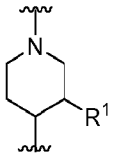
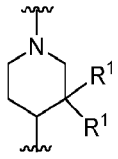
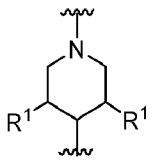
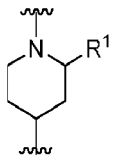
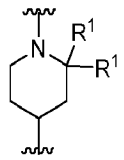
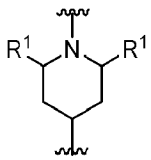
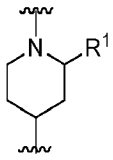
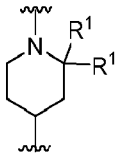





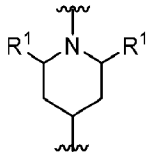
, or .

[0438] As defined generally above, A^2 is

, or ; wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

[0439] In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  ,  , or  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  . In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  ,  , or  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -

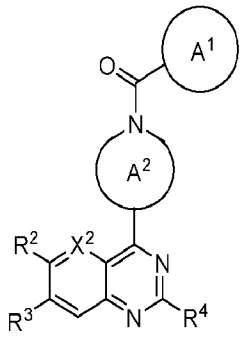


C(O)-A^1. In certain embodiments, A^2 is wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

[0440] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3.

[0441] The description above describes multiple embodiments relating to compounds of Formula II-A. The patent application specifically contemplates all combinations of the embodiments.

[0442] Another aspect of the invention provides a compound represented by Formula II-A1:



(II-A1)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen,

oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

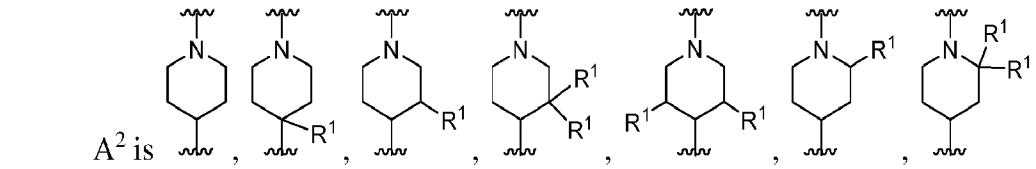
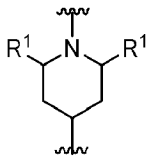
R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

X^2 is N or $C(R^2)$;

A^1 is 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

A^2 is  , or  ; wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1; and

m is 0, 1, 2, or 3.

[0443] The definitions of variables in Formula II-A1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a

variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0444] In certain embodiments, the compound is a compound of Formula II-A1.

[0445] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0446] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0447] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$.

[0448] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Table 2, below.

[0449] As defined generally above, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0450] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0451] In certain embodiments, R^2 and R^3 are each independently C_{1-4} alkoxyl. In certain embodiments, R^2 and R^3 are methoxy.

[0452] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table 2, below.

[0453] As defined generally above, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

[0454] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is hydrogen.

[0455] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and

halo. In certain embodiments, R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo. In certain embodiments, R^3 is 4-methylpiperazin-1-yl .

[0456] In certain embodiments, R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 is C_{1-4} alkoxyl or C_{1-4} alkyl.

[0457] In certain embodiments, R^3 is C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 is C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Table 2, below.

[0458] As defined generally above, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Table 2, below.

[0459] As defined generally above, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Table 2, below.

[0460] As defined generally above, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Table 2, below.

[0461] As defined generally above, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl.

[0462] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are selected from the groups depicted in the compounds in Table 2, below.

[0463] As defined generally above, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0464] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0465] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, $-N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -

$N(R^5)(R^6)$. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$, $–NH_2$, $–CF_3$, fluoro, or chloro. In certain embodiments, R^7 represents independently for each occurrence $–OCF_3$ or $–NH_2$.

[0466] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence $-N(R^5)(R^6)$, halo, or cyano.

[0467] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl.

[0468] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^7 is $–OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence $-N(R^5)(R^6)$. In certain embodiments, R^7 is $–NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano.

[0469] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0470] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted

with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl.

[0471] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Table 2, below.

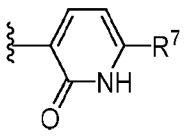
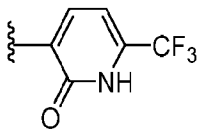
[0472] As defined generally above, X^2 is N or $C(R^2)$. In certain embodiments, X^2 is N. In certain embodiments, X^2 is $C(R^2)$. In certain embodiments, X^2 is C(H). In certain embodiments, X^2 is selected from the groups depicted in the compounds in Table 2, below.

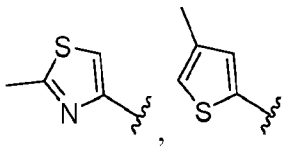
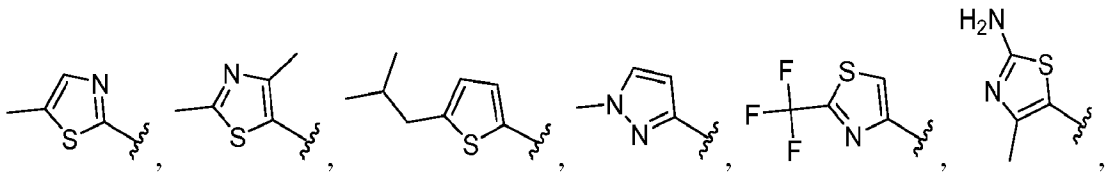
[0473] As defined generally above, A^1 is 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

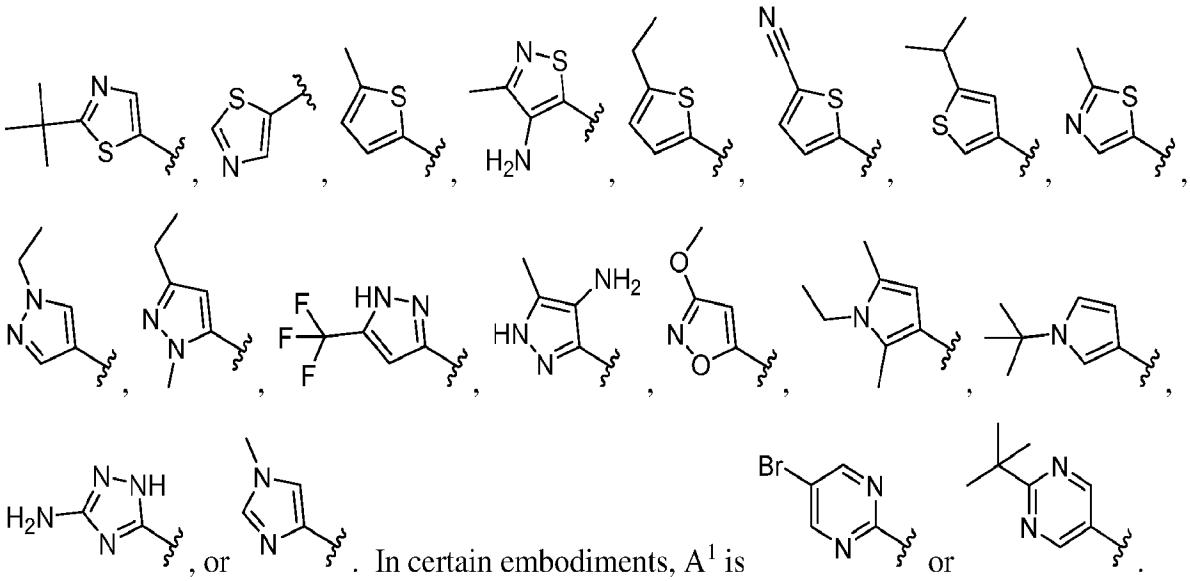
[0474] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

[0475] In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having

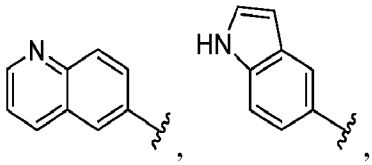
2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

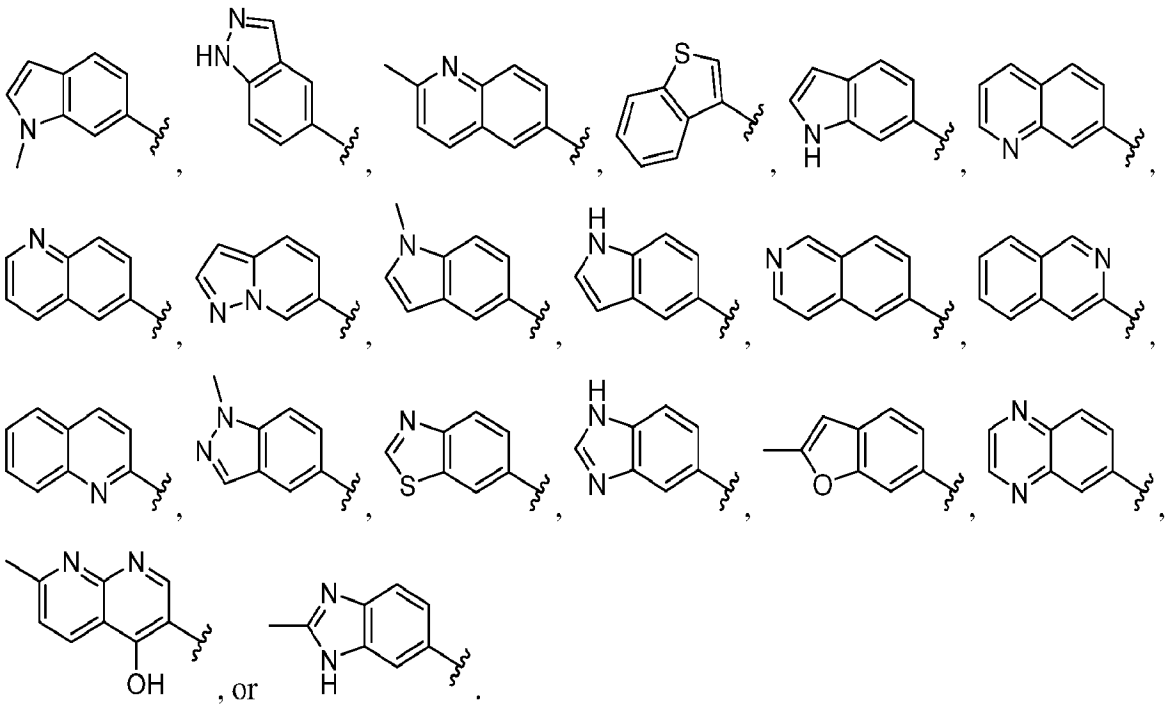
[0476] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0477] In certain embodiments, A^1 is one of the following:  ,  .

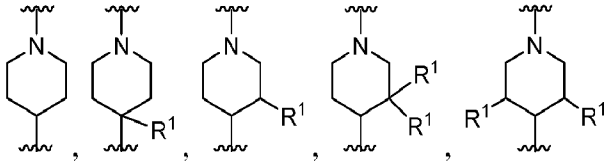
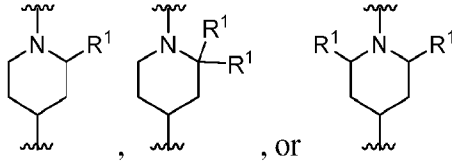


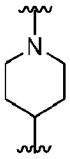
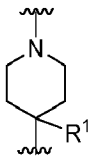
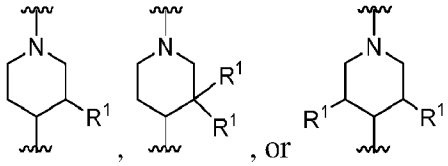
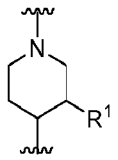
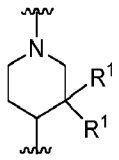
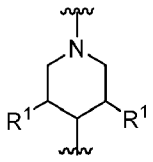
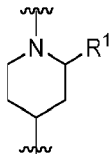
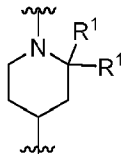
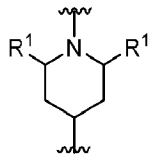
. In certain embodiments, A^1 is or .

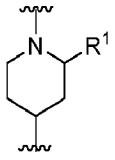
[0478] In certain embodiments, A^1 is one of the following:  ,

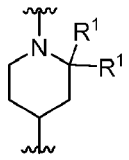
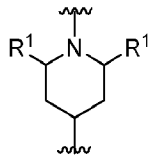


[0479] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Table 2, below.

[0480] As defined generally above, A^2 is  ,  , or ; wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

[0481] In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  , , or wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  . In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  ,  , or  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain

embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

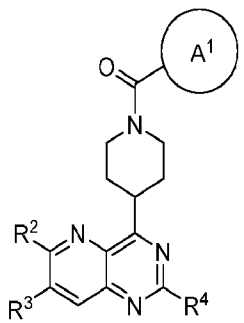
In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1. In certain embodiments, A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

[0482] In certain embodiments, A^2 is selected from the groups represented in the compounds in Table 2, below.

[0483] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Table 2, below.

[0484] The description above describes multiple embodiments relating to compounds of Formula II-A1. The patent application specifically contemplates all combinations of the embodiments.

[0485] Another aspect of the invention provides a compound represented by Formula III:



(III)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), or halo;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is:

(i) a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1; or

(ii) a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with p occurrences of R^1;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl; wherein R^7 is additionally selected from C_{1-6} haloalkoxyl when (i) m is 3, or (ii) m is 1 or 2, and q is 1;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl

having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

m is 0, 1, 2, or 3;

p is 0, 1, or 2; and

q is 0 or 1.

[0486] The definitions of variables in Formula III above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0487] In certain embodiments, the compound is a compound of Formula III.

[0488] As defined generally above, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), or halo.

[0489] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxyl, -C(O)N(R^5)(R^6), or halo. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or halo.

[0490] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), -(C_{1-4} alkylene)-C(O)N(R^5)(R^6), or halo. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, or -(C_{1-4} alkylene)-(C_{1-4} alkoxyl). In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0491] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl, -C(O)N(R^5)(R^6), or halo. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or halo.

[0492] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^1 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^1 is cyclopropyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{0-4} alkylene)-(C_{1-4} alkoxyl). In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkylene)-(C_{1-4} alkoxyl). In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkylene)-$C(O)N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence -$C(O)N(R^5)(R^6)$. In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro.

[0493] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Table 6, below.

[0494] As defined generally above, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0495] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^2 is methoxy. In certain embodiments, R^2 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^2 is $-OCF_3$.

[0496] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table 6, below.

[0497] As defined generally above, R^3 is:

(i) a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1; or

(ii) a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with p occurrences of R^1.

[0498] In certain embodiments, R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1.

[0499] In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of C_{2-4} haloalkyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of trifluoromethyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of C_{1-4} haloalkyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences

of C_{2-4} haloalkyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of trifluoromethyl, and (b) p occurrences of R^1.

[0500] In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of C_{3-6} cycloalkyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of cyclopropyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of C_{3-6} cycloalkyl, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of cyclopropyl, and (b) p occurrences of R^1.

[0501] In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), and (b) p occurrences of R^1.

[0502] In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of -(C_{1-4} alkylene)-$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen, wherein said heterocyclyl is substituted with (a) q occurrences of -

$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of -(C_{1-4} alkylene)-$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1. In certain embodiments, R^3 is piperazinyl substituted with (a) q occurrences of -$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1.

[0503] In certain embodiments, R^3 is a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with p occurrences of R^1. In certain embodiments, R^3 is a 5-6 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen and oxygen; wherein said heterocyclyl is substituted with p occurrences of R^1. In certain embodiments, R^3 is piperazin-2-onyl substituted with p occurrences of R^1. In certain embodiments, R^3 is 1-methylpiperazin-2-on-4-yl.

[0504] In certain embodiments, R^3 is selected from the groups depicted in the compounds in Table 6, below.

[0505] As defined generally above, R^4 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Table 6, below.

[0506] As defined generally above, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Table 6, below.

[0507] As defined generally above, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^6 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain

embodiments, R^6 is hydrogen. In certain embodiments, R^6 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Table 6, below.

[0508] In certain embodiments, R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 and R^6 are hydrogen. In certain embodiments, R^5 and R^6 each represent independently for each occurrence C_{1-4} alkyl.

[0509] In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0510] As defined generally above, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl; wherein R^7 is additionally selected from C_{1-6} haloalkoxyl when (i) m is 3, or (ii) m is 1 or 2, and q is 1.

[0511] In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0512] In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic

ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0513] In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence m is 3; or m is 1 or 2, and q is 1; and C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), or C_{1-6} alkyl. In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, -N(R^5)(R^6), C_{1-6} haloalkyl, or halo. In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or -N(R^5)(R^6). In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, or chloro. In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence –OCF_3 or –NH_2.

[0514] In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, halo, or cyano. In certain

embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), or hydroxyl. In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl.

[0515] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0516] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -N(R^5)(R^6), or C_{1-6} alkyl. In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), C_{1-6} haloalkyl, or halo. In certain embodiments, R^7 represents independently for each occurrence $-NH_2$, $-CF_3$, fluoro, or chloro.

[0517] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^7 represents independently for each occurrence C_{1-6}

alkoxyl, -N(R^5)(R^6), hydroxyl, halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl or hydroxyl. In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6), halo, or cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl) or -S-(C_{1-6} alkyl).

[0518] In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl.

[0519] In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, m is 3; or m is 1 or 2, and q is 1; and R^7 is $-OCF_3$. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 represents independently for each occurrence -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{1-4} alkylene)-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -O-(C_{3-4} cycloalkyl). In certain embodiments, R^7 represents independently for each occurrence -N(R^5)(R^6). In certain embodiments, R^7 is $-NH_2$. In certain embodiments, R^7 is hydroxyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^7 is trifluoromethyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^7 represents independently for each occurrence halo. In certain embodiments, R^7 is fluoro. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} haloalkyl). In certain embodiments, R^7 is -S-CF_3. In certain embodiments, R^7 represents independently for each occurrence -S-(C_{1-6} alkyl). In certain embodiments, R^7 is phenyl.

[0520] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is

substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0521] In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^7 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

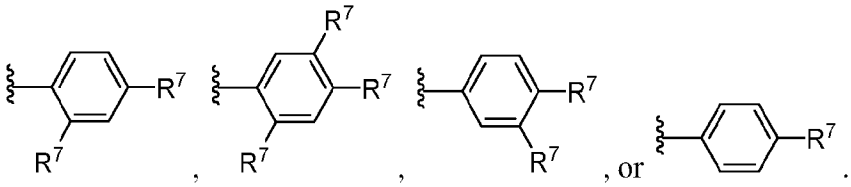
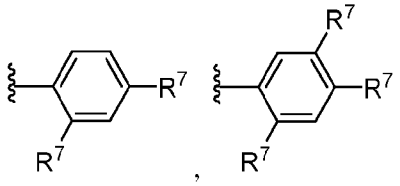
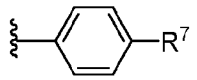
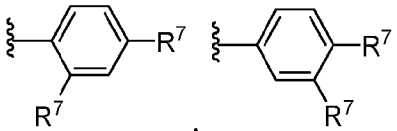
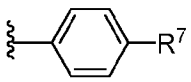
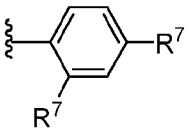
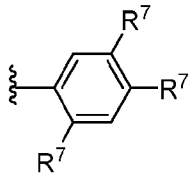
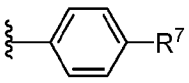
[0522] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Table 6, below.

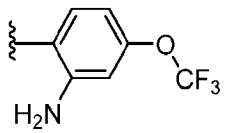
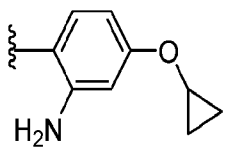
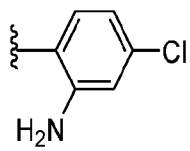
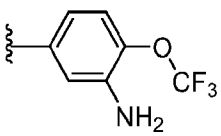
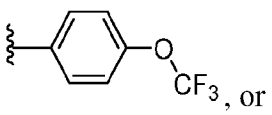
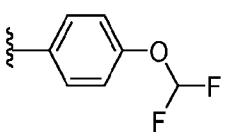
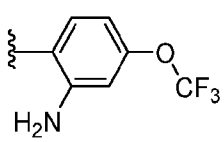
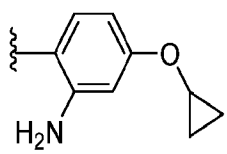
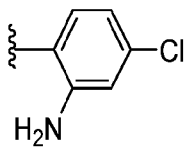
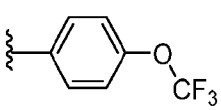
[0523] As defined generally above, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

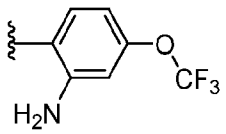
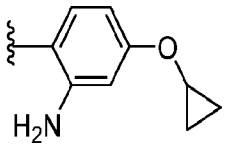
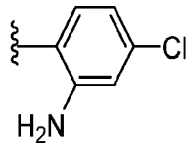
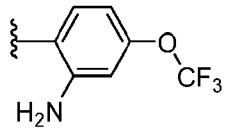
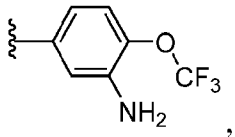
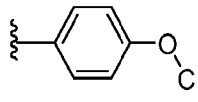
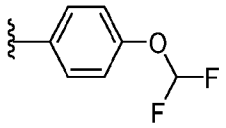
[0524] In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

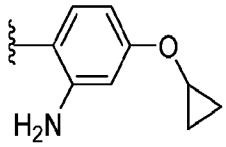
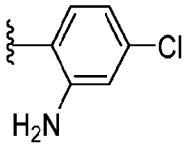
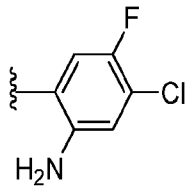
[0525] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen,

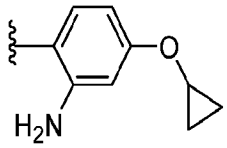
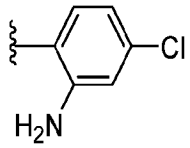
oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

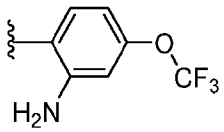
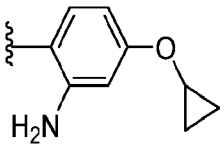
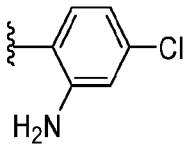
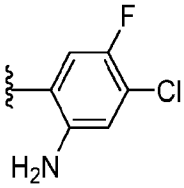
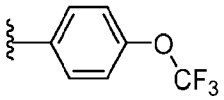
[0526] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, A^1 is  , , , or . In certain embodiments, A^1 is  , , or  . In certain embodiments, A^1 is  , , or  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0527] In certain embodiments, m is 1 or 2, and q is 1; and A^1 is  ,  ,  ,  ,  , or  . In certain embodiments, m is 1 or 2, and q is 1; and A^1 is  ,  ,  , or  . In certain embodiments, m is 1 or 2, and q is 1; and A^1 is

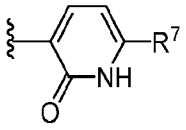
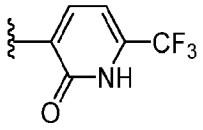


, or 
. In certain embodiments, m is 1 or 2, and q is 1; and A^1 is 
, 
, 
, or 
.

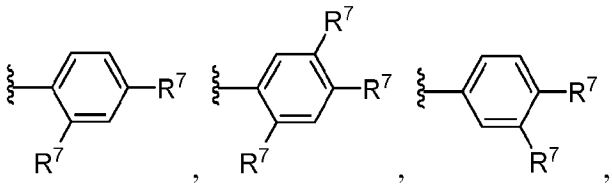
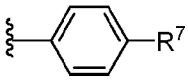
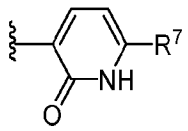
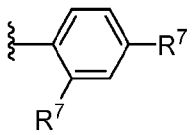
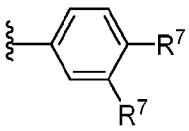
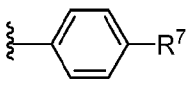
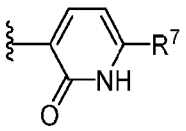
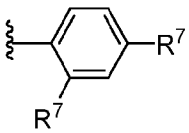
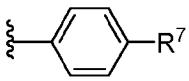
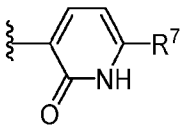
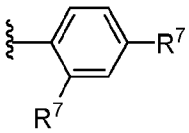
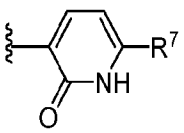
[0528] In certain embodiments, A^1 is 
, 
, or 
.

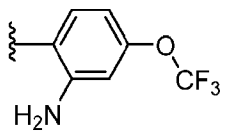
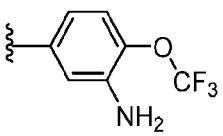
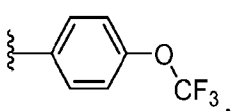
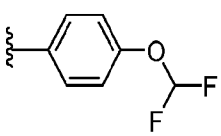
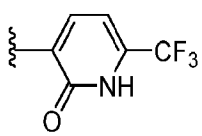
In certain embodiments, A^1 is 
or 
.

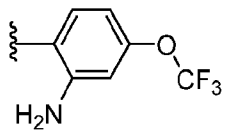
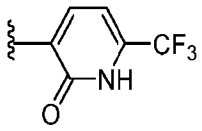
[0529] In certain embodiments, q is 1, and A^1 is 
. In certain embodiments, A^1 is 
. In certain embodiments, A^1 is 
. In certain embodiments, A^1 is 
. In certain embodiments, q is 1, and A^1 is 
.

[0530] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-

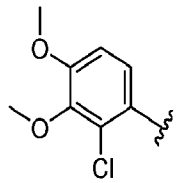
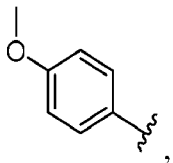
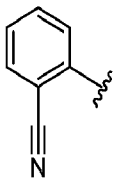
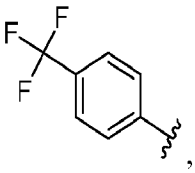
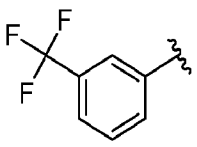
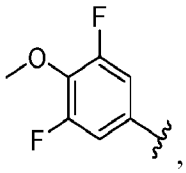
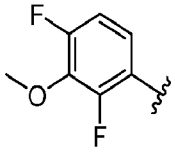
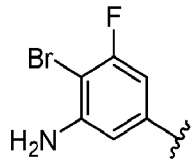
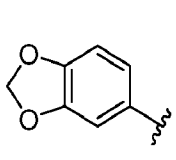
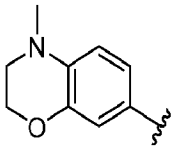
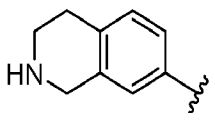
membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

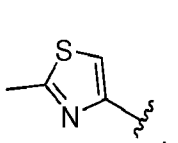
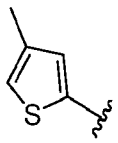
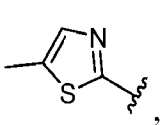
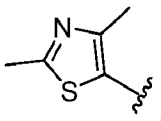
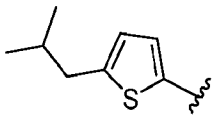
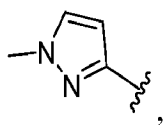
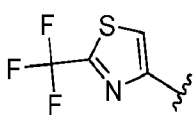
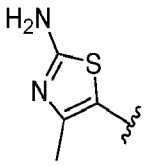
[0531] In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  or  .

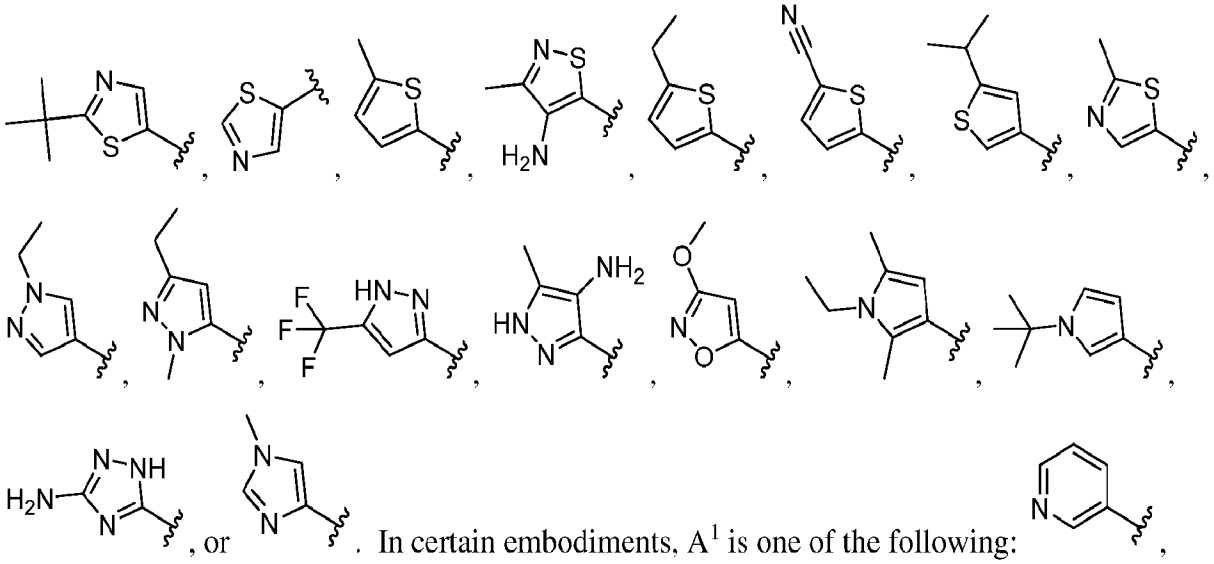
[0532] In certain embodiments, m is 1 or 2, and q is 1; and A^1 is  ,  ,  ,  , or  . In certain

embodiments, m is 1 or 2, and q is 1; and A^1 is  or  .

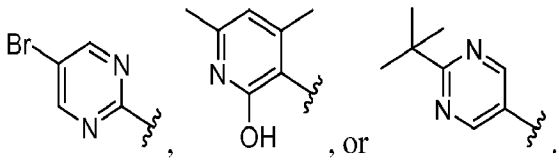
[0533] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^7. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

[0534] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is one of the following:  ,  , or  .

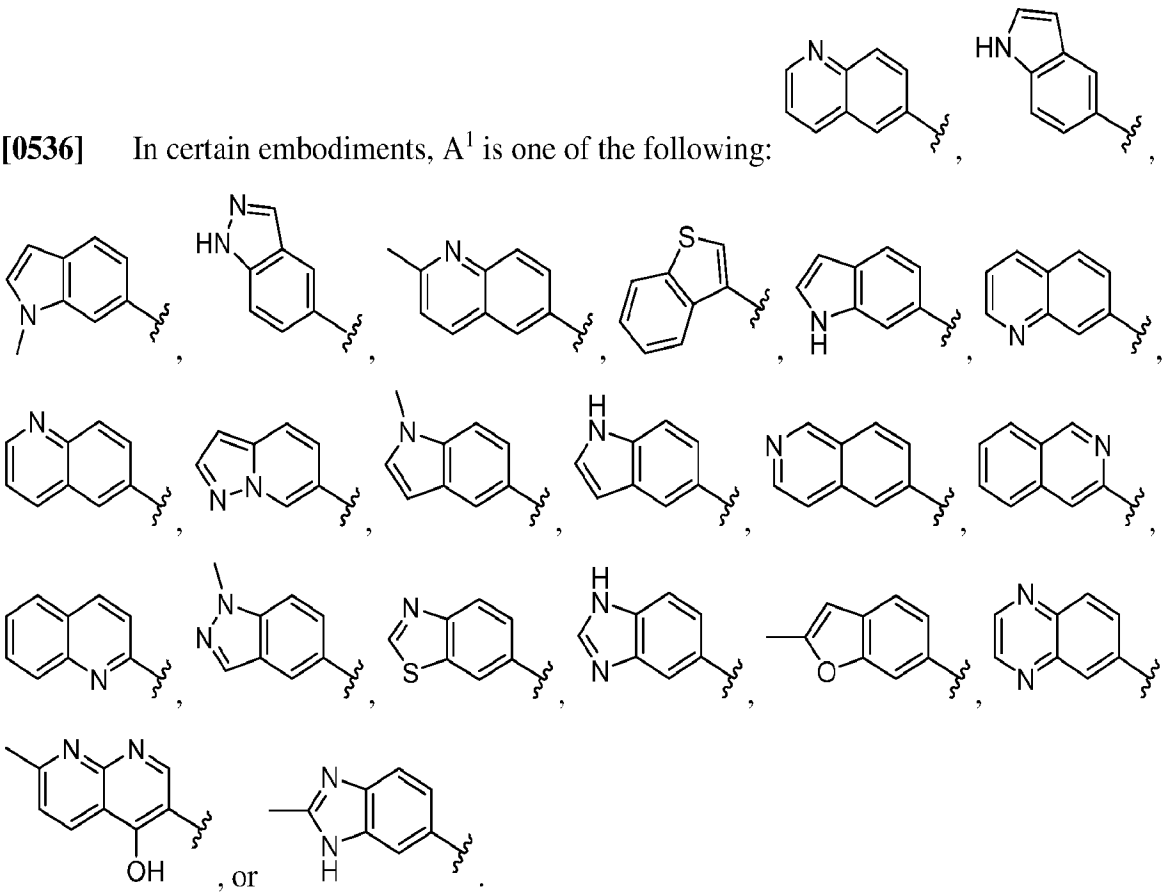
[0535] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  ,  .



. In certain embodiments, A^1 is one of the following:



[0536] In certain embodiments, A^1 is one of the following:



[0537] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Table 6, below.

[0538] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 1 or 2, and q is 1. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Table 6, below.

[0539] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 0 or 1. In certain embodiments, p is 1 or 2. In certain embodiments, p is selected from the values represented in the compounds in Table 6, below.

[0540] As defined generally above, q is 0 or 1. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is selected from the values represented in the compounds in Table 6, below.

[0541] The description above describes multiple embodiments relating to compounds of Formula III. The patent application specifically contemplates all combinations of the embodiments.

[0542] In certain embodiments, the compound is a compound in Table 1, 1-A, 2, 2-A, 3, 4, 5, 6, or 7 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 1-A, 2, 2-A, 3, 4, 5, 6, or 7 below. In certain embodiments, the compound is a compound in Table 1, 1-A, 2, 2-A, 3, 4, 5, or 6 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 1-A, 2, 2-A, 3, 4, 5, or 6 below. In certain embodiments, the compound is a compound in Table 1, 1-A, 2, 2-A, 3, 4, or 5 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 1-A, 2, 2-A, 3, 4, or 5 below. In certain embodiments, the compound is a compound in Table 1, 2, 3, 4, or 5 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 2, 3, 4, or 5 below.

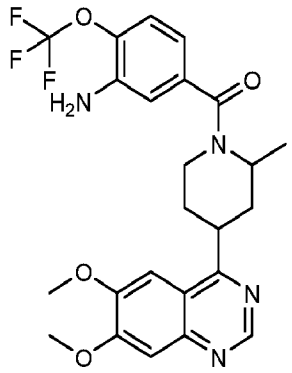
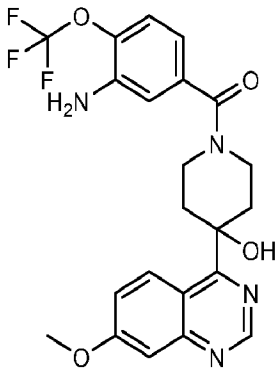
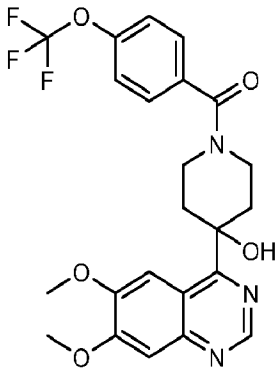
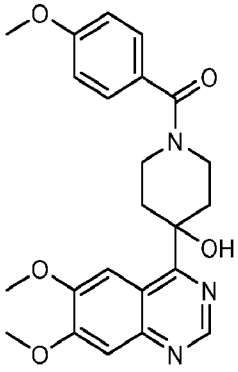
[0543] In certain embodiments, the compound is a compound in Table 1, 2, or 3 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 2, or 3 below. In certain embodiments, the compound is a compound in Table 1, 1-A,

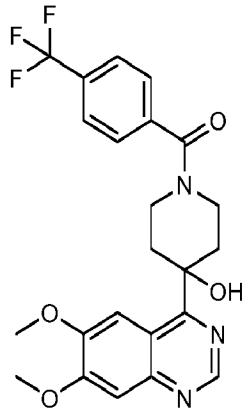
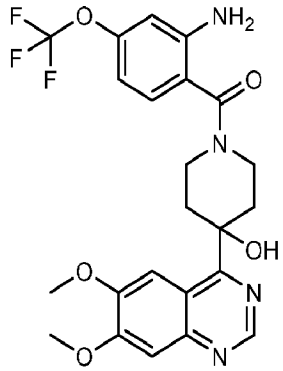
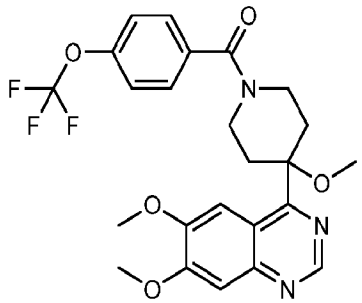
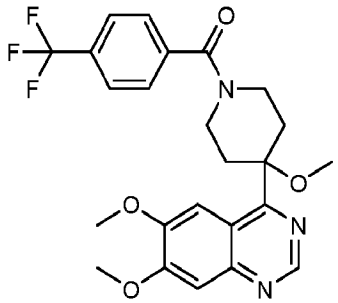
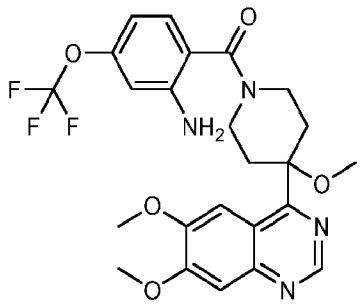
2, or 2-A below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 1-A, 2, or 2-A below. In certain embodiments, the compound is a compound in Table 1 or 2 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 2 below. In certain embodiments, the compound is a compound in Table 1 or 1-A below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 1-A below. In certain embodiments, the compound is a compound in Table 1 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 below. In certain embodiments, the compound is a compound in Table 2 or 2-A below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 2 or 2-A below. In certain embodiments, the compound is a compound in Table 2 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 2 below.

[0544] In certain embodiments, the compound is a compound in Table 6 or 7 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 6 or 7 below. In certain embodiments, the compound is a compound in Table 6 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 6 below. In certain embodiments, the compound is a compound in Table 7 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 7 below.

[0545] In certain embodiments, the compound is a compound in Table 1 or 5 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 5 below. In certain embodiments, the compound is a compound in Table 5 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 5 below. In certain embodiments, the compound is a compound in Table 2, 3, or 4 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 2, 3, or 4 below. In certain embodiments, the compound is a compound in Table 3 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 3 below. In certain embodiments, the compound is a compound in Table 4 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 4 below.

TABLE 1.

Compound No.	Chemical Structure
I-1	
I-2	
I-3	
I-4	

Compound No.	Chemical Structure
I-5	
I-6	
I-7	
I-8	
I-9	

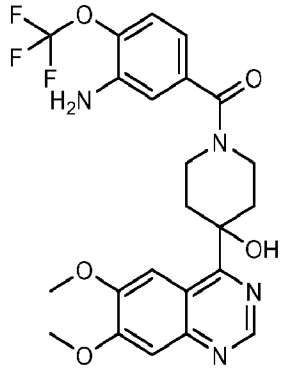
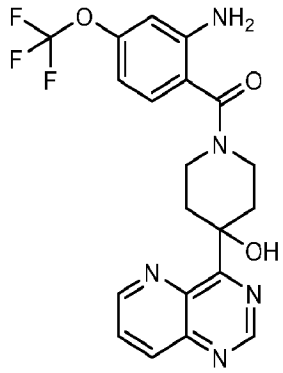
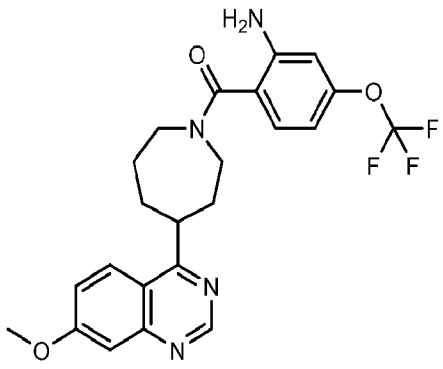
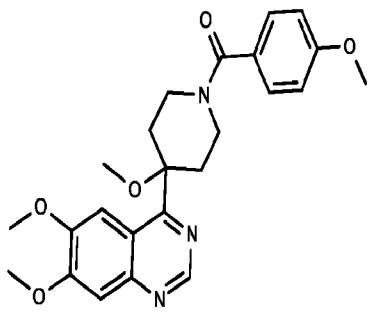
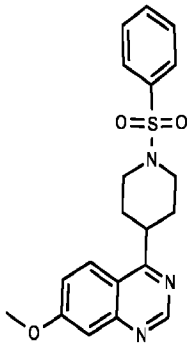
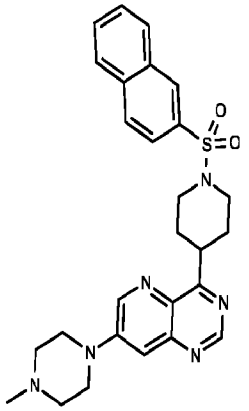
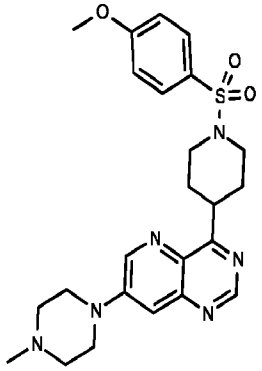
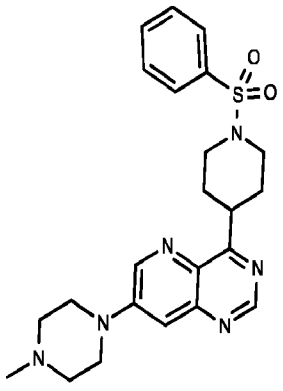
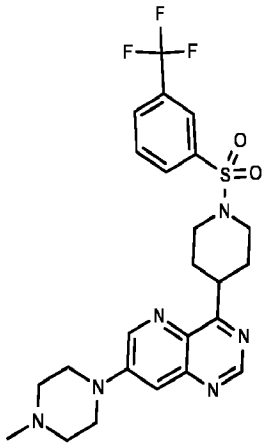
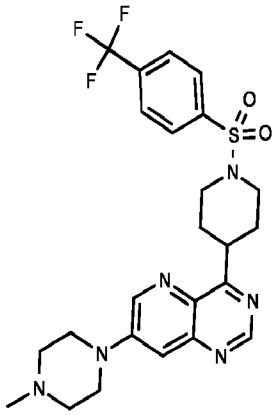
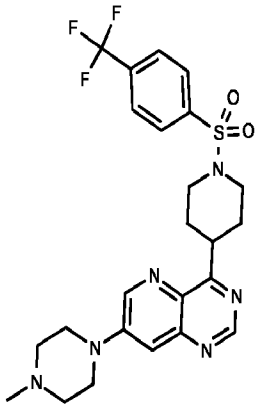
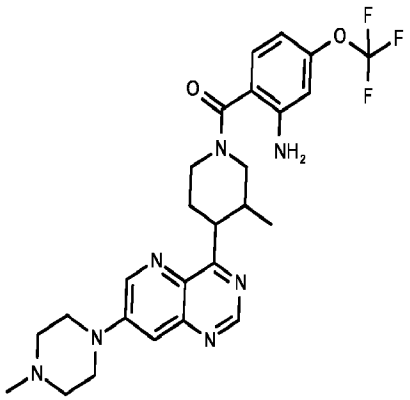
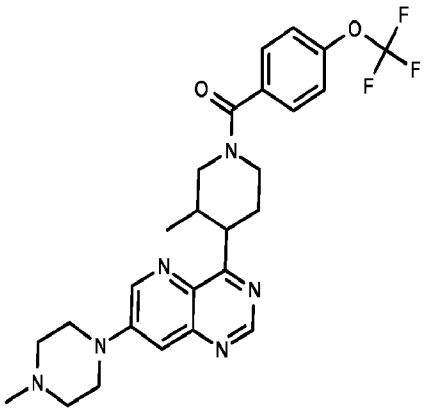
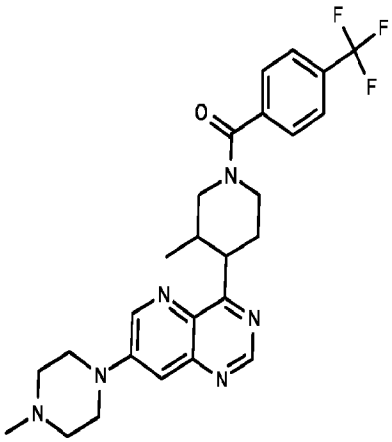
Compound No.	Chemical Structure
I-10	
I-11	
I-12	

TABLE 1-A.

Compound No.	Chemical Structure
I-13	

Compound No.	Chemical Structure
I-14	
I-15	
I-16	
I-17	

Compound No.	Chemical Structure
I-18	
I-19	
I-20	

Compound No.	Chemical Structure
I-21	
I-22	
I-23	

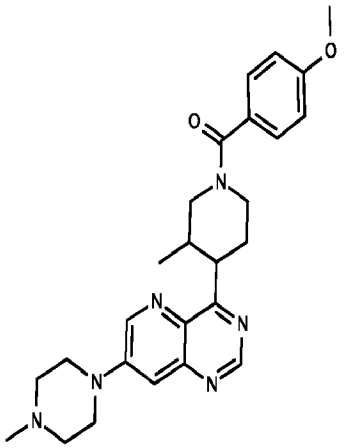
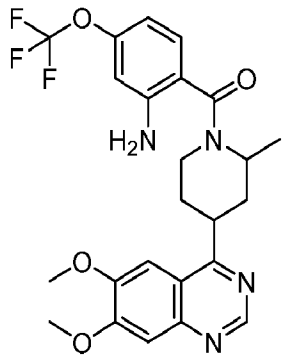
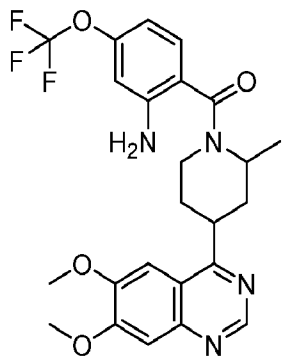
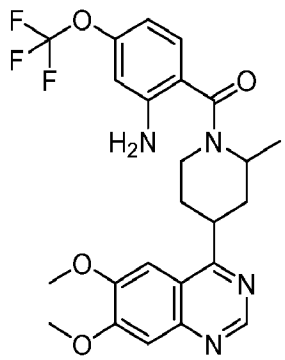
Compound No.	Chemical Structure
I-24	
I-25	 Stereoisomer 1
I-26	 Stereoisomer 2
I-27	 Stereoisomer 3

TABLE 2.

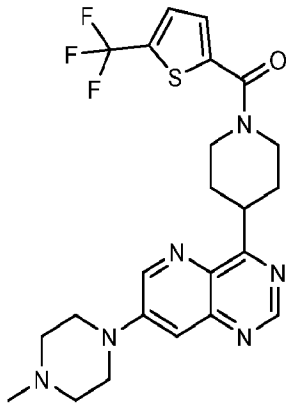
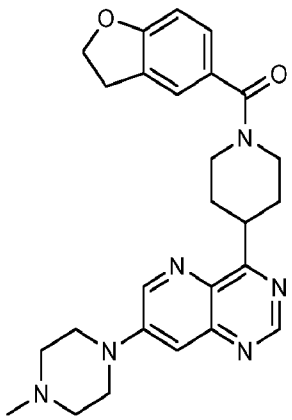
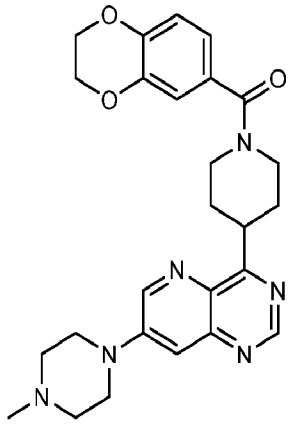
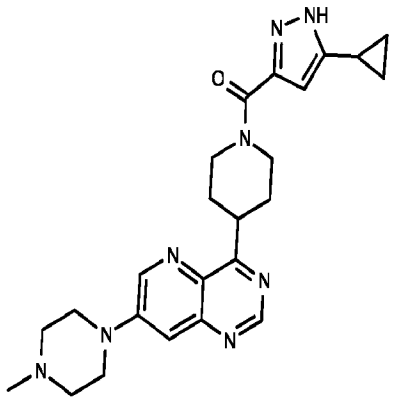
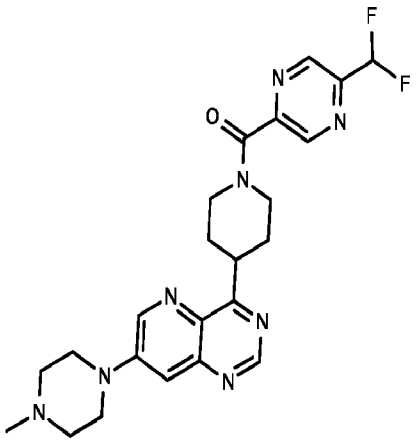
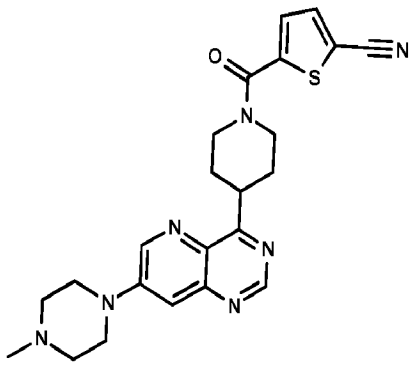
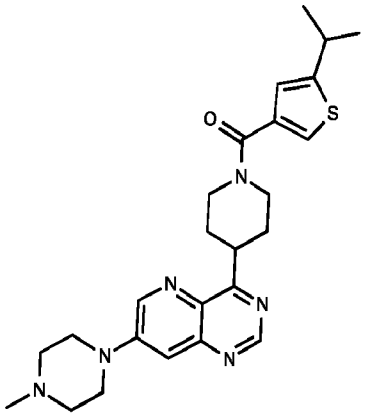
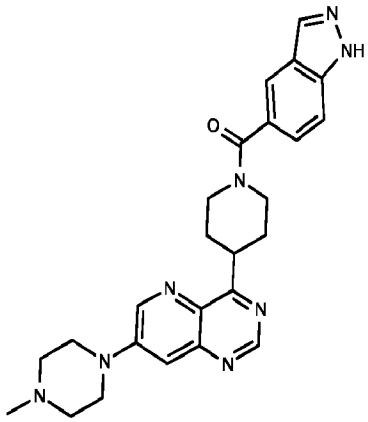
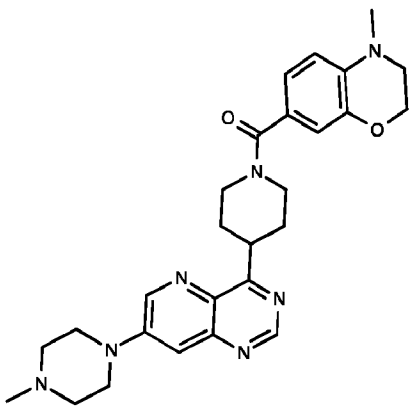
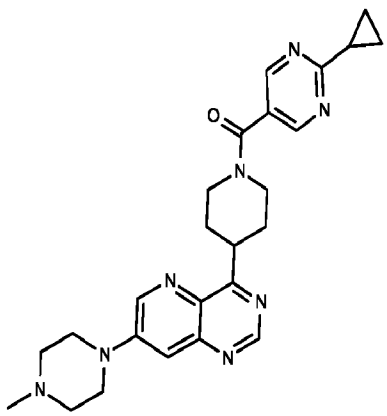
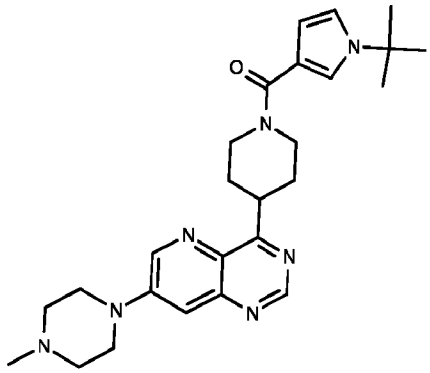
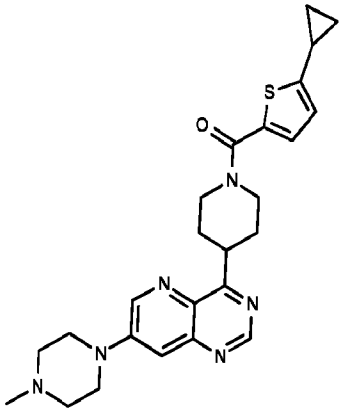
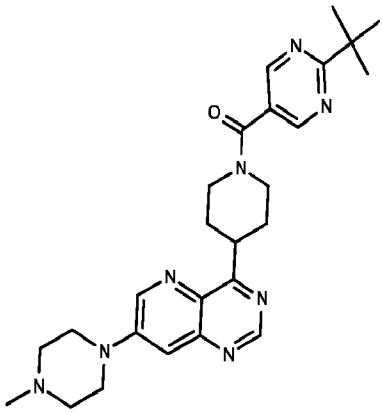
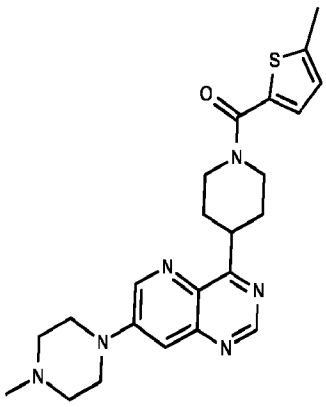
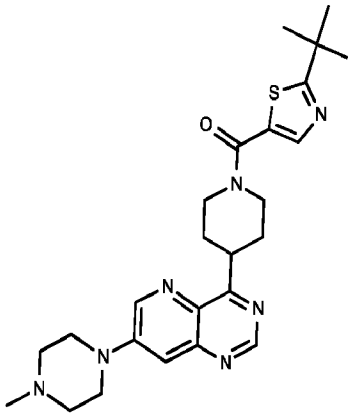
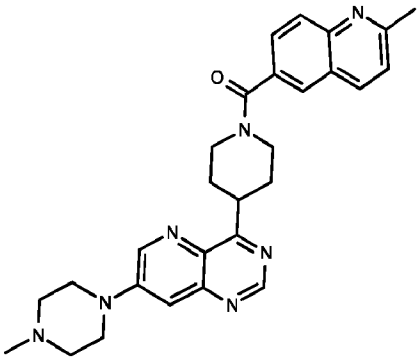
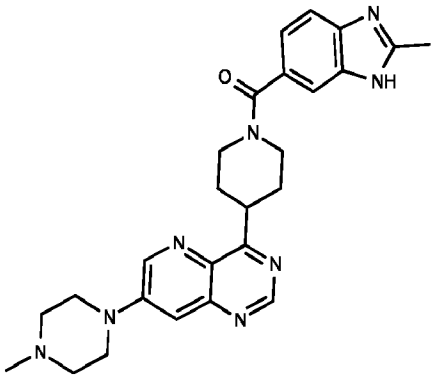
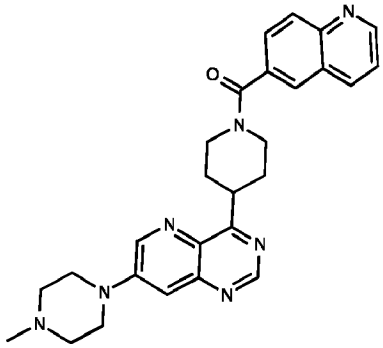
Compound No.	Chemical Structure
II-1	
II-2	
II-3	

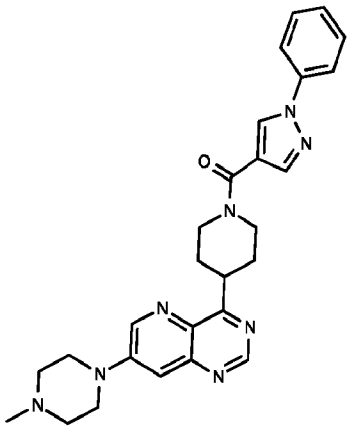
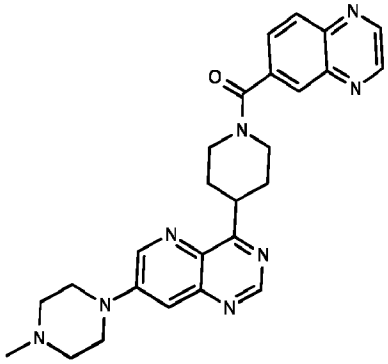
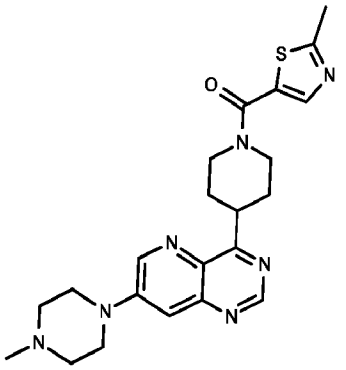
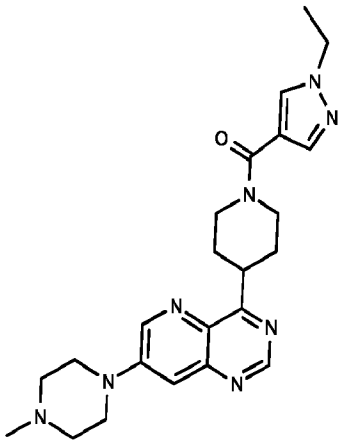
TABLE 2-A.

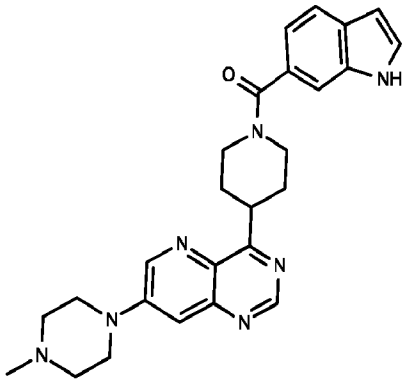
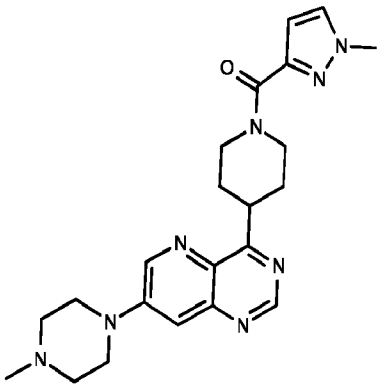
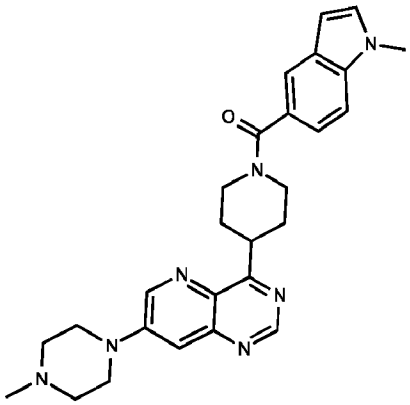
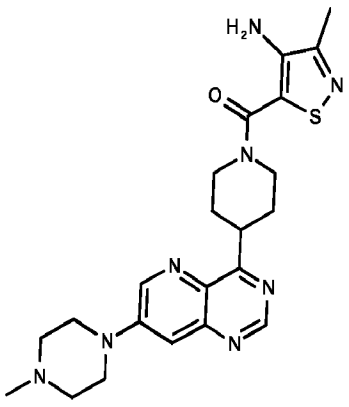
Compound No.	Chemical Structure
II-4	
II-5	
II-6	

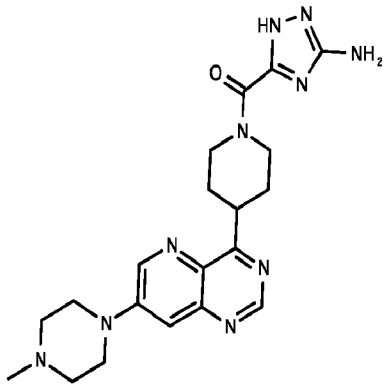
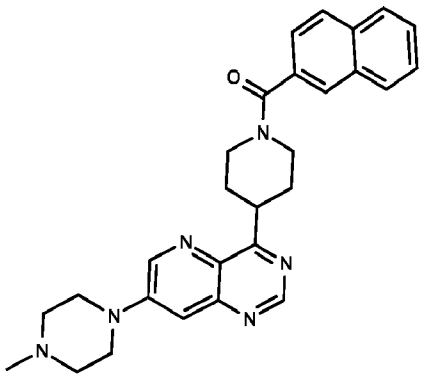
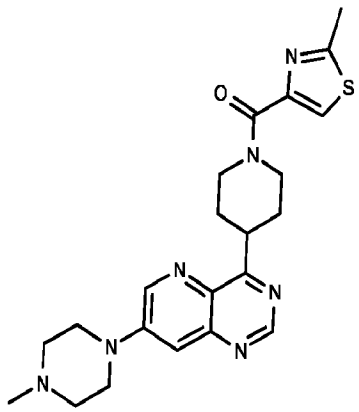
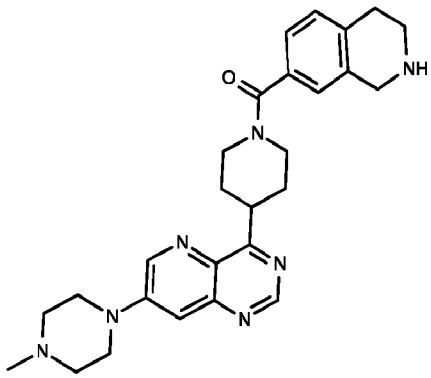
Compound No.	Chemical Structure
II-7	
II-8	
II-9	
II-10	

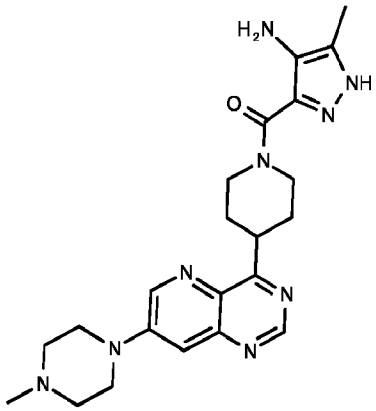
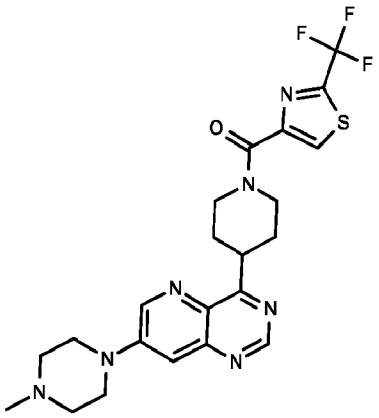
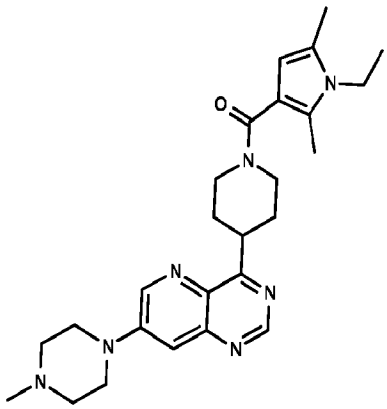
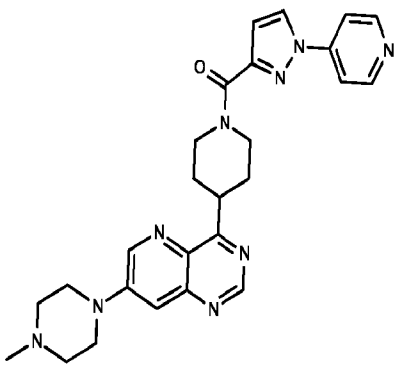
Compound No.	Chemical Structure
II-11	
II-12	
II-13	
II-14	

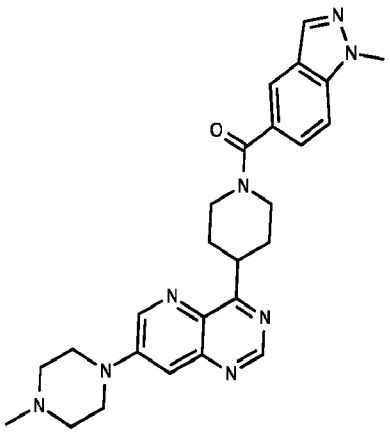
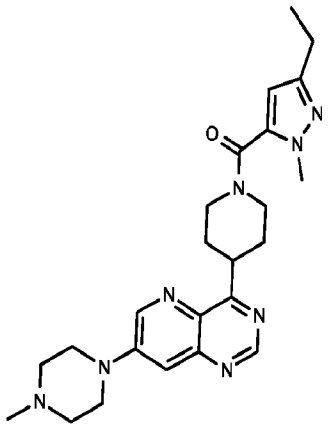
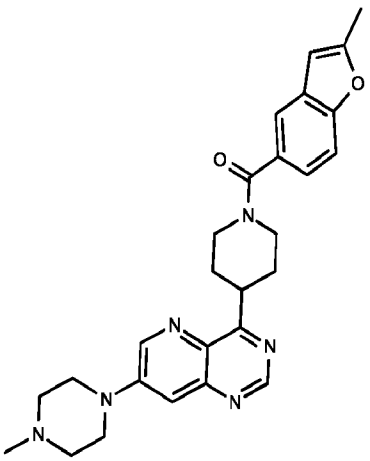
Compound No.	Chemical Structure
II-15	
II-16	
II-17	
II-18	

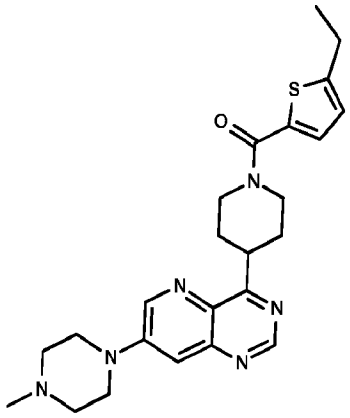
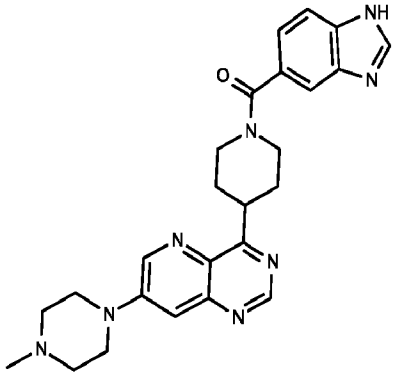
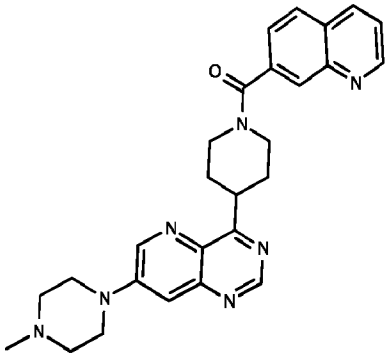
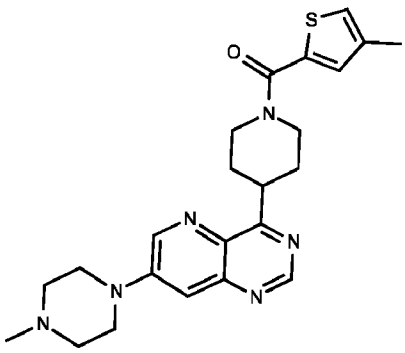
Compound No.	Chemical Structure
II-19	
II-20	
II-21	
II-22	

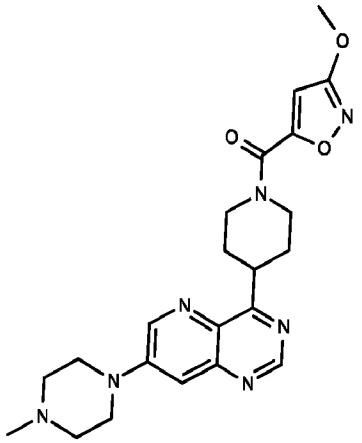
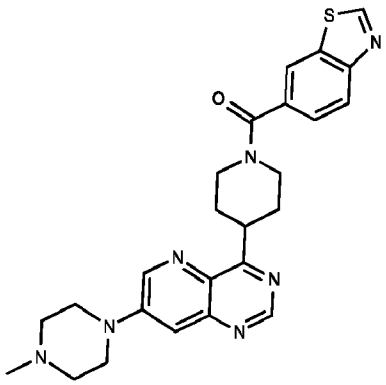
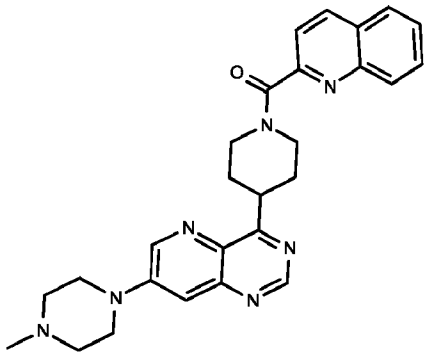
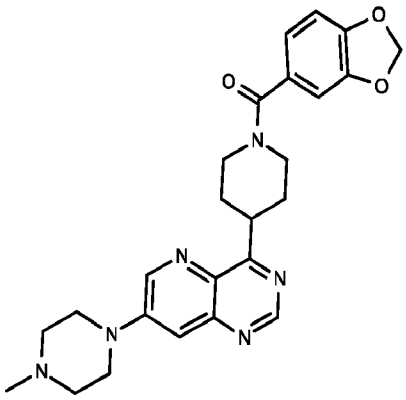
Compound No.	Chemical Structure
II-23	
II-24	
II-25	
II-26	

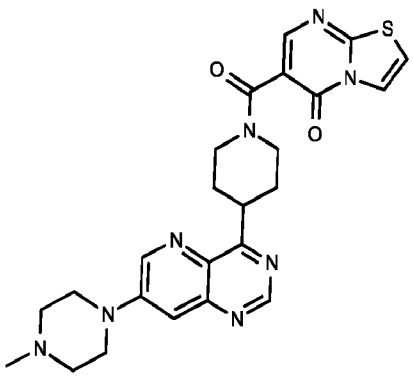
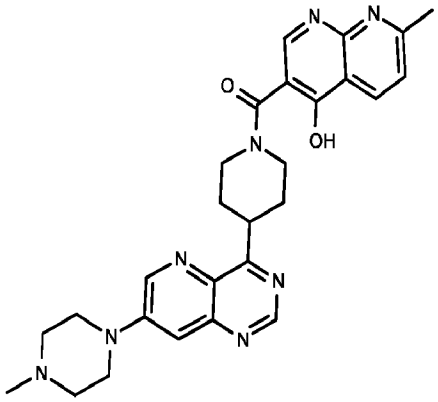
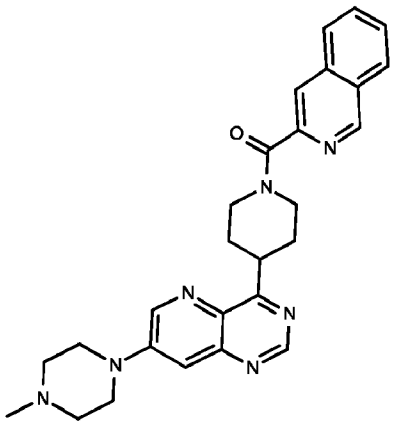
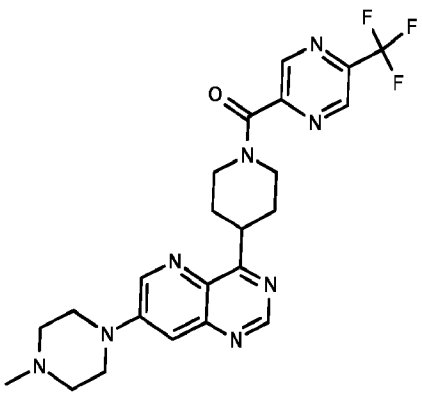
Compound No.	Chemical Structure
II-27	
II-28	
II-29	
II-30	

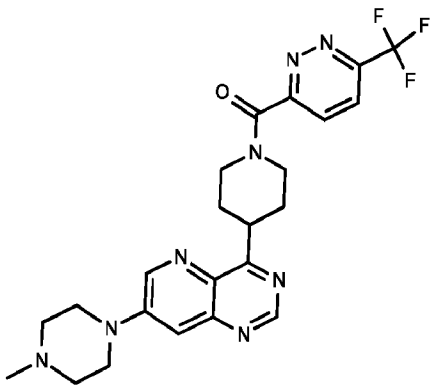
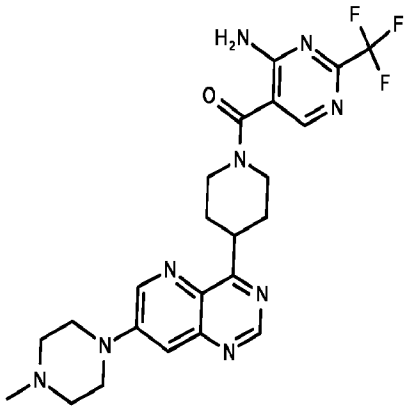
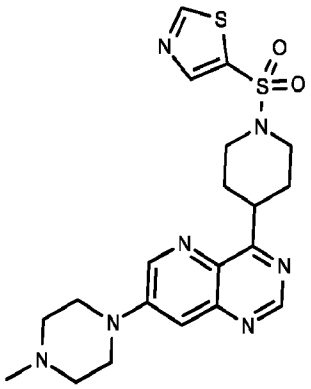
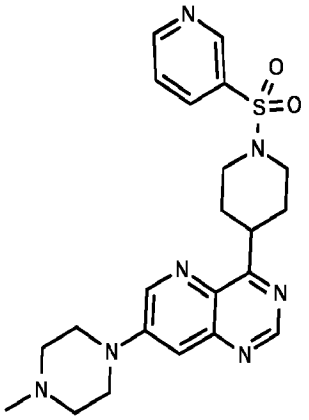
Compound No.	Chemical Structure
II-31	
II-32	
II-33	
II-34	

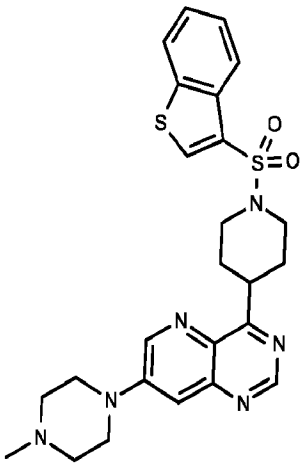
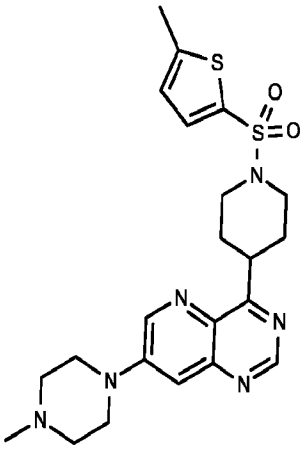
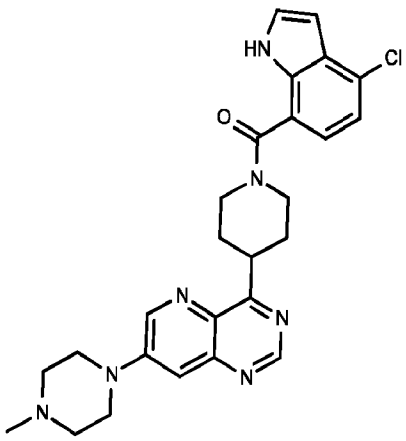
Compound No.	Chemical Structure
II-35	
II-36	
II-37	

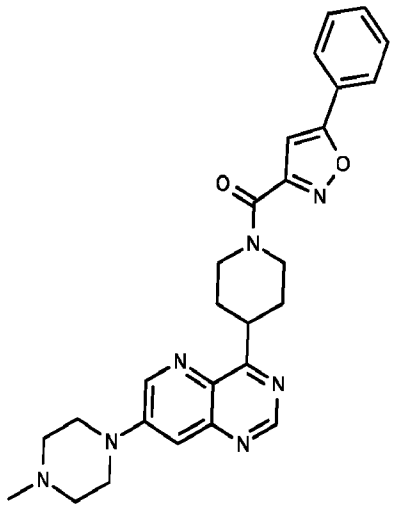
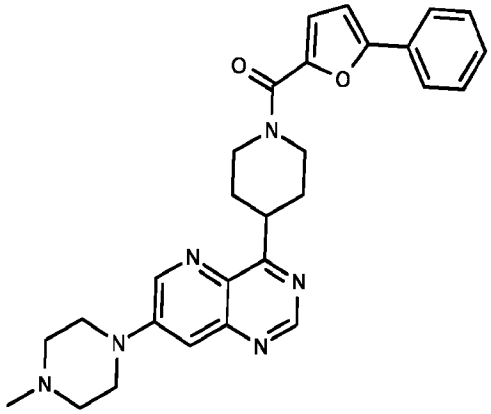
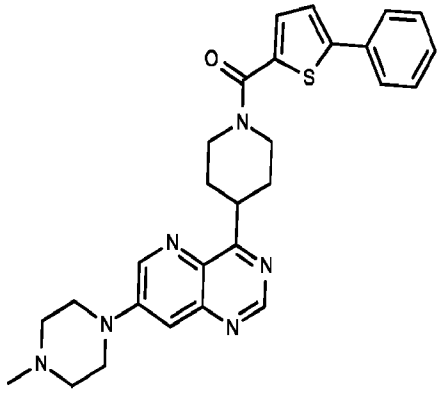
Compound No.	Chemical Structure
II-38	
II-39	
II-40	
II-41	

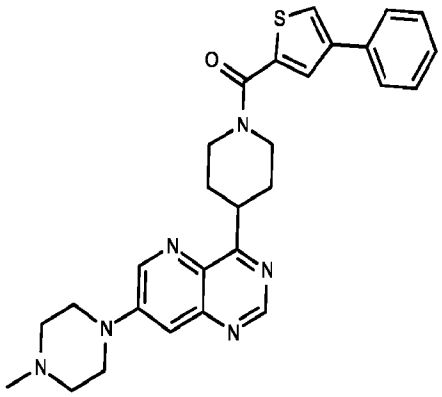
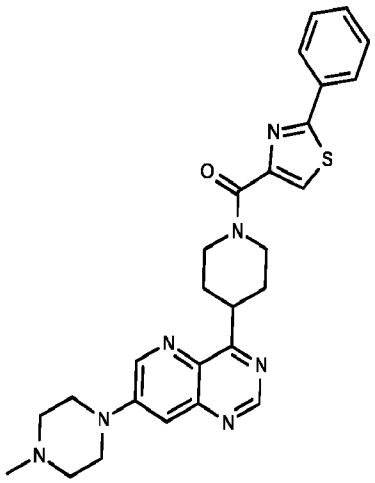
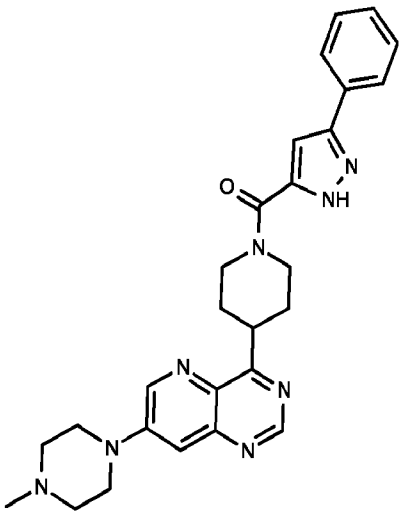
Compound No.	Chemical Structure
II-42	
II-43	
II-44	
II-45	

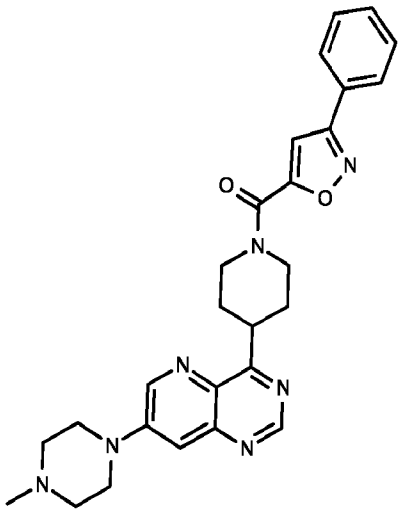
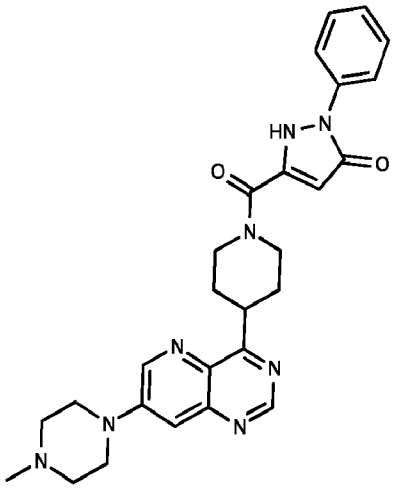
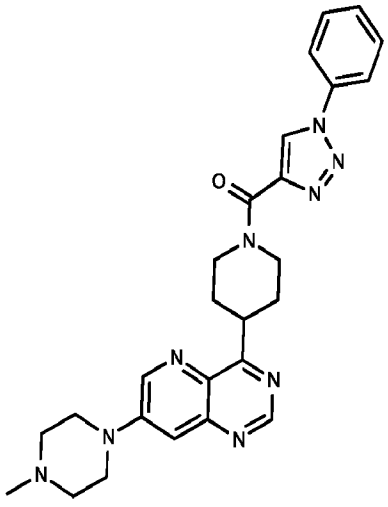
Compound No.	Chemical Structure
II-46	
II-47	
II-48	
II-49	

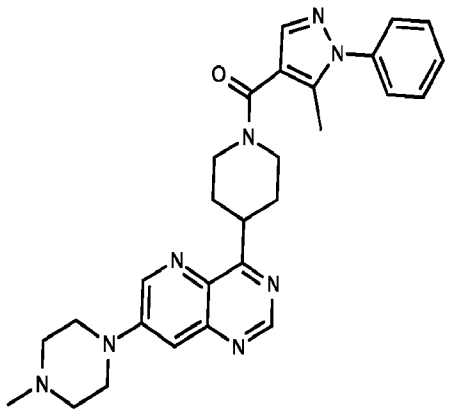
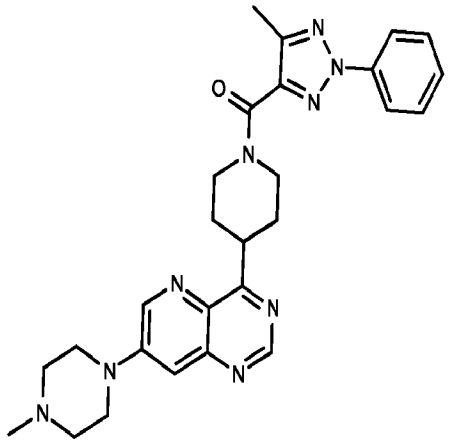
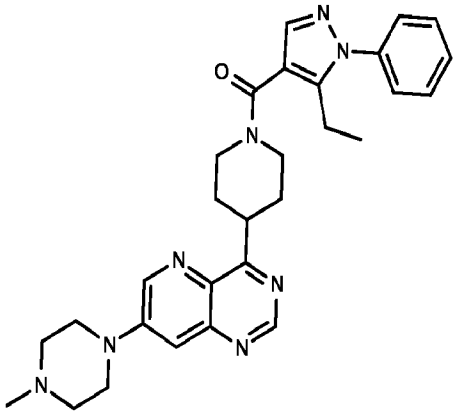
Compound No.	Chemical Structure
II-50	
II-51	
II-52	
II-53	

Compound No.	Chemical Structure
II-54	
II-55	
II-56	

Compound No.	Chemical Structure
II-57	
II-58	
II-59	

Compound No.	Chemical Structure
II-60	
II-61	
II-62	

Compound No.	Chemical Structure
II-63	
II-64	
II-65	

Compound No.	Chemical Structure
II-66	
II-67	
II-68	

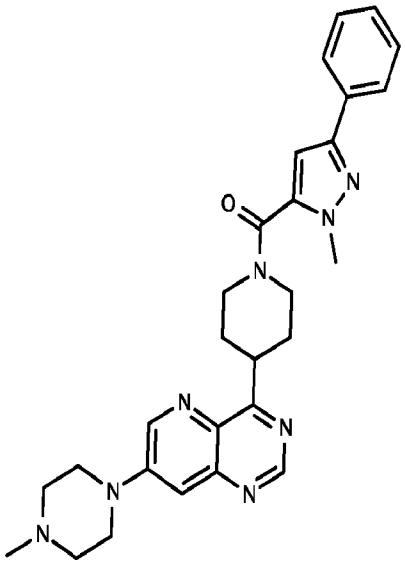
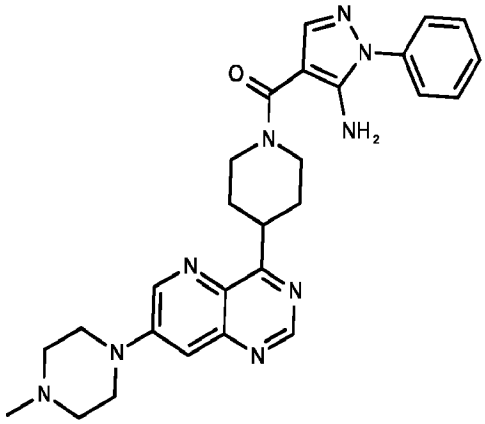
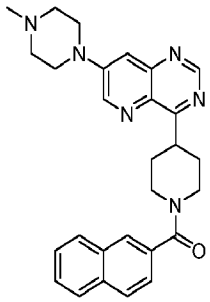
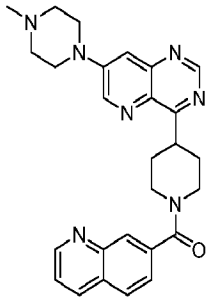
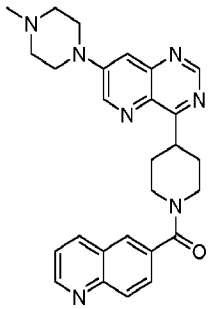
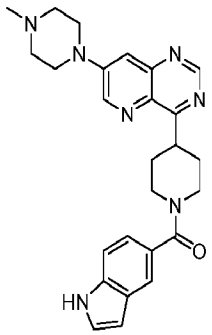
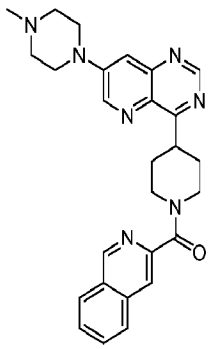
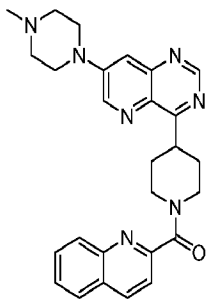
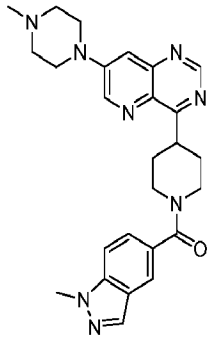
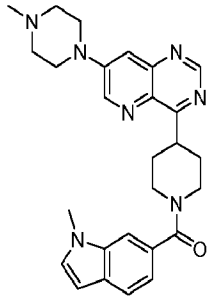
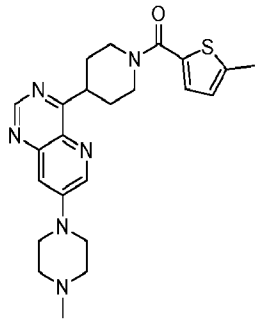
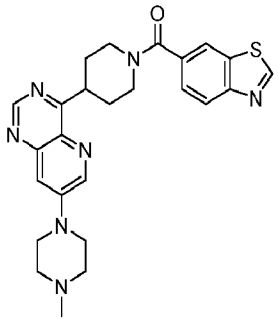
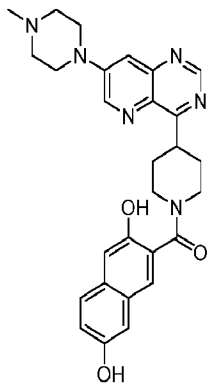
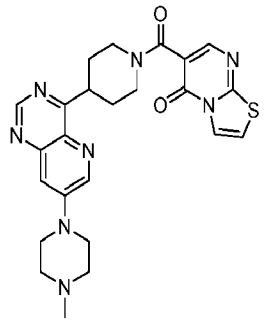
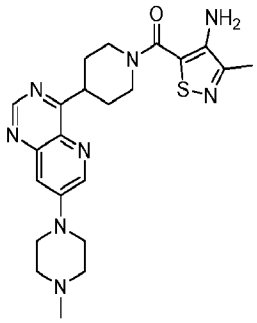
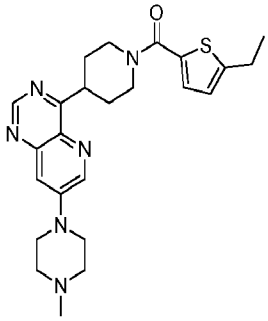
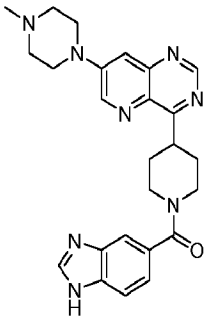
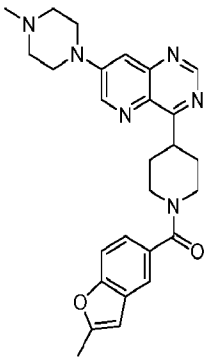
Compound No.	Chemical Structure
II-69	
II-70	

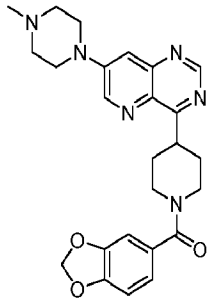
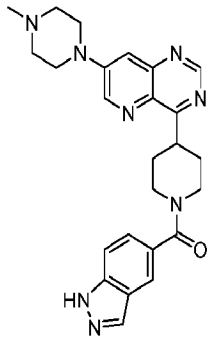
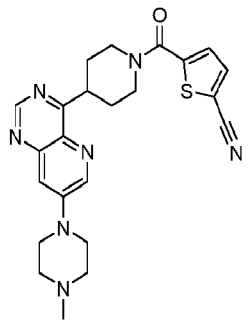
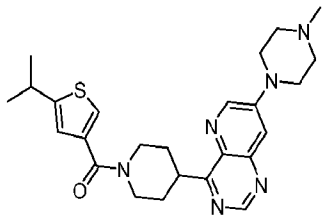
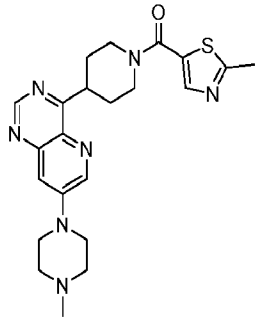
TABLE 3.

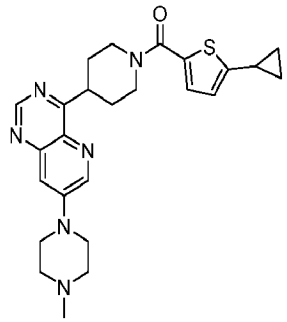
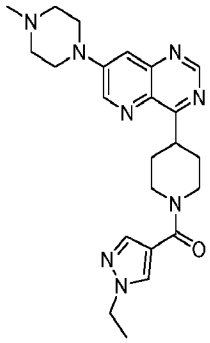
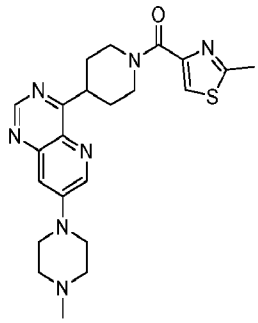
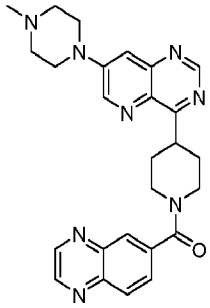
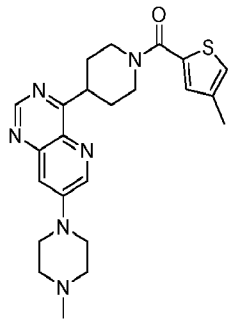
Compound No.	Chemical Structure
III-1	

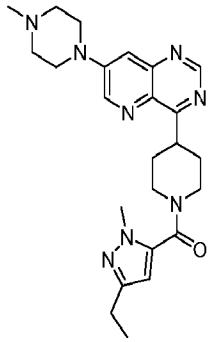
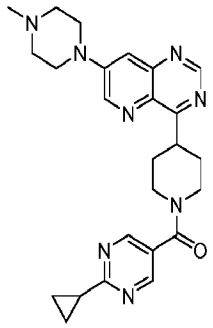
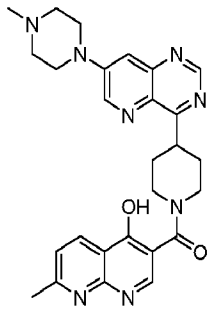
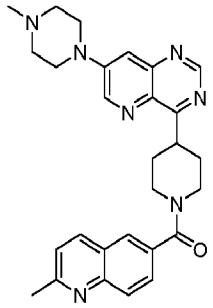
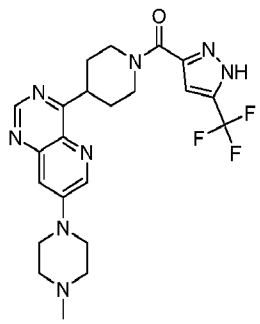
Compound No.	Chemical Structure
III-2	
III-3	
III-4	
III-5	
III-6	

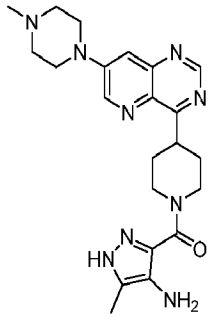
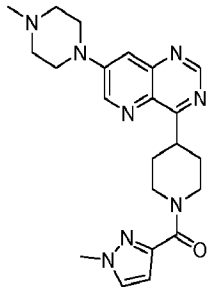
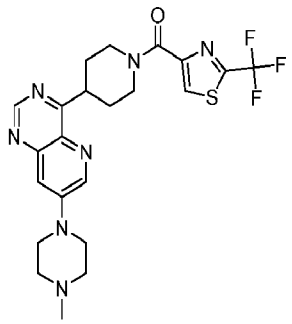
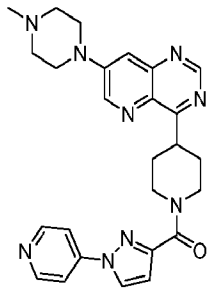
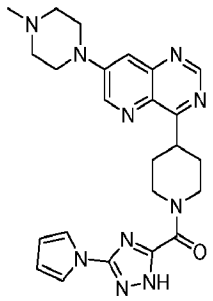
Compound No.	Chemical Structure
III-7	
III-8	
III-9	
III-10	
III-11	

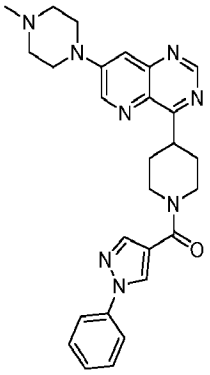
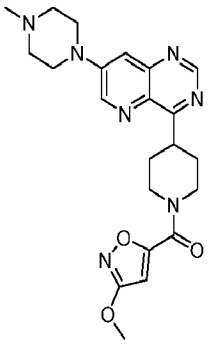
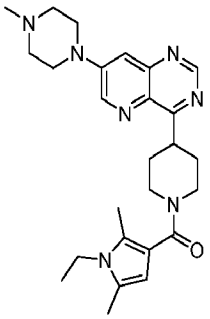
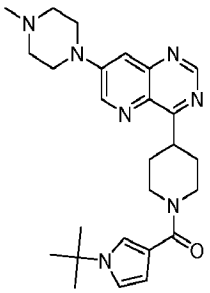
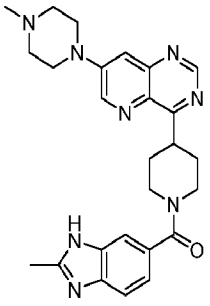
Compound No.	Chemical Structure
III-12	
III-13	
III-14	
III-15	
III-16	

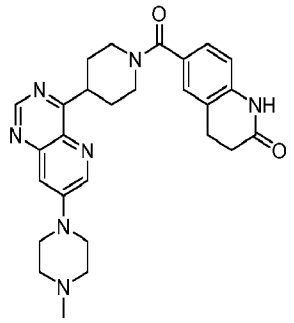
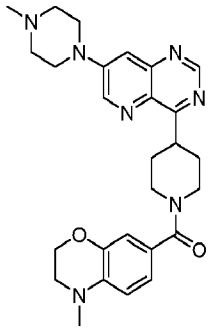
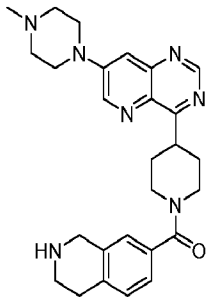
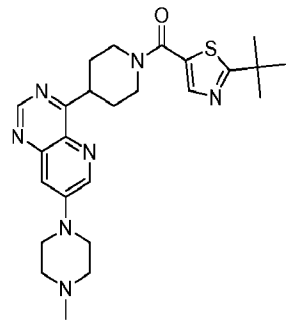
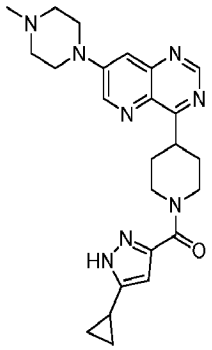
Compound No.	Chemical Structure
III-17	
III-18	
III-19	
III-20	
III-21	

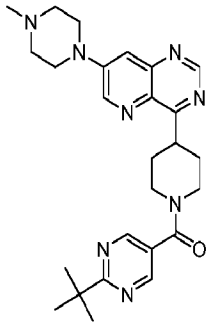
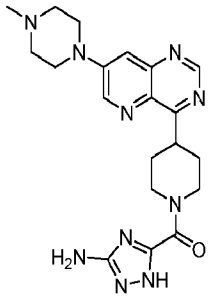
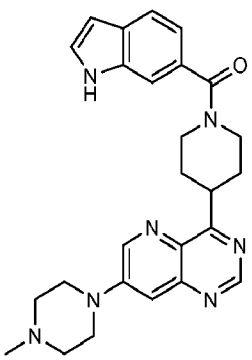
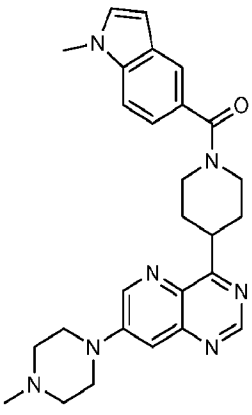
Compound No.	Chemical Structure
III-22	
III-23	
III-24	
III-25	
III-26	

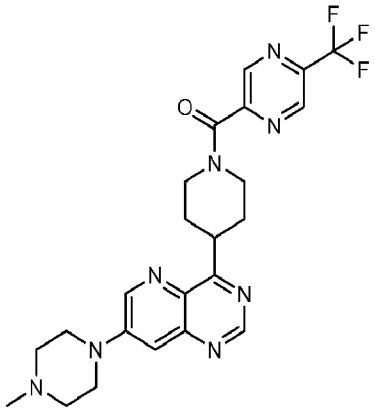
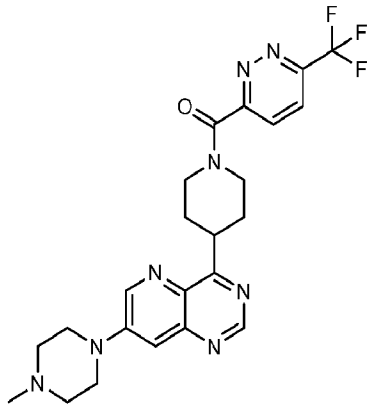
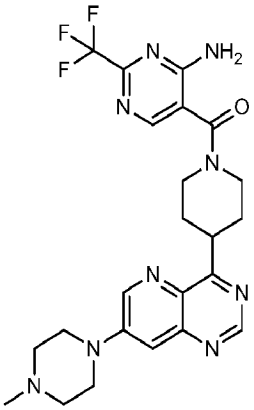
Compound No.	Chemical Structure
III-27	
III-28	
III-29	
III-30	
III-31	

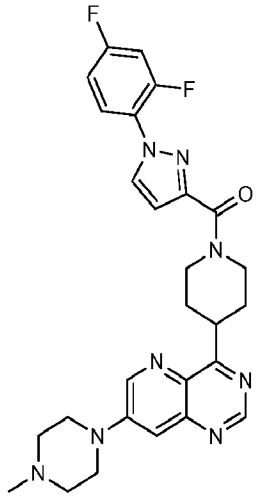
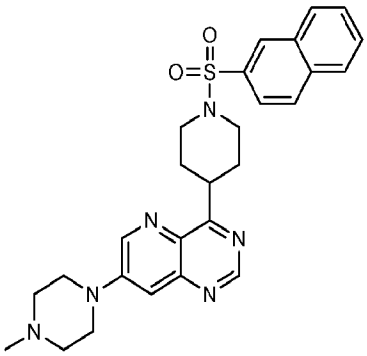
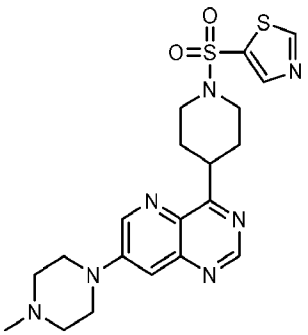
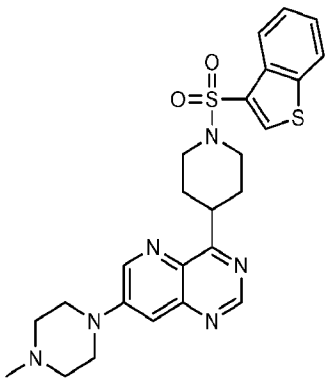
Compound No.	Chemical Structure
III-32	
III-33	
III-34	
III-35	
III-36	

Compound No.	Chemical Structure
III-37	
III-38	
III-39	
III-40	
III-41	

Compound No.	Chemical Structure
III-42	
III-43	
III-44	
III-45	
III-46	

Compound No.	Chemical Structure
III-47	
III-48	
III-49	
III-50	

Compound No.	Chemical Structure
III-51	
III-52	
III-53	

Compound No.	Chemical Structure
III-54	
III-55	
III-56	
III-57	

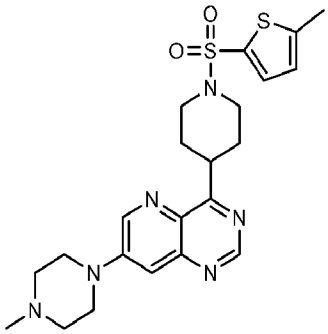
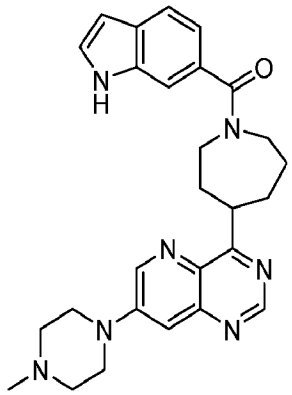
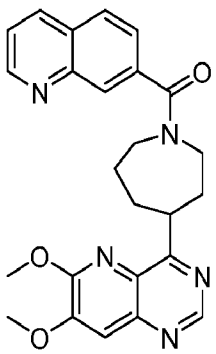
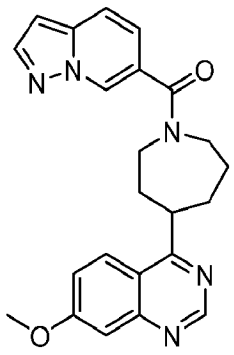
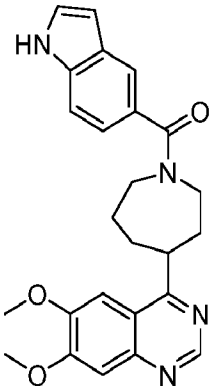
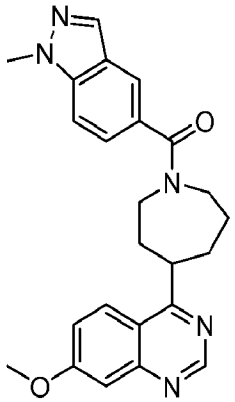
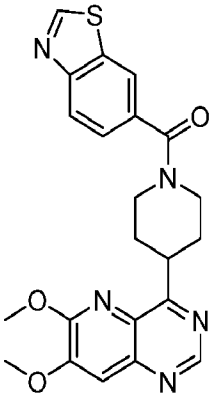
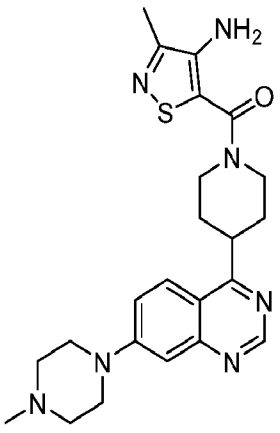
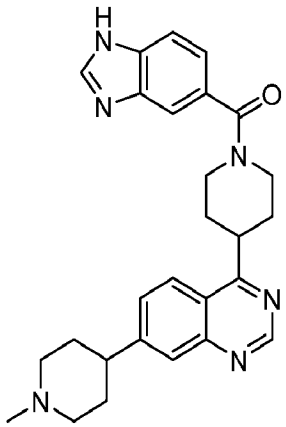
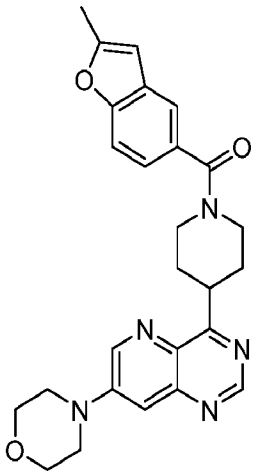
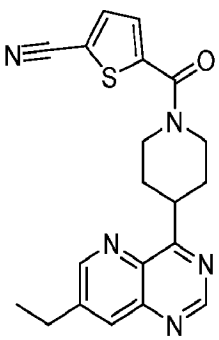
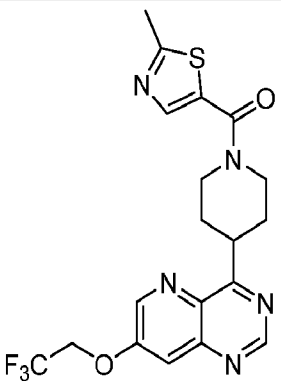
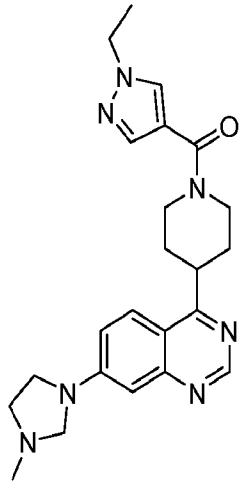
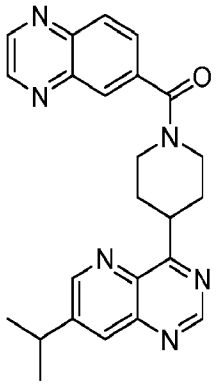
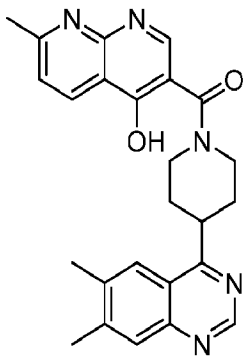
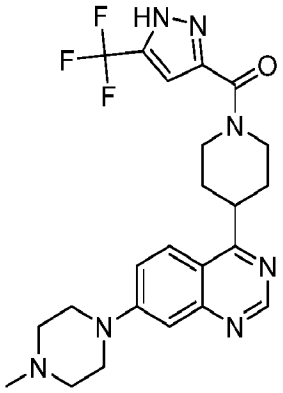
Compound No.	Chemical Structure
III-58	

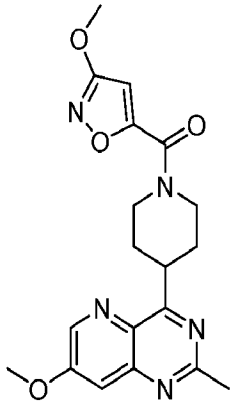
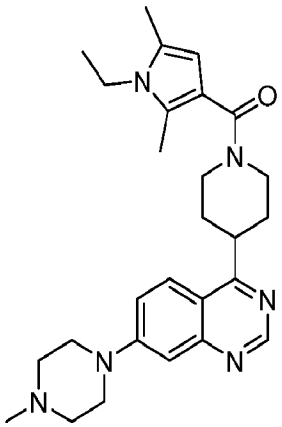
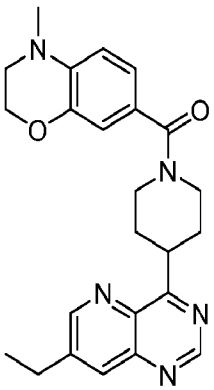
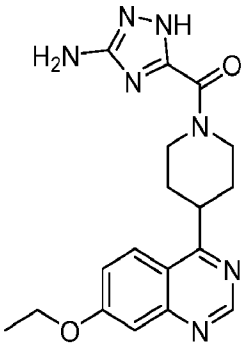
TABLE 4.

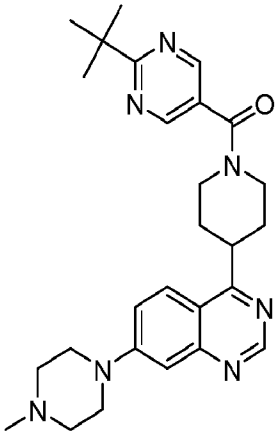
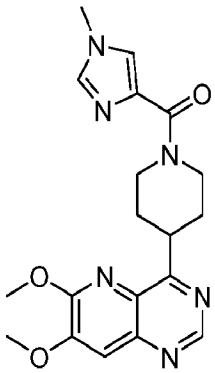
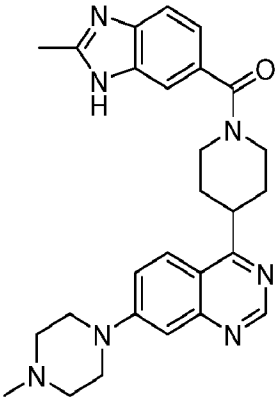
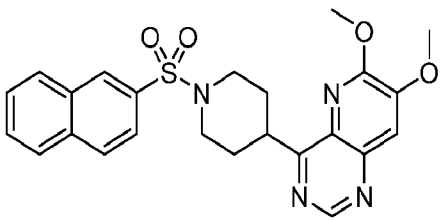
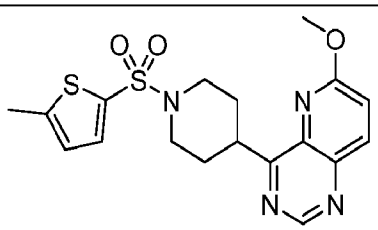
Compound No.	Chemical Structure
IV-1	
IV-2	
IV-3	

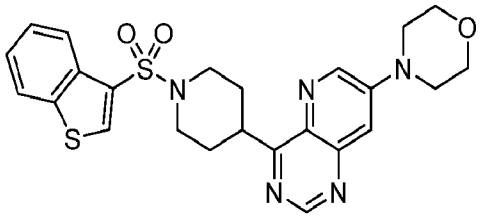
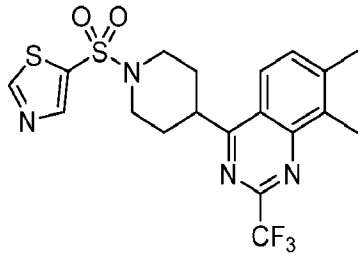
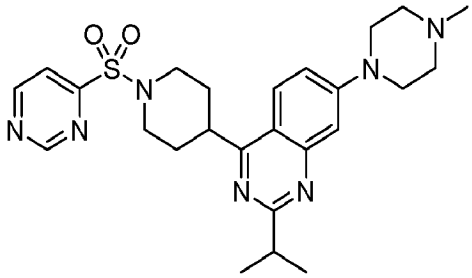
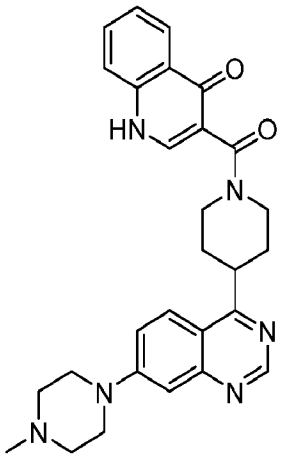
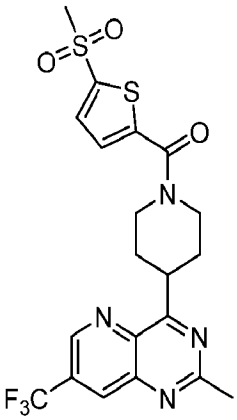
Compound No.	Chemical Structure
IV-4	
IV-5	
IV-6	
IV-7	

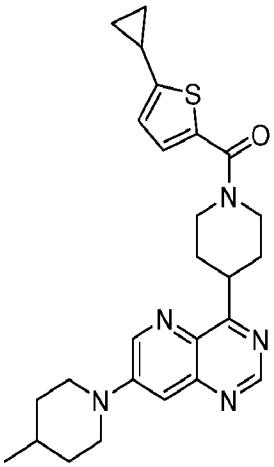
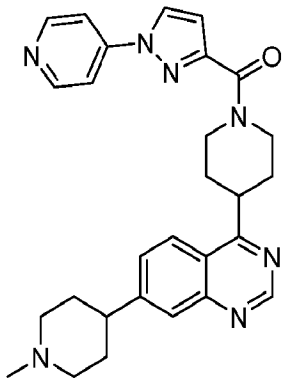
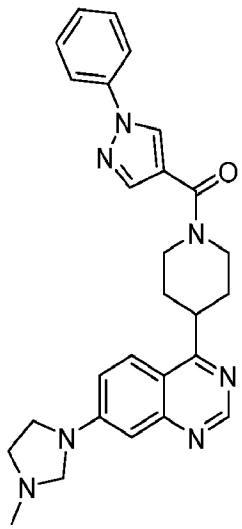
Compound No.	Chemical Structure
IV-8	
IV-9	
IV-10	
IV-11	

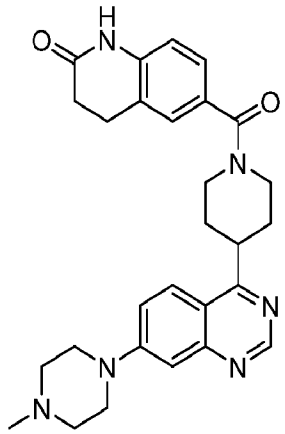
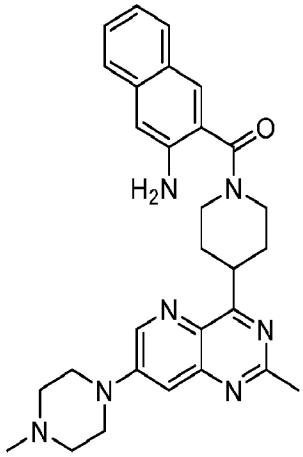
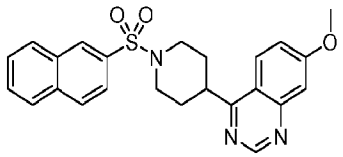
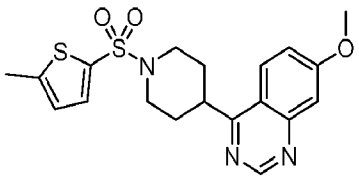
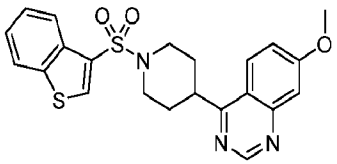
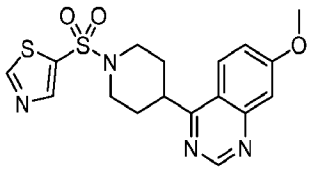
Compound No.	Chemical Structure
IV-12	
IV-13	
IV-14	
IV-15	

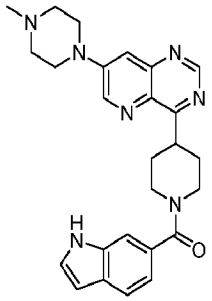
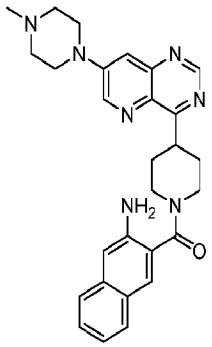
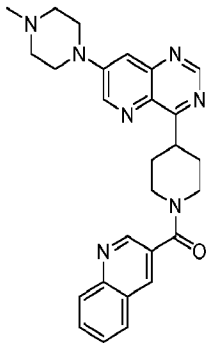
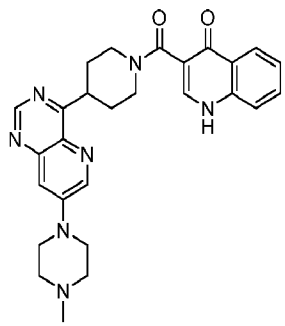
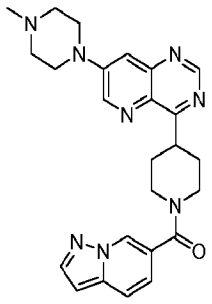
Compound No.	Chemical Structure
IV-16	
IV-17	
IV-18	
IV-19	

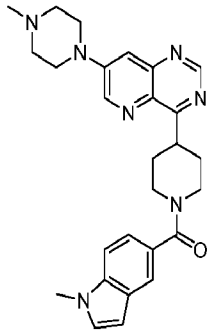
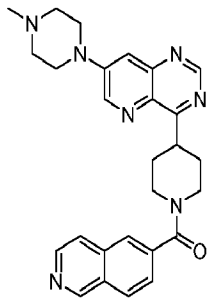
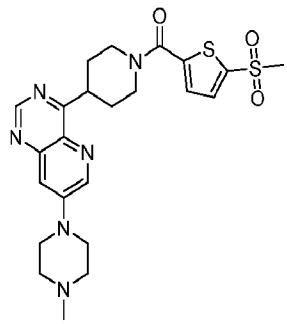
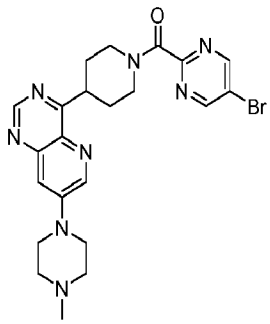
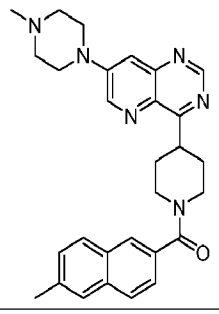
Compound No.	Chemical Structure
IV-20	
IV-21	
IV-22	
IV-23	
IV-24	

Compound No.	Chemical Structure
IV-25	
IV-26	
IV-27	
IV-28	
IV-29	

Compound No.	Chemical Structure
IV-30	
IV-31	
IV-32	

Compound No.	Chemical Structure
IV-33	
IV-34	
IV-35	
IV-36	
IV-37	
IV-38	

Compound No.	Chemical Structure
IV-39	
IV-40	
IV-41	
IV-42	
IV-43	

Compound No.	Chemical Structure
IV-44	
IV-45	
IV-46	
IV-47	
IV-48	

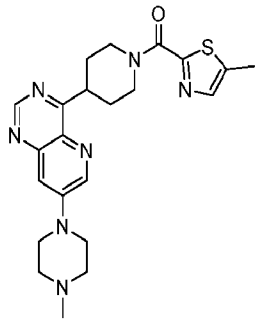
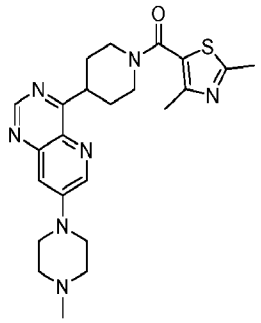
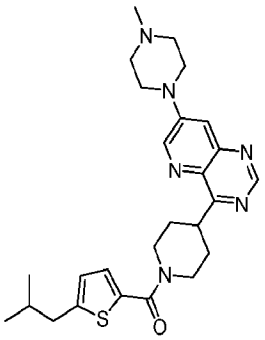
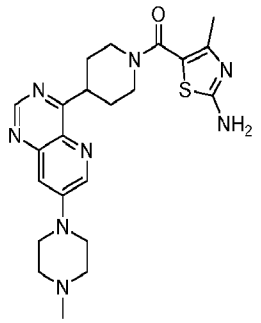
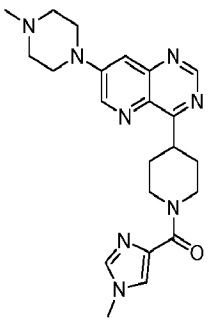
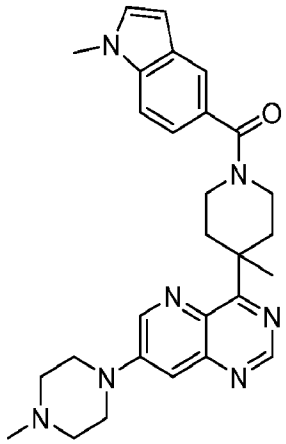
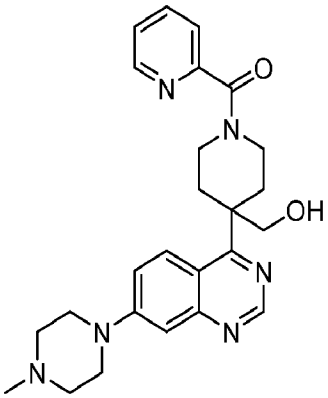
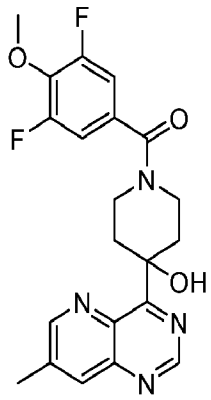
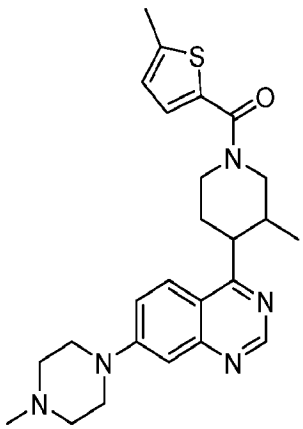
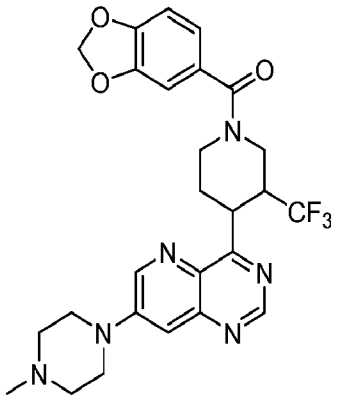
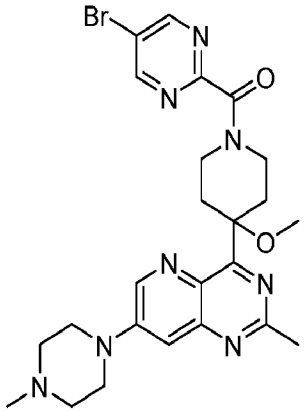
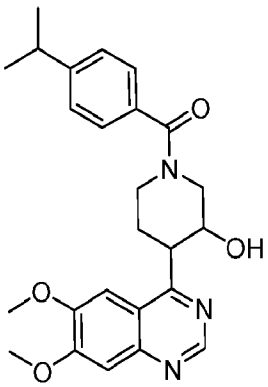
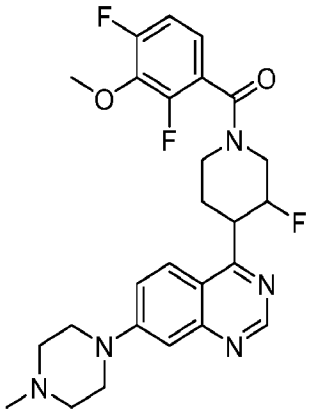
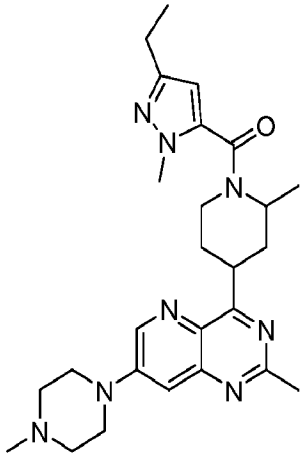
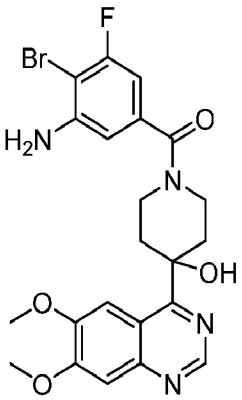
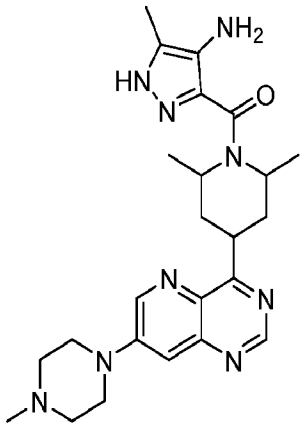
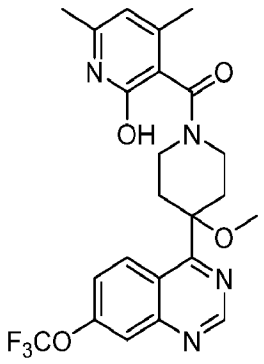
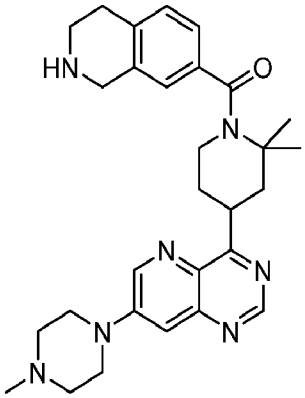
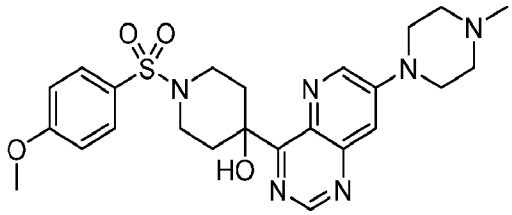
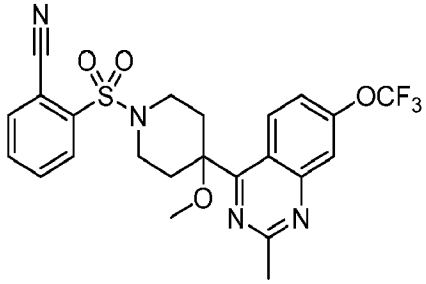
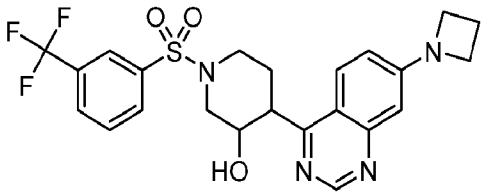
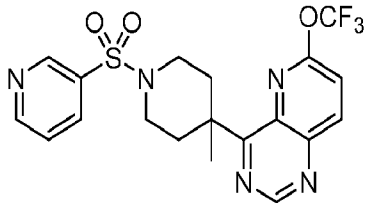
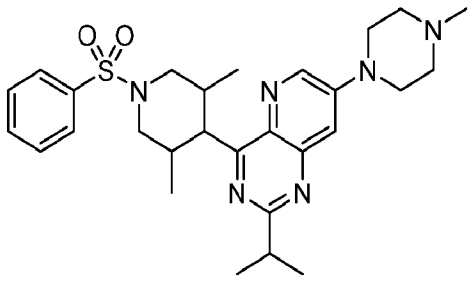
Compound No.	Chemical Structure
IV-49	
IV-50	
IV-51	
IV-52	
IV-53	

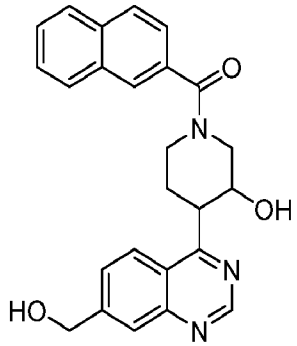
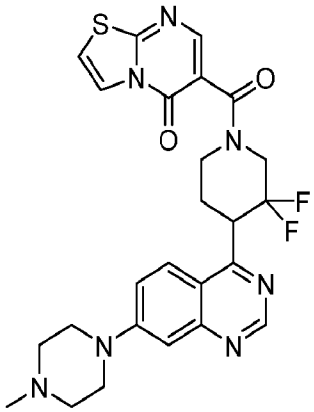
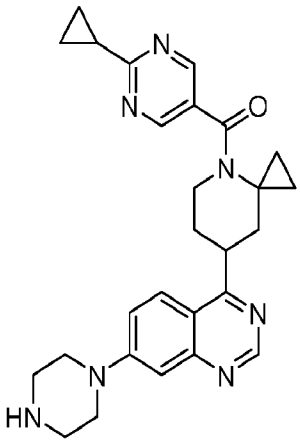
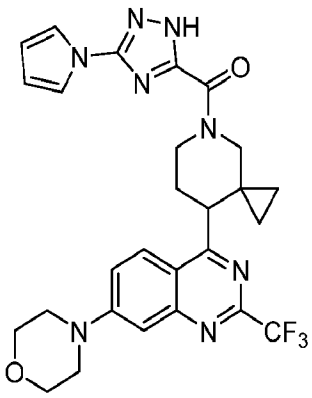
TABLE 5.

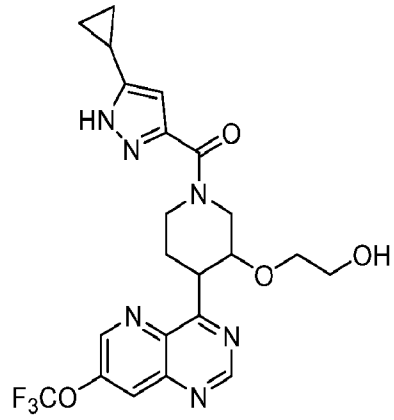
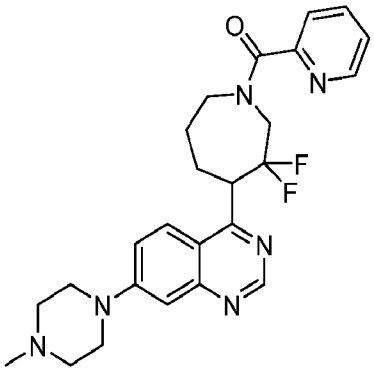
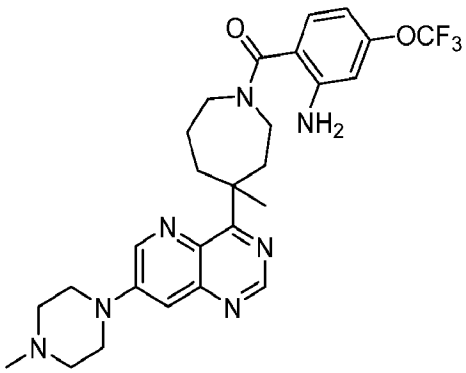
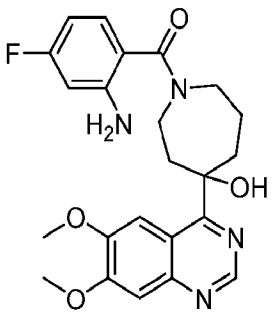
Compound No.	Chemical Structure
V-1	
V-2	
V-3	
V-4	

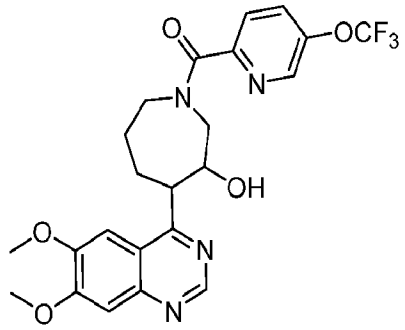
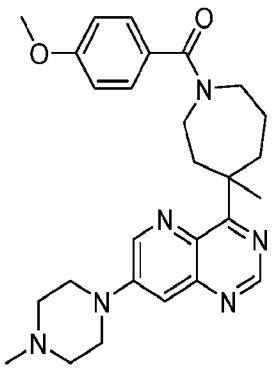
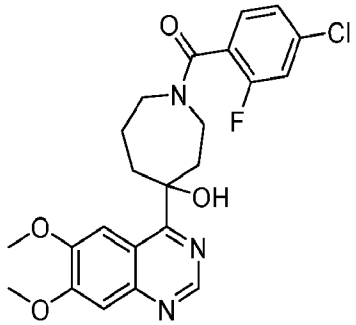
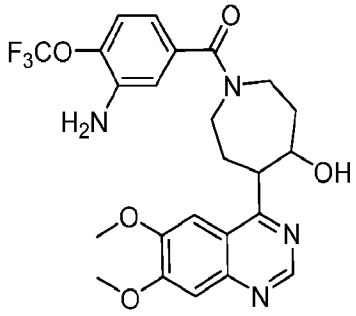
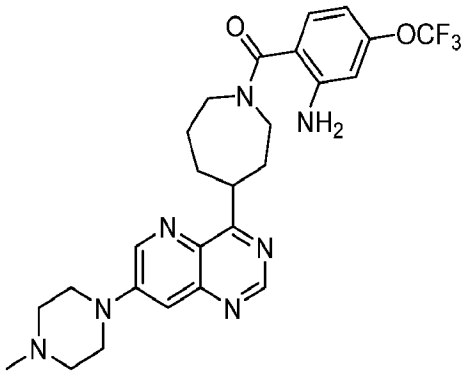
Compound No.	Chemical Structure
V-5	
V-6	
V-7	
V-8	

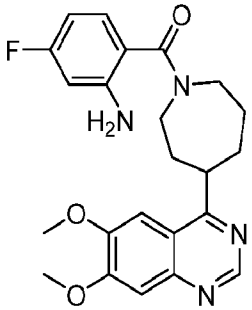
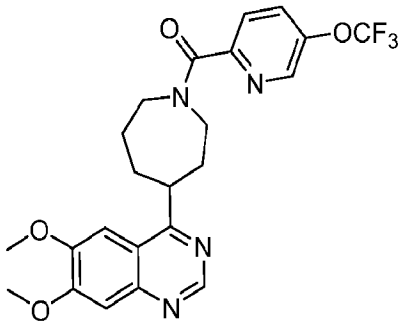
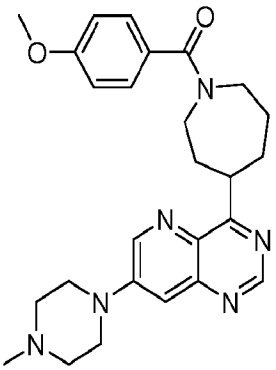
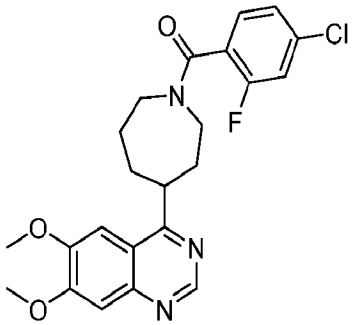
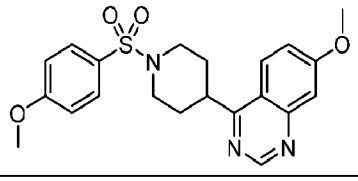
Compound No.	Chemical Structure
V-9	
V-10	
V-11	
V-12	

Compound No.	Chemical Structure
V-13	
V-14	
V-15	
V-16	
V-17	
V-18	

Compound No.	Chemical Structure
V-19	
V-20	
V-21	
V-22	

Compound No.	Chemical Structure
V-23	
V-24	
V-25	
V-26	

Compound No.	Chemical Structure
V-27	
V-28	
V-29	
V-30	
V-31	

Compound No.	Chemical Structure
V-32	
V-33	
V-34	
V-35	
V-36	

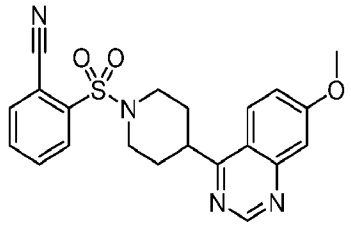
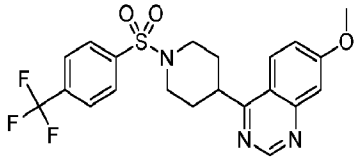
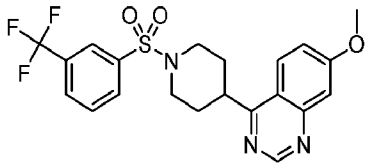
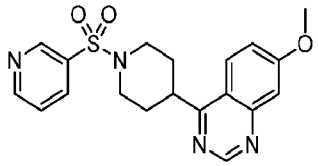
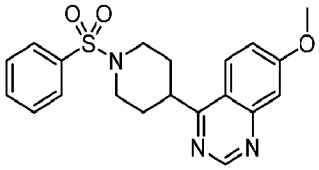
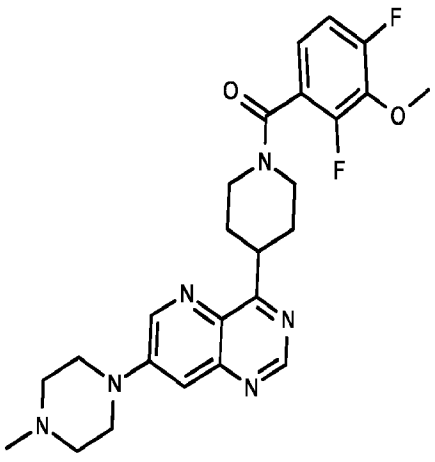
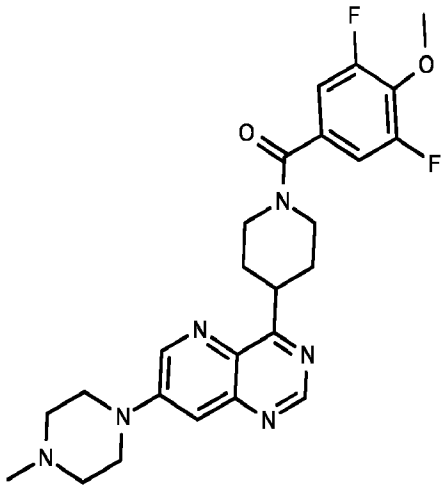
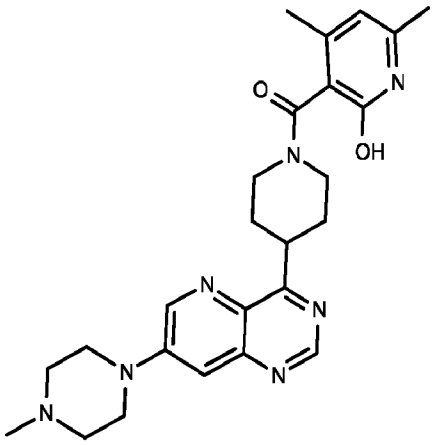
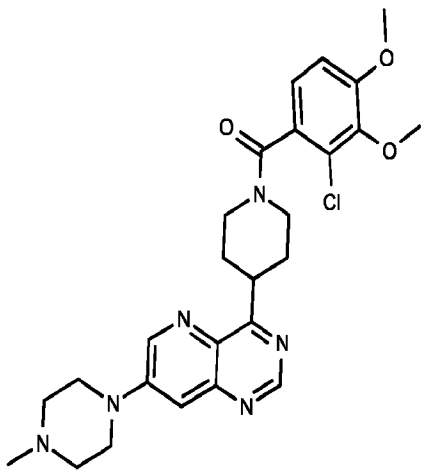
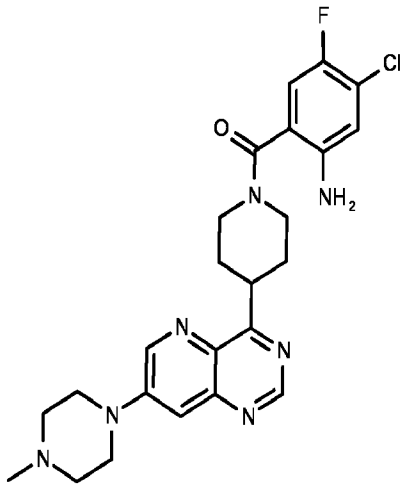
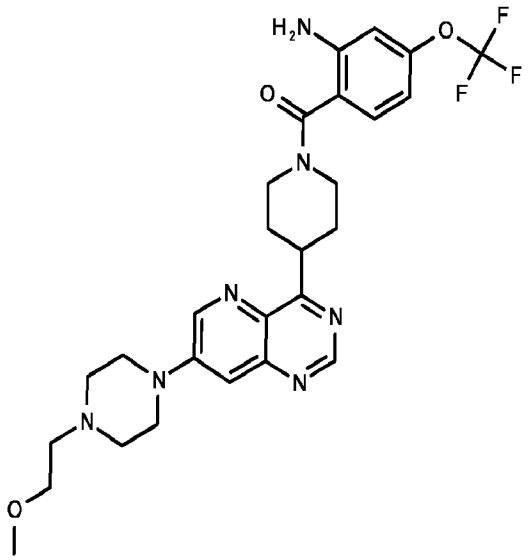
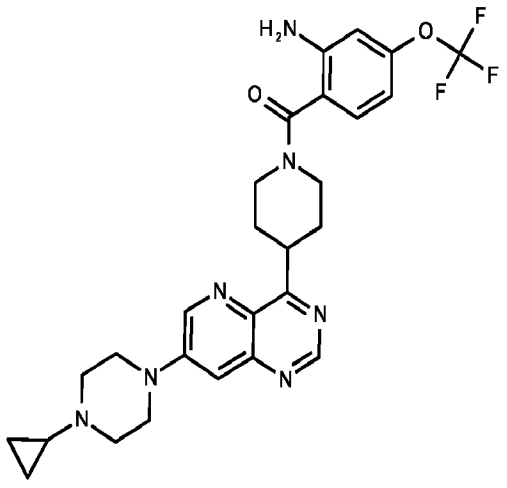
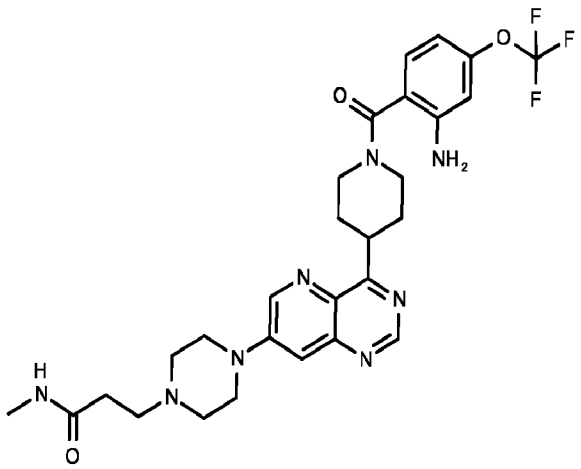
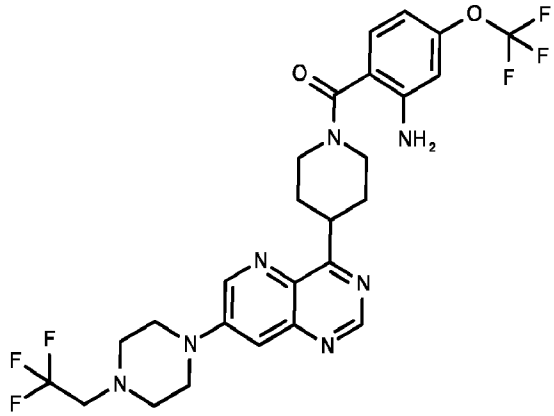
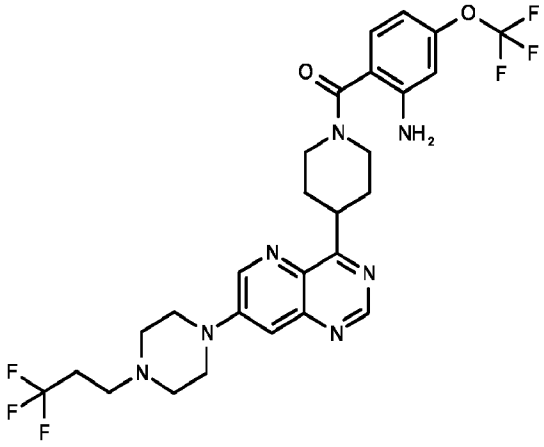
Compound No.	Chemical Structure
V-37	
V-38	
V-39	
V-40	
V-41	

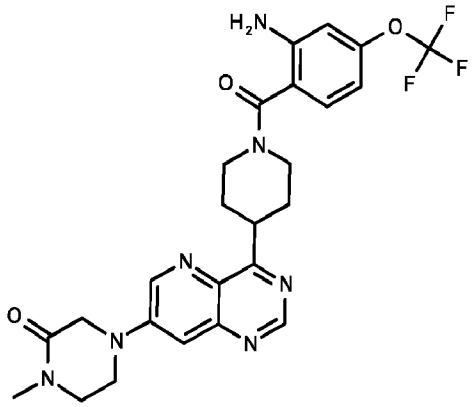
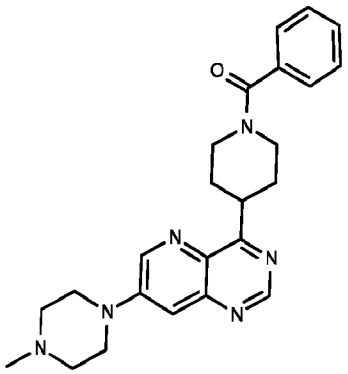
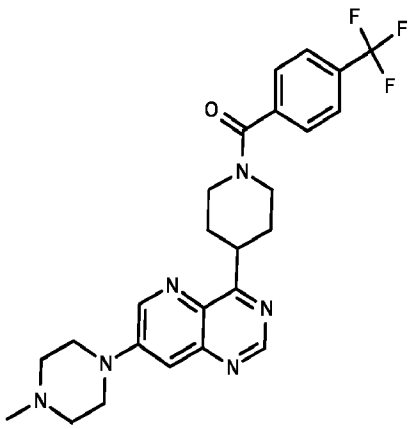
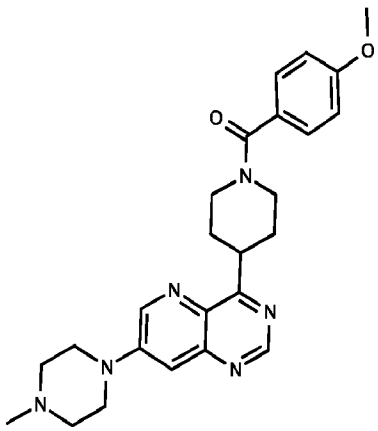
TABLE 6.

Compound No.	Chemical Structure
VI-1	

Compound No.	Chemical Structure
VI-2	
VI-3	
VI-4	

Compound No.	Chemical Structure
VI-5	
VI-6	
VI-7	

Compound No.	Chemical Structure
VI-8	
VI-9	
VI-10	

Compound No.	Chemical Structure
VI-11	
VI-12	
VI-13	
VI-14	

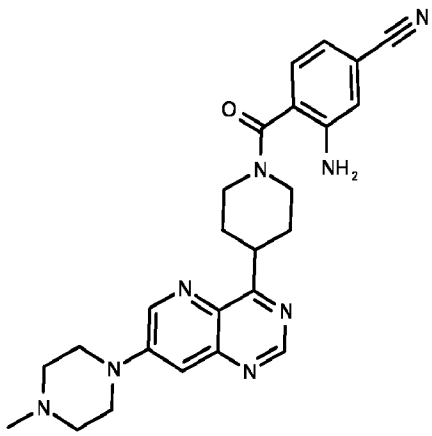
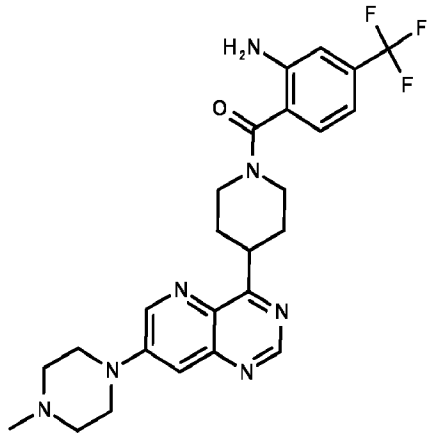
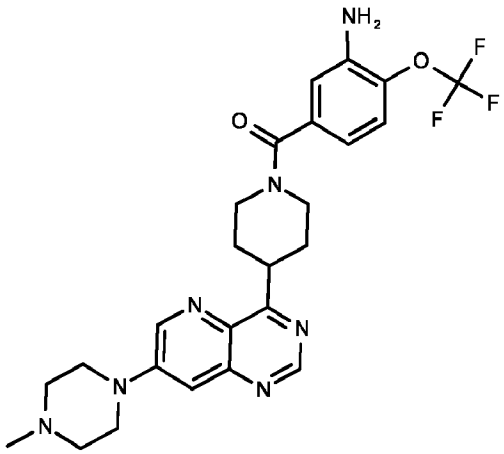
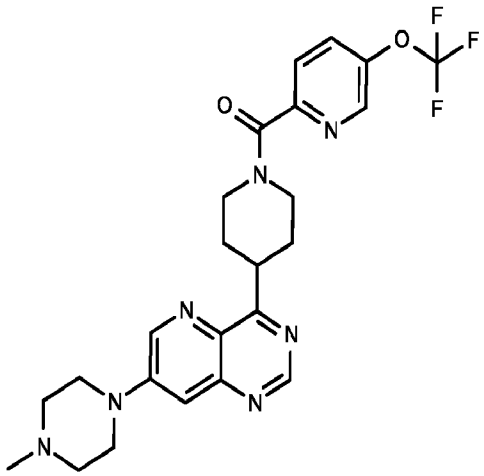
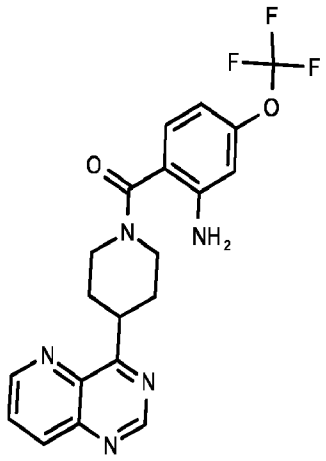
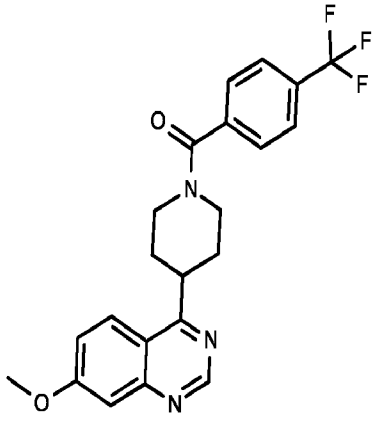
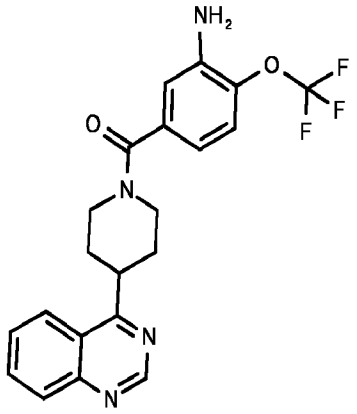
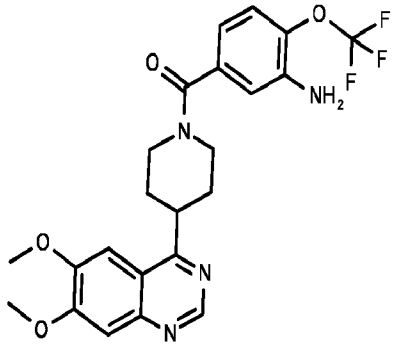
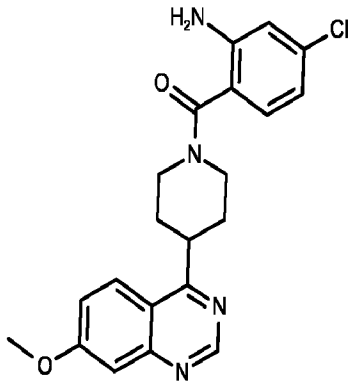
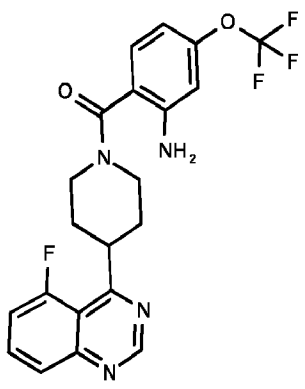
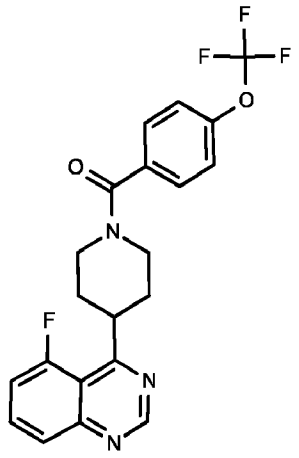
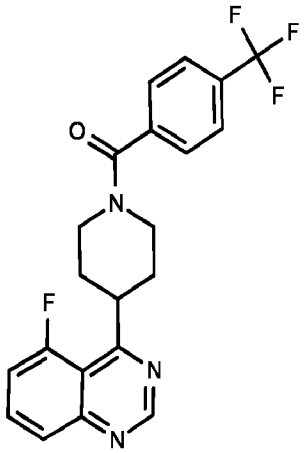
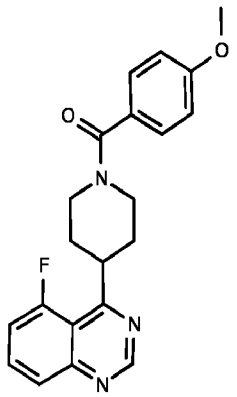
Compound No.	Chemical Structure
VI-15	
VI-16	

TABLE 7.

Compound No.	Chemical Structure
VII-1	

Compound No.	Chemical Structure
VII-2	
VII-3	
VII-4	

Compound No.	Chemical Structure
VII-5	
VII-6	
VII-7	
VII-8	

Compound No.	Chemical Structure
VII-9	
VII-10	
VII-11	

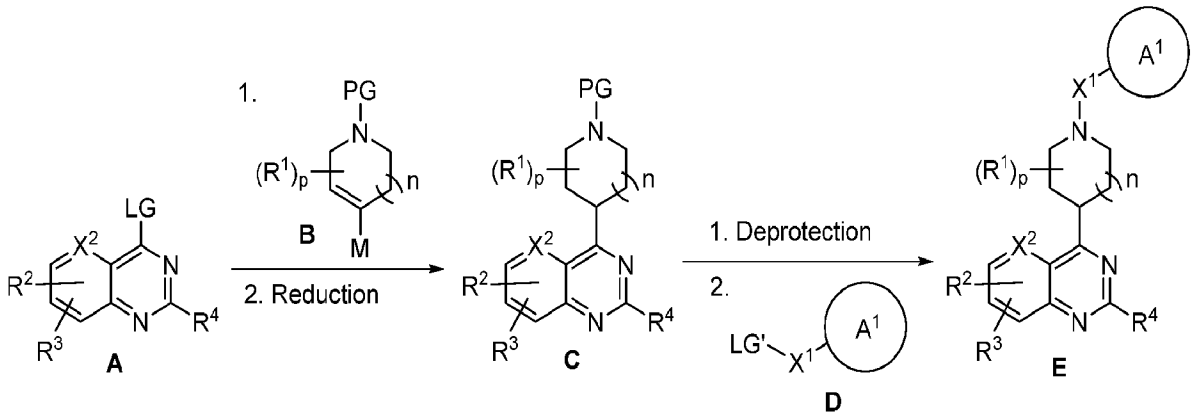
[0546] Compounds may be further characterized according to their inhibitory activity against ERK5. In certain embodiments, a preferred compound has an IC_{50} less than 2 μM against ERK5. In certain embodiments, a more preferred compound has an IC_{50} less than 0.5 μM against ERK5. In certain embodiments, an even more preferred compound has an IC_{50} less than or equal to 0.05 μM against ERK5.

[0547] Methods for preparing compounds described herein are illustrated in the following synthetic Schemes, and in the Examples below. The Schemes are given for the purpose of illustrating the invention, and are not intended to limit the scope or spirit of the invention. Starting materials shown in the Schemes can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[0548] In the Schemes, it is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated (for example, use of protecting groups or alternative reactions). Protecting group chemistry and strategy is well known in the art, for example, as described in detail in "Protecting Groups in Organic Synthesis", T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entire contents of which are hereby incorporated by reference.

[0549] The synthetic route illustrated in Scheme 1 is a general method for preparing substituted 4-piperidinyl-quinazolines and related compounds **E**. Transition-metal-mediated coupling of bicyclic heteroaryl **A** (wherein LG is a leaving group, such as bromide, chloride, or a sulfonate) with cyclic metal reagent **B** (wherein M is a metal, such as a boronic acid or ester, or a trialkylstannane; and PG is a protecting group, such as Boc), followed by reduction (using, for example, hydrogen and a transition-metal catalyst, such as Pd on carbon), affords protected piperidinyl-substituted heteroaryl **C**. Deprotection (using, for example, an acid, such as HCl or TFA, when PG is Boc), followed by coupling with cyclic compound **D** (wherein LG' is a leaving group, such as a halide, or a hydroxyl group that can be activated using, for example, an amide coupling reagent, such as HATU), affords substituted 4-piperidinyl-pyrimidine-2-amines and related compounds **E**.

SCHEME 1.

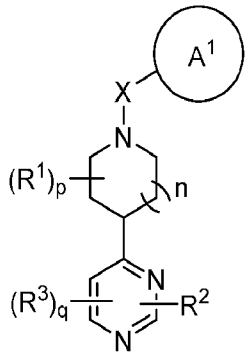


[0550] The modular synthetic route illustrated in Scheme 1 can also be readily modified by one of skill in the art to provide additional substituted 4-piperidinyl-quinazolines and related compounds by conducting functional group transformations on the intermediate and final compounds. Such functional group transformations are well known in the art, as described in, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992). For example, the alkene functional group in the coupling product of bicyclic heteroaryl **A** with cyclic metal reagent **B** can be oxidized, instead of reduced, to afford, for example, an alcohol (using, for example, Mukaiyama hydration conditions) or a 1,2-diol (using, for example, OsO_4 and a stoichiometric oxidant, such as NMO). The resulting alcohol(s) can be further functionalized, for example, by alkylation (using, for example, a base, such as NaH, and an electrophile, such as an alkyl halide).

I-A. Substituted 4-Piperidinyl-pyrimidine-2-amines and Related Compounds

[0551] The invention provides substituted 4-piperidinyl-pyrimidine-2-amines and related compounds. The compounds may be used in the pharmaceutical compositions and therapeutic methods described herein. Exemplary compounds are described in the following sections, along with exemplary procedures for making the compounds.

[0552] One aspect of the invention provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or $-N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond;

R^2 is $-N(R^4)C(O)(R^7)$, $-N(R^6)(R^7)$, $-C(O)N(R^6)(R^7)$, or hydrogen;

R^3 is halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or cyano;

R^4 and R^5 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of $-C(O)N(R^4)(R^5)$, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), $-S(O)_2$-(C_{1-6} alkyl), C_{3-}

$_6$ cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X is -C(O)-, -S(O)-, or -$S(O)_2$-;

A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

n is 1 or 2;

m and p are each independently 0, 1, 2, or 3; and

q is 0, 1, or 2.

[0553] The definitions of variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0554] In certain embodiments, the compound is a compound of Formula I.

[0555] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or -$N(R^4)(R^5)$; or two occurrences of R^1

attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond.

[0556] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0557] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or -$N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0558] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or -$N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0559] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or -$N(R^4)(R^5)$. In certain embodiments, two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond.

[0560] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, or -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0561] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0562] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkoxyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$. In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro. In certain embodiments, R^1 represents independently for each occurrence $-N(R^4)(R^5)$.

[0563] In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is hydroxyl. In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; and any additional occurrence of R^1 is C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.

[0564] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0565] As defined generally above, R^2 is $-N(R^4)C(O)(R^7)$, $-N(R^6)(R^7)$, $-C(O)N(R^6)(R^7)$, or hydrogen. In certain embodiments, R^2 is $-N(R^4)C(O)(R^7)$, $-N(R^6)(R^7)$, or $-C(O)N(R^6)(R^7)$. In certain embodiments, R^2 is $-N(R^4)C(O)(R^7)$ or $-N(R^6)(R^7)$. In certain embodiments, R^2 is $-N(R^4)C(O)(R^7)$. In certain embodiments, R^2 is $-N(R^6)(R^7)$. In certain embodiments, R^2 is $-C(O)N(R^6)(R^7)$. In certain embodiments, R^2 is $-C(O)N(R^6)(R^7)$, and m is 1, 2, or 3. In certain embodiments, R^2 is hydrogen.

[0566] In certain embodiments, R^2 is $-N(H)C(O)(C_{1-6}$ alkyl) or $-N(H)(R^7)$. In certain embodiments, R^2 is $-N(H)C(O)(C_{1-6}$ alkyl). In certain embodiments, R^2 is $-N(H)C(O)(C_{1-4}$ alkyl). In certain embodiments, R^2 is $-N(H)C(O)CH_3$. In certain embodiments, R^2 is $-N(H)(R^7)$.

[0567] In certain embodiments, R^2 is attached at the 2-position of the pyrimidine. In certain embodiments, R^2 is attached at the 4-position of the pyrimidine.

[0568] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0569] As defined generally above, R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or cyano. In certain embodiments, R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 represents independently for each occurrence halo, C_{1-4} haloalkoxyl, or C_{1-4} haloalkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0570] In certain embodiments, R^3 represents independently for each occurrence halo. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^3 is $-CF_3$. In certain embodiments, R^3

is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0571] As defined generally above, R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0572] In certain embodiments, R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^4 represents independently for each occurrence C_{3-5} cycloalkyl.

[0573] In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0574] As defined generally above, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0575] In certain embodiments, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{3-5} cycloalkyl.

[0576] In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0577] In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0578] In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^4 and R^5 are hydrogen. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{3-5} cycloalkyl.

[0579] In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0580] In certain embodiments, R^4 and R^5 are selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0581] As defined generally above, R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^6 and R^7 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring containing one nitrogen atom. In certain embodiments, R^6 and R^7 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring containing one nitrogen atom.

[0582] In certain embodiments, R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 is C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is C_{1-4} alkyl. In certain embodiments, R^6 is methyl. In certain embodiments, R^6 is C_{3-5} cycloalkyl. In certain embodiments, R^6 is cyclopropyl. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0583] As defined generally above, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano.

[0584] In certain embodiments, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0585] In certain embodiments, R^7 is C_{3-6} cycloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl, phenyl, or pyrazolyl.

[0586] In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl.

[0587] In certain embodiments, R^7 is phenyl or pyrazolyl; each of which is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is phenyl or pyrazolyl; each of which is substituted with 1, 2, or 3 substituents independently selected from

the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is phenyl or pyrazolyl.

[0588] In certain embodiments, R^7 is C_{1-6} alkyl. In certain embodiments, R^7 is C_{1-4} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 is C_{3-6} cycloalkyl. In certain embodiments, R^7 is cyclopropyl. In certain embodiments, R^7 is C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-4} haloalkyl. In certain embodiments, R^7 is trifluoromethyl.

[0589] In certain embodiments, R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with one -C(O)N(R^4)(R^5). In certain embodiments, R^7 is phenyl.

[0590] In certain embodiments, R^7 is pyrazolyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is pyrazolyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is pyrazolyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is pyrazolyl.

[0591] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0592] As defined generally above, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6

membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0593] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl); or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0594] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0595] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6}

haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0596] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -$N(R^4)(R^5)$, C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, or C_{1-6} alkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, -$N(R^4)(R^5)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^4)(R^5)$. In certain embodiments, R^8 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, or chloro. In certain embodiments, R^8 represents independently for each occurrence –OCF_3 or –NH_2.

[0597] In certain embodiments, one occurrence of R^8 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^8 represent independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, one occurrence of R^8 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^8 represent independently for each occurrence -$N(R^4)(R^5)$, hydroxyl, halo, or cyano. In certain embodiments, one occurrence of R^8 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^8 represent independently for each occurrence -$N(R^4)(R^5)$ or halo. In certain embodiments, one occurrence of R^8 is C_{1-4} haloalkoxyl, C_{1-4} haloalkyl, -S-(C_{1-4} haloalkyl), or -O-(C_{3-4} cycloalkyl), and any further occurrences of R^8 are –NH_2.

[0598] In certain embodiments, one occurrence of R^8 is $-OCF_3$, $-CF_3$, $-SCF_3$, or -O-(cyclopropyl), and any further occurrences of R^8 are independently $-NH_2$, –F, or –Cl. In certain embodiments, one occurrence of R^8 is $-OCF_3$, $-CF_3$, or -O-(cyclopropyl), and any further occurrences of R^8 are independently $-NH_2$, –F, or –Cl. In certain embodiments, one occurrence of R^8 is $-OCF_3$, $-CF_3$, or -O-(cyclopropyl), and any further occurrences of R^8 are independently $-NH_2$.

[0599] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, $-S(O)_2-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0600] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-O-(C_{0-4}$ alkylene)$-(C_{3-6}$ cycloalkyl), $-N(R^4)(R^5)$, hydroxyl, halo, cyano, $-S-(C_{1-6}$ haloalkyl), or $-S-(C_{1-6}$ alkyl). In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^4)(R^5)$, hydroxyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-O-(C_{0-4}$ alkylene)$-(C_{3-6}$ cycloalkyl), or hydroxyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^8 represents independently for each occurrence $-N(R^4)(R^5)$, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence $-S-(C_{1-6}$ haloalkyl) or $-S-(C_{1-6}$ alkyl).

[0601] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} cycloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl. In certain embodiments, R^8 represents independently for each

occurrence C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0602] In certain embodiments, R^8 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^8 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^8 represents independently for each occurrence phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0603] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^8 is $-OCF_3$. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^8 is methoxy. In certain embodiments, R^8 represents independently for each occurrence -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^8 represents independently for each occurrence -O-(C_{1-4} alkylene)-(C_{3-4} cycloalkyl). In certain embodiments, R^8 represents independently for each occurrence -O-(C_{3-4} cycloalkyl). In certain embodiments, R^8 represents independently for each occurrence -N(R^4)(R^5). In certain embodiments, R^8 is $-NH_2$. In certain embodiments, R^8 is hydroxyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^8 is methyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^8 is trifluoromethyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{2-6} alkenyl. In certain embodiments, R^8 represents independently for each occurrence C_{2-6} alkynyl. In certain embodiments, R^8 represents independently for each occurrence halo. In certain embodiments, R^8 is fluoro. In certain embodiments, R^8 is cyano. In certain embodiments, R^8 represents independently for each occurrence -S-(C_{1-6} haloalkyl). In certain embodiments, R^8 is -S-CF_3. In

certain embodiments, R^8 represents independently for each occurrence -S-(C_{1-6} alkyl). In certain embodiments, R^8 represents independently for each occurrence -$S(O)_2$-(C_{1-6} alkyl).

[0604] In certain embodiments, R^8 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^8 is phenyl. In certain embodiments, R^8 represents independently for each occurrence a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^8 represents independently for each occurrence a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0605] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo. In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0606] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0607] In certain embodiments, R^8 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

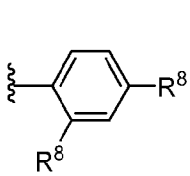
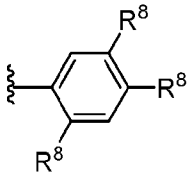
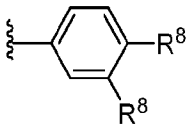
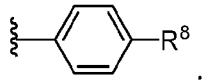
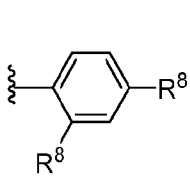
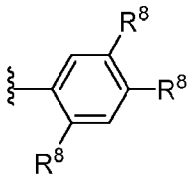
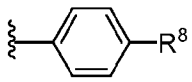
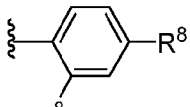
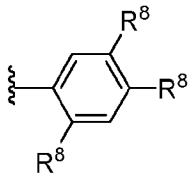
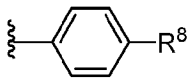
[0608] As defined generally above, X is -C(O)-, -S(O)-, or -$S(O)_2$-. In certain embodiments, X is -C(O)-. In certain embodiments, X is -S(O)- or -$S(O)_2$-. In certain embodiments, X is -S(O)-. In certain embodiments, X is -$S(O)_2$-. In certain embodiments, X is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

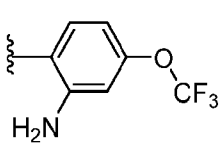
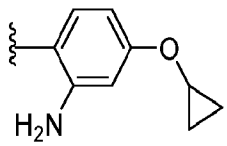
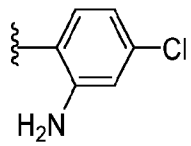
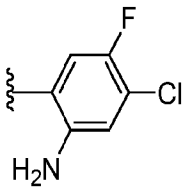
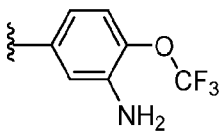
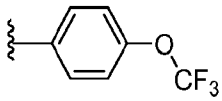
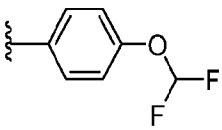
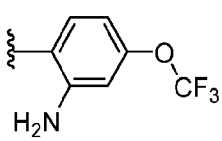
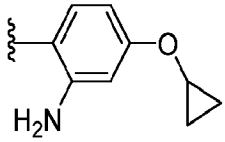
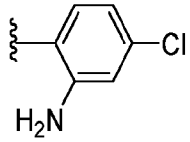
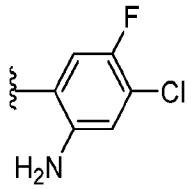
[0609] As defined generally above, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

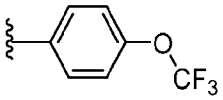
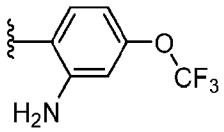
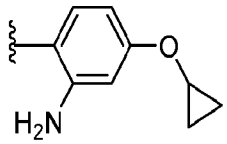
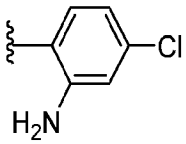
[0610] In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

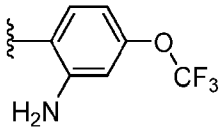
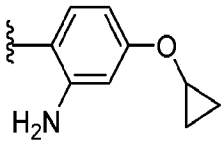
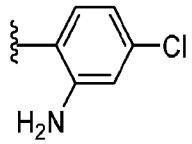
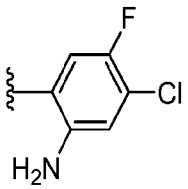
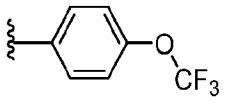
[0611] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3

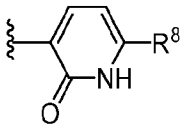
heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

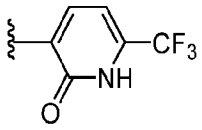
[0612] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

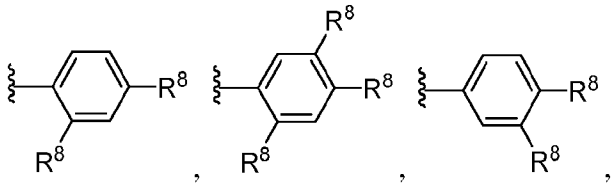
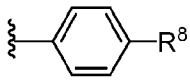
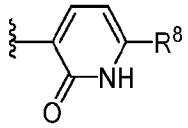
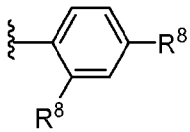
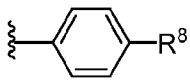
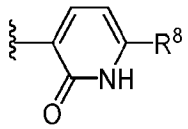
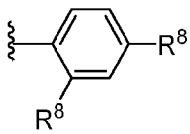
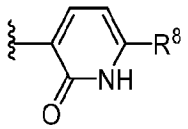
[0613] In certain embodiments, A^1 is  ,  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is  ,  ,  ,  , or

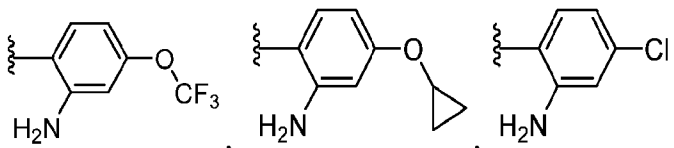
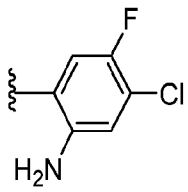
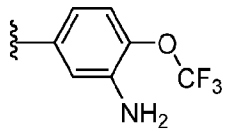
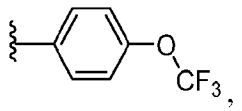
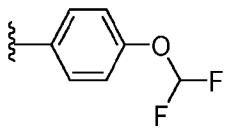
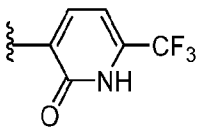
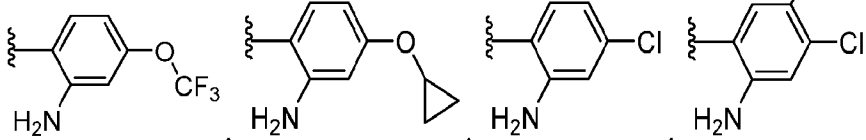
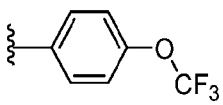
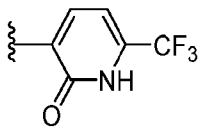
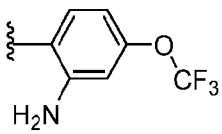
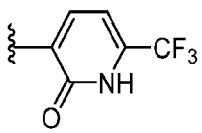

. In certain embodiments, A^1 is  ,  ,  .

[0614] In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0615] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is  . In certain

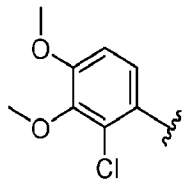
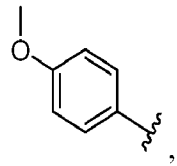
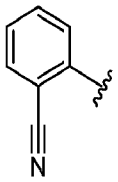
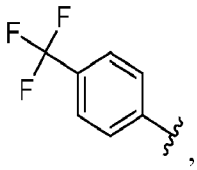
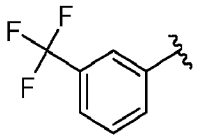
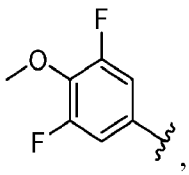
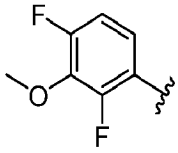
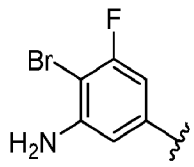
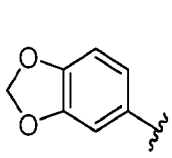
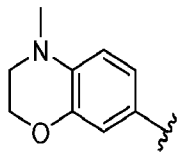
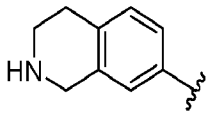
embodiments, A^1 is  .

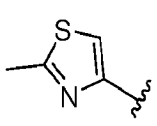
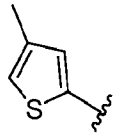
[0616] In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  or  .

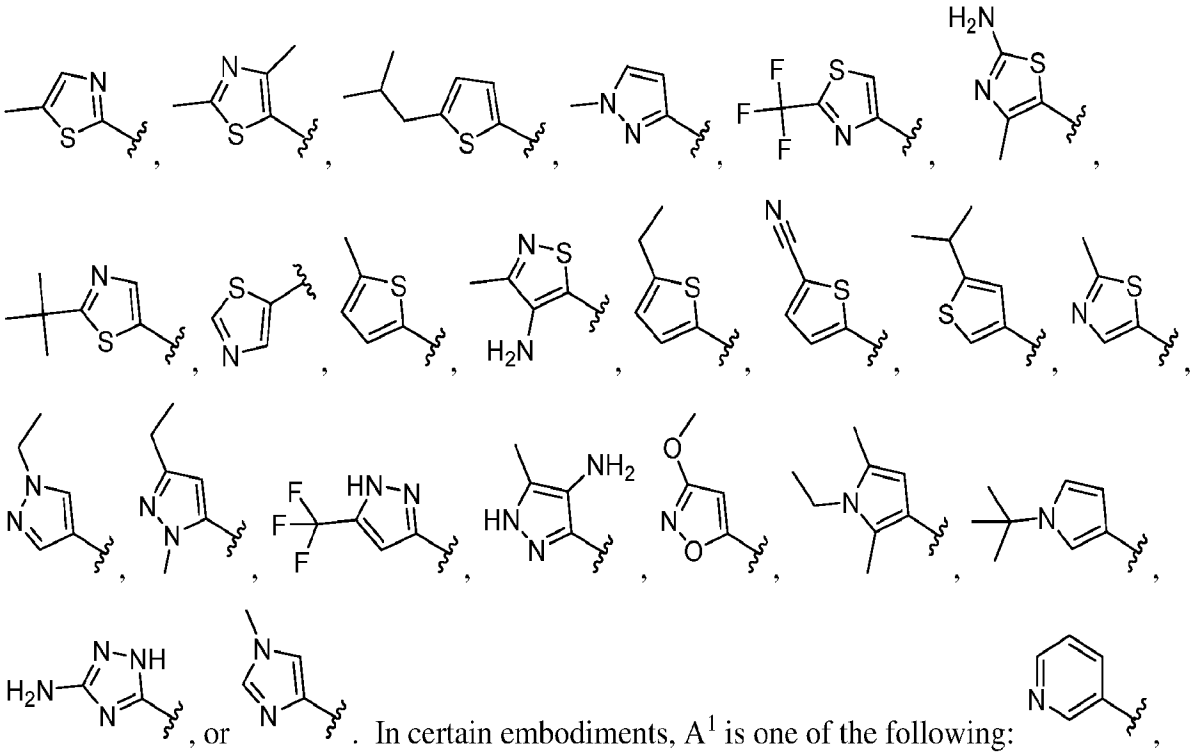
[0617] In certain embodiments, A^1 is  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is  ,  ,  , or . In certain embodiments, A^1 is  or  .

[0618] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8.

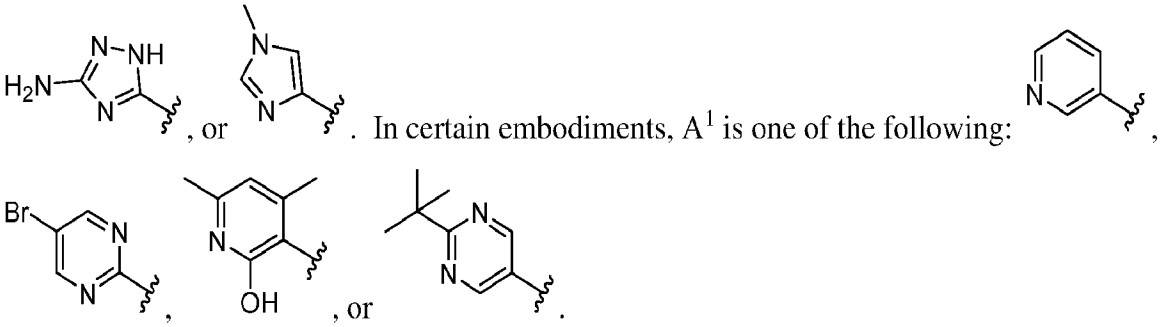
[0619] In certain embodiments, A^1 is naphthyl substituted with m occurrences of R^8. In certain embodiments, A^1 is an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8.

[0620] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is one of the following:  ,  , or  .

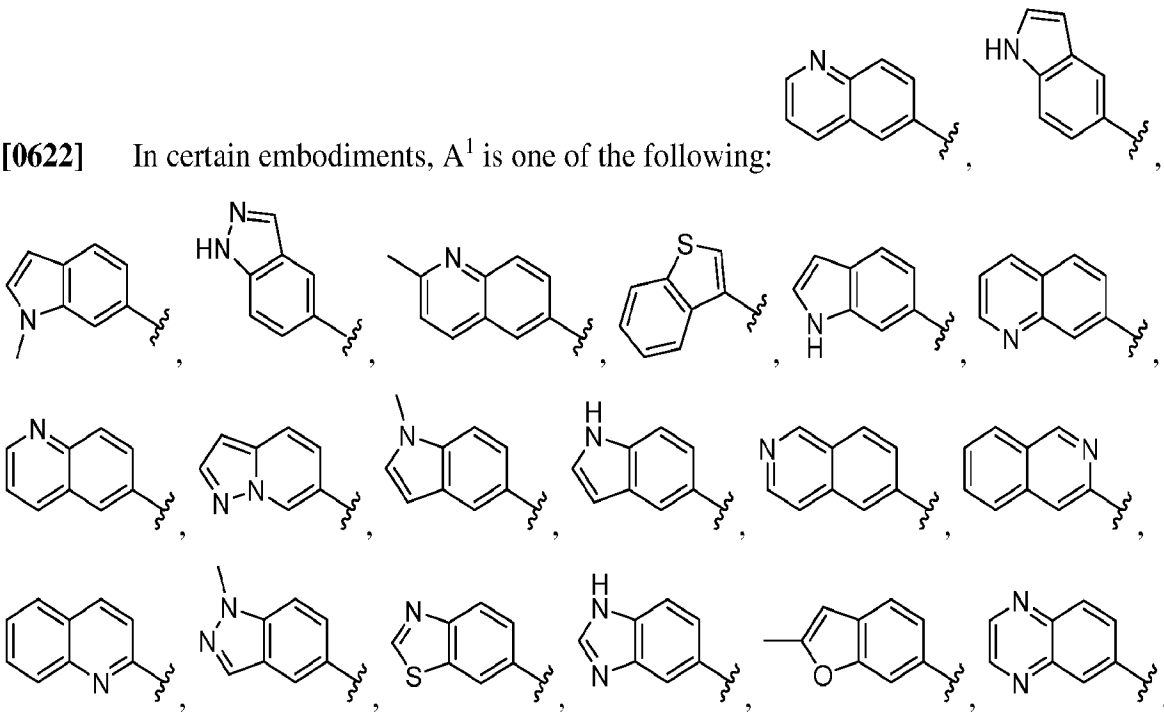
[0621] In certain embodiments, A^1 is one of the following:  ,  ,

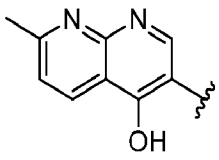
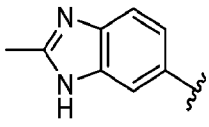


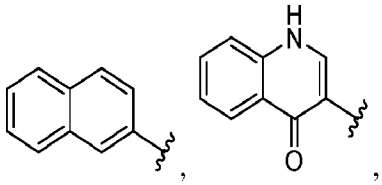
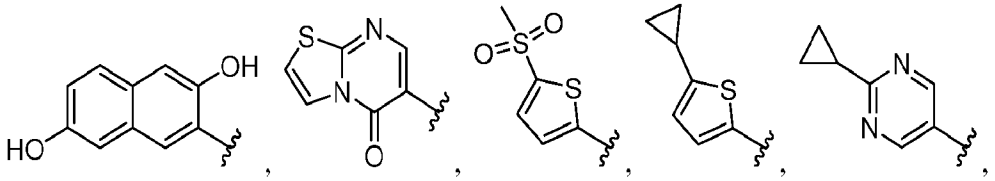
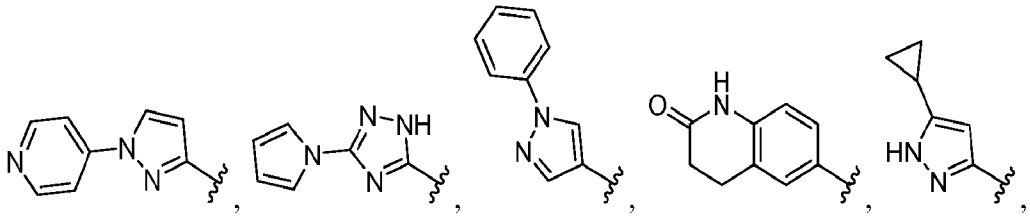
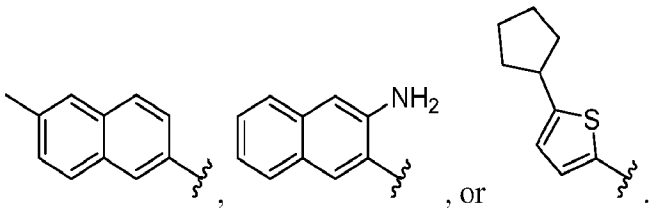
. In certain embodiments, A^1 is one of the following:



[0622] In certain embodiments, A^1 is one of the following:




, or 
.

[0623] In certain embodiments, A^1 is one of the following: 
, 
, 
, 
,
,
, or
.

[0624] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0625] As defined generally above, n is 1 or 2. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is selected from the values represented in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

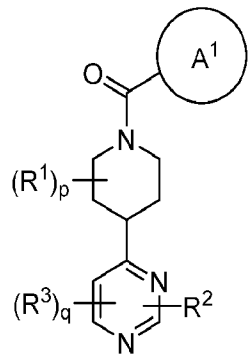
[0626] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0627] As defined generally above, p is 0, 1, 2, or 3. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 0 or 1. In certain embodiments, p is 1 or 2. In certain embodiments, p is 2 or 3. In certain embodiments, p is 0, 1, or 2. In certain embodiments, p is 1, 2, or 3. In certain embodiments, p is selected from the values represented in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0628] As defined generally above, q is 0, 1, or 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. n certain embodiments, q is 0 or 1. In certain embodiments, q is 1 or 2. In certain embodiments, q is selected from the values represented in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0629] The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

[0630] Another aspect of the invention provides a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms;

R^2 is -N(H)C(O)(C_{1-6} alkyl) or -N(H)(R^7);

R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl;

R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl); or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

m is 0, 1, 2, or 3; and

p and q are each independently 0, 1, or 2.

[0631] The definitions of variables in Formula I-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0632] In certain embodiments, the compound is a compound of Formula I-A.

[0633] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0634] In certain embodiments, two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms.

[0635] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0636] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$.

[0637] As defined generally above, R^2 is $-N(H)C(O)(C_{1-6}$ alkyl) or $-N(H)(R^7)$. In certain embodiments, R^2 is $-N(H)C(O)(C_{1-6}$ alkyl). In certain embodiments, R^2 is $-N(H)C(O)(C_{1-4}$ alkyl). In certain embodiments, R^2 is $-N(H)C(O)CH_3$. In certain embodiments, R^2 is $-N(H)(R^7)$.

[0638] In certain embodiments, R^2 is attached at the 2-position of the pyrimidine. In certain embodiments, R^2 is attached at the 4-position of the pyrimidine.

[0639] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0640] As defined generally above, R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0641] In certain embodiments, R^3 represents independently for each occurrence halo. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0642] As defined generally above, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 represents independently for each occurrence C_{1-4} alkyl.

[0643] As defined generally above, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl.

[0644] In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 and R^5 are hydrogen. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{1-4} alkyl.

[0645] In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0646] As defined generally above, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano.

[0647] In certain embodiments, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0648] In certain embodiments, R^7 is C_{3-6} cycloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl, phenyl, or pyrazolyl.

[0649] In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl.

[0650] In certain embodiments, R^7 is phenyl or pyrazolyl; each of which is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is phenyl or pyrazolyl; each of which is substituted with 1, 2, or 3 substituents independently selected from

the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is phenyl or pyrazolyl.

[0651] In certain embodiments, R^7 is C_{1-6} alkyl. In certain embodiments, R^7 is C_{1-4} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 is C_{3-6} cycloalkyl. In certain embodiments, R^7 is cyclopropyl. In certain embodiments, R^7 is C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-4} haloalkyl. In certain embodiments, R^7 is trifluoromethyl.

[0652] In certain embodiments, R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with one -C(O)N(R^4)(R^5). In certain embodiments, R^7 is phenyl.

[0653] In certain embodiments, R^7 is pyrazolyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is pyrazolyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is pyrazolyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is pyrazolyl.

[0654] As defined generally above, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl); or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0655] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0656] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), C_{1-6} alkyl, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), or C_{1-6} alkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, -N(R^4)(R^5), C_{1-6} haloalkyl, or halo. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl or -N(R^4)(R^5). In certain embodiments, R^8 represents independently for each occurrence –OCF_3, –NH_2, –CF_3, fluoro, or chloro. In certain embodiments, R^8 represents independently for each occurrence –OCF_3 or –NH_2.

[0657] In certain embodiments, one occurrence of R^8 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^8 represent independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, one occurrence of R^8 is C_{1-6}

haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^8 represent independently for each occurrence -N(R^4)(R^5), hydroxyl, halo, or cyano. In certain embodiments, one occurrence of R^8 is C_{1-6} haloalkoxyl, C_{1-6} haloalkyl, -S-(C_{1-6} haloalkyl), or -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), and any further occurrences of R^8 represent independently for each occurrence -N(R^4)(R^5) or halo. In certain embodiments, one occurrence of R^8 is C_{1-4} haloalkoxyl, C_{1-4} haloalkyl, -S-(C_{1-4} haloalkyl), or -O-(C_{3-4} cycloalkyl), and any further occurrences of R^8 are $–NH_2$.

[0658] In certain embodiments, one occurrence of R^8 is $–OCF_3$, $–CF_3$, $–SCF_3$, or -O-(cyclopropyl), and any further occurrences of R^8 are independently $–NH_2$, –F, or –Cl. In certain embodiments, one occurrence of R^8 is $–OCF_3$, $–CF_3$, or -O-(cyclopropyl), and any further occurrences of R^8 are independently $–NH_2$, –F, or –Cl. In certain embodiments, one occurrence of R^8 is $–OCF_3$, $–CF_3$, or -O-(cyclopropyl), and any further occurrences of R^8 are independently $–NH_2$.

[0659] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl). In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), or hydroxyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^8 represents independently for each occurrence -N(R^4)(R^5), halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence -S-(C_{1-6} haloalkyl) or -S-(C_{1-6} alkyl).

[0660] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl.

[0661] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^8 is $–OCF_3$. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^8 is methoxy. In certain embodiments, R^8 represents independently for each occurrence -O-(C_{0-4} alkylene)-(C_{3-6}

cycloalkyl). In certain embodiments, R^8 represents independently for each occurrence -O-(C_{1-4} alkylene)-(C_{3-4} cycloalkyl). In certain embodiments, R^8 represents independently for each occurrence -O-(C_{3-4} cycloalkyl). In certain embodiments, R^8 represents independently for each occurrence -N(R^4)(R^5). In certain embodiments, R^8 is $-NH_2$. In certain embodiments, R^8 is hydroxyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^8 is methyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^8 is trifluoromethyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence halo. In certain embodiments, R^8 is fluoro. In certain embodiments, R^8 is cyano. In certain embodiments, R^8 represents independently for each occurrence -S-(C_{1-6} haloalkyl). In certain embodiments, R^8 is -S-CF_3. In certain embodiments, R^8 represents independently for each occurrence -S-(C_{1-6} alkyl).

[0662] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

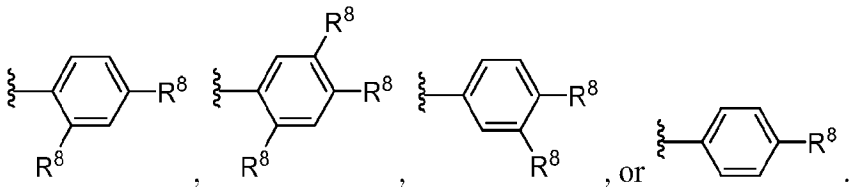
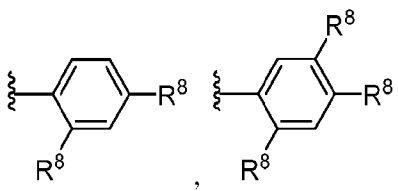
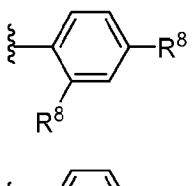
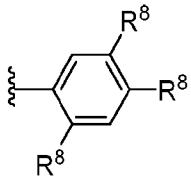
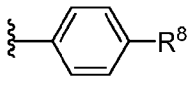
[0663] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

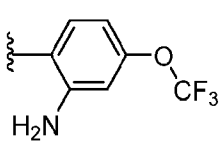
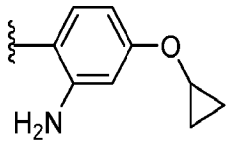
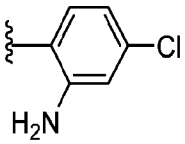
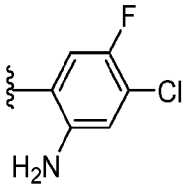
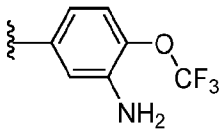
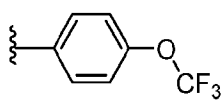
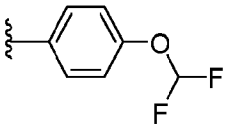
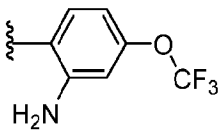
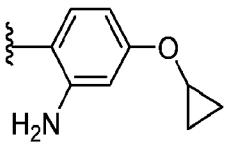
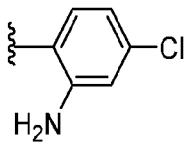
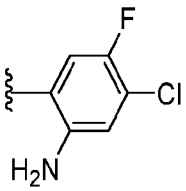
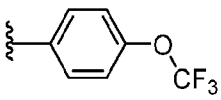
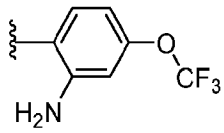
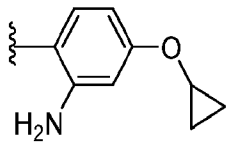
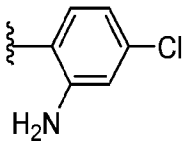
[0664] As defined generally above, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-

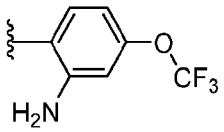
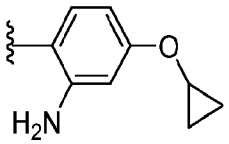
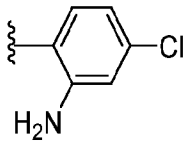
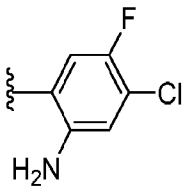
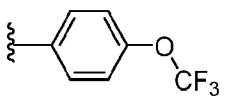
heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

[0665] In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

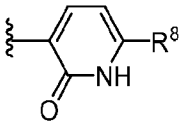
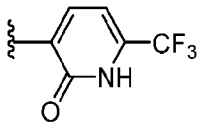
[0666] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

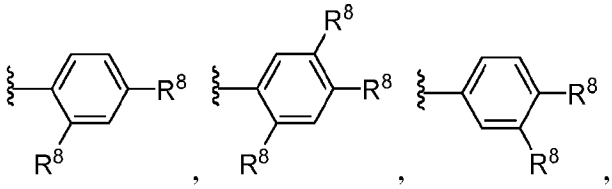
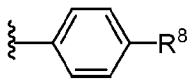
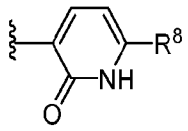
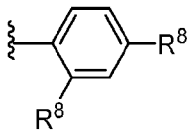
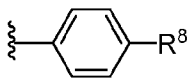
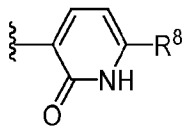
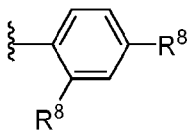
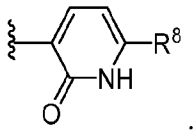
[0667] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^7. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

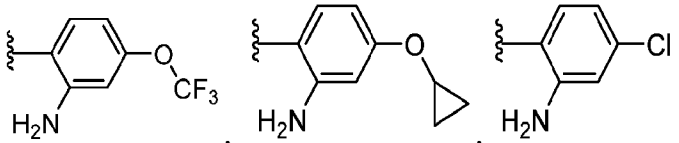
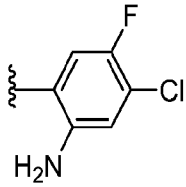
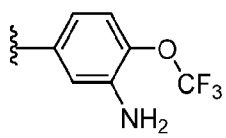
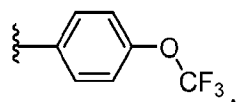
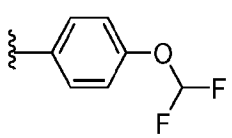
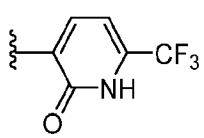
[0668] In certain embodiments, A^1 is  ,  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is  ,  ,  ,  , or  . In certain embodiments, A^1 is  ,  ,  .

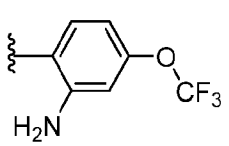
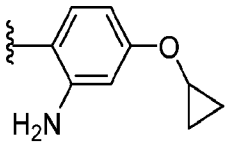
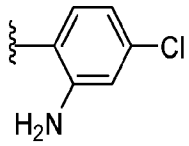
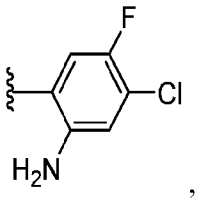
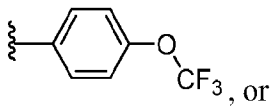
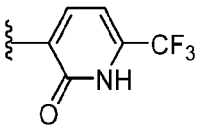
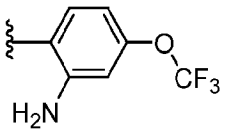
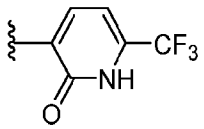
[0669] In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0670] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-

heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

[0671] In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  or  .

[0672] In certain embodiments, A^1 is  ,  ,  ,  ,  , or  . In

certain embodiments, A^1 is  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is  or  .

[0673] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8.

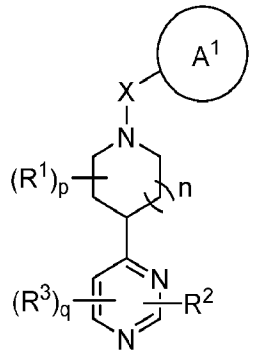
[0674] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3.

[0675] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 0 or 1. In certain embodiments, p is 1 or 2.

[0676] As defined generally above, q is 0, 1, or 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. n certain embodiments, q is 0 or 1. In certain embodiments, q is 1 or 2.

[0677] The description above describes multiple embodiments relating to compounds of Formula I-A. The patent application specifically contemplates all combinations of the embodiments.

[0678] Another aspect of the invention provides a compound represented by Formula I-1:



(I-1)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or $-N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring;

R^2 is $-N(R^4)C(O)(R^7)$, $-N(R^6)(R^7)$, $-C(O)N(R^6)(R^7)$, or hydrogen;

R^3 is halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or cyano;

R^4 and R^5 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, $-S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3

heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X is -C(O)-, -S(O)-, or -$S(O)_2$-;

A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

n is 1 or 2;

m is 0, 1, 2, or 3; and

p and q are each independently 0, 1, or 2.

[0679] The definitions of variables in Formula I-1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0680] In certain embodiments, the compound is a compound of Formula I-1.

[0681] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or -$N(R^4)(R^5)$; or two occurrences of R^1

attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0682] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or $-N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0683] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, $-(C_{1-4}$ alkoxylene$)-N(R^4)(R^5)$, halo, or $-N(R^4)(R^5)$. In certain embodiments, two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

[0684] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, or $-(C_{1-4}$ alkoxylene$)-N(R^4)(R^5)$. In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0685] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0686] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$. In certain embodiments, R^1

represents independently for each occurrence C_{1-4} hydroxyalkoxyl. In certain embodiments, R^1 represents independently for each occurrence -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$. In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 is fluoro. In certain embodiments, R^1 represents independently for each occurrence -$N(R^4)(R^5)$.

[0687] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0688] As defined generally above, R^2 is -$N(R^4)C(O)(R^7)$, -$N(R^6)(R^7)$, -$C(O)N(R^6)(R^7)$, or hydrogen. In certain embodiments, R^2 is -$N(R^4)C(O)(R^7)$, -$N(R^6)(R^7)$, or -$C(O)N(R^6)(R^7)$. In certain embodiments, R^2 is -$N(R^4)C(O)(R^7)$ or -$N(R^6)(R^7)$. In certain embodiments, R^2 is -$N(R^4)C(O)(R^7)$. In certain embodiments, R^2 is -$N(R^6)(R^7)$. In certain embodiments, R^2 is -$C(O)N(R^6)(R^7)$. In certain embodiments, R^2 is -$C(O)N(R^6)(R^7)$, and m is 1, 2, or 3. In certain embodiments, R^2 is hydrogen.

[0689] In certain embodiments, R^2 is -$N(H)C(O)(C_{1-6}$ alkyl) or -$N(H)(R^7)$. In certain embodiments, R^2 is -$N(H)C(O)(C_{1-6}$ alkyl). In certain embodiments, R^2 is -$N(H)C(O)(C_{1-4}$ alkyl). In certain embodiments, R^2 is -$N(H)C(O)CH_3$. In certain embodiments, R^2 is -$N(H)(R^7)$.

[0690] In certain embodiments, R^2 is attached at the 2-position of the pyrimidine. In certain embodiments, R^2 is attached at the 4-position of the pyrimidine.

[0691] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0692] As defined generally above, R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or cyano. In certain embodiments, R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^3 represents independently for each occurrence halo, C_{1-4} haloalkoxyl, or C_{1-4} haloalkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0693] In certain embodiments, R^3 represents independently for each occurrence halo. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3

represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^3 is $-OCF_3$. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^3 is $-CF_3$. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0694] As defined generally above, R^4 and R^5 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom.

[0695] In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^4 and R^5 are hydrogen. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{3-5} cycloalkyl.

[0696] In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom.

[0697] In certain embodiments, R^4 and R^5 are selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0698] In certain embodiments, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In

certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^4 represents independently for each occurrence C_{3-5} cycloalkyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables A-1, A-1-A, A-2, and A-3, below.

[0699] In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^5 represents independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 represents independently for each occurrence C_{3-5} cycloalkyl. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0700] As defined generally above, R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^6 and R^7 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring containing one nitrogen atom. In certain embodiments, R^6 and R^7 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring containing one nitrogen atom.

[0701] In certain embodiments, R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^6 is C_{1-4} alkyl or C_{3-5} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is C_{1-4} alkyl. In certain embodiments, R^6 is methyl. In certain embodiments, R^6 is C_{3-5} cycloalkyl. In certain embodiments, R^6 is cyclopropyl. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0702] As defined generally above, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0703] In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl.

[0704] In certain embodiments, R^7 is C_{1-6} alkyl. In certain embodiments, R^7 is C_{1-4} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 is C_{3-6} cycloalkyl. In certain embodiments, R^7 is cyclopropyl. In certain embodiments, R^7 is C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-4} haloalkyl. In certain embodiments, R^7 is trifluoromethyl.

[0705] In certain embodiments, R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano. In certain embodiments, R^7 is phenyl.

[0706] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0707] As defined generally above, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, $-S(O)_2-(C_{1-6}$ alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0708] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a

4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0709] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, or C_{1-6} alkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, -$N(R^4)(R^5)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^4)(R^5)$. In certain embodiments, R^8 represents independently for each occurrence $–OCF_3$, $–NH_2$, $–CF_3$, fluoro, or chloro. In certain embodiments, R^8 represents independently for each occurrence $–OCF_3$ or $–NH_2$.

[0710] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0711] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^8 represents independently for each occurrence -$N(R^4)(R^5)$, halo, or cyano.

[0712] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0713] In certain embodiments, R^8 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^8 represents independently for each occurrence C_{3-6} cycloalkyl, phenyl, or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^8 represents independently for each occurrence phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0714] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^8 is $-OCF_3$. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^8 is methoxy. In certain embodiments, R^8 represents independently for each occurrence $-N(R^4)(R^5)$. In certain embodiments, R^8 is $-NH_2$. In certain embodiments, R^8 is hydroxyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^8 is methyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^8 is trifluoromethyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence halo. In certain embodiments, R^8 is fluoro. In certain embodiments, R^8 is cyano. In certain embodiments, R^8 represents independently for each occurrence $-S(O)_2-(C_{1-6}$ alkyl).

[0715] In certain embodiments, R^8 represents independently for each occurrence C_{3-6} cycloalkyl. In certain embodiments, R^8 is phenyl. In certain embodiments, R^8 represents independently for each occurrence a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R^8 represents independently for each occurrence a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0716] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo. In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0717] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo.

[0718] In certain embodiments, R^8 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0719] As defined generally above, X is -C(O)-, -S(O)-, or $-S(O)_2-$. In certain embodiments, X is -C(O)-. In certain embodiments, X is -S(O)- or $-S(O)_2-$. In certain embodiments, X is -

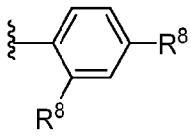
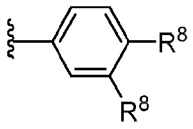
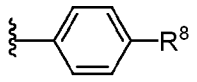
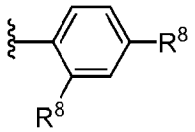
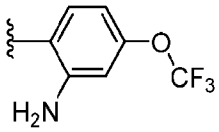
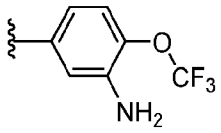
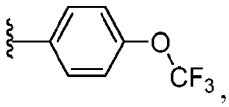
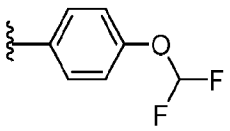
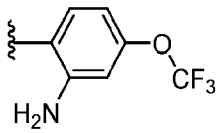
S(O)-. In certain embodiments, X is -$S(O)_2$-. In certain embodiments, X is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0720] As defined generally above, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

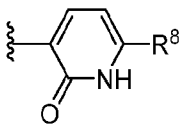
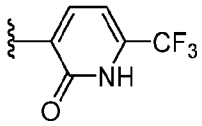
[0721] In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

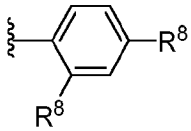
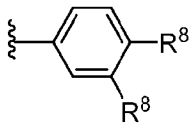
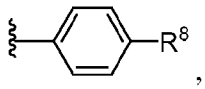
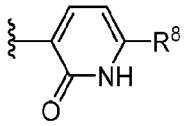
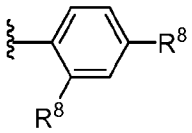
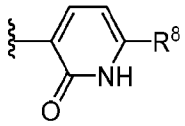
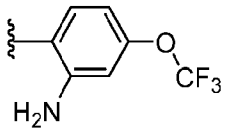
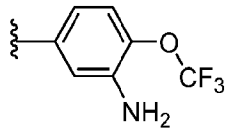
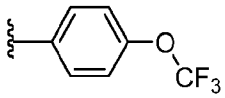
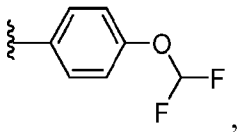
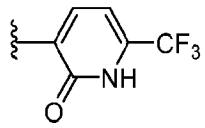
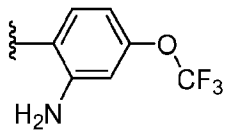
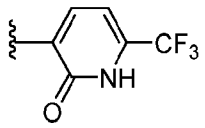
[0722] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-6 membered

monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

[0723] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^8. In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  .

[0724] In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic partially unsaturated oxo-heterocyclyl having 1 or 2 nitrogen atoms; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8. In certain embodiments, A^1 is pyridin-2(1*H*)-on-3-yl substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is

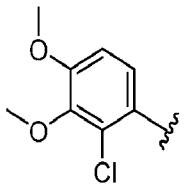
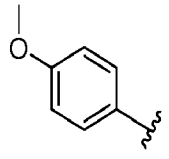
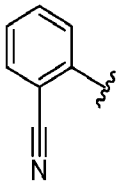
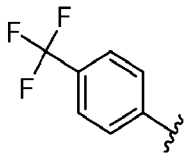
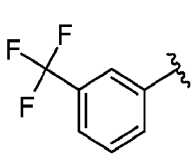
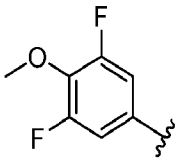
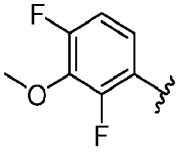
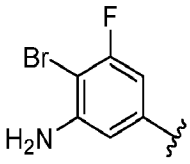
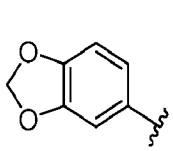
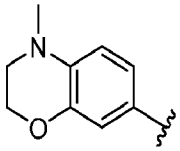
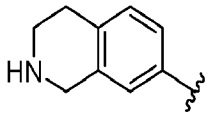
substituted with m occurrences of R^8. In certain embodiments, A^1 is  . In certain embodiments, A^1 is  .

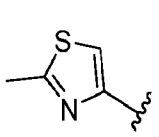
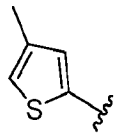
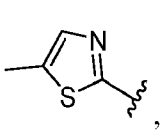
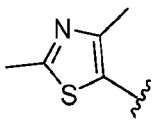
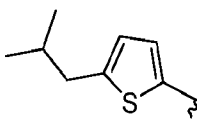
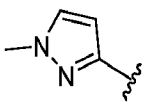
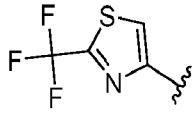
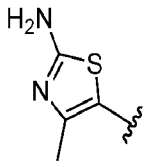
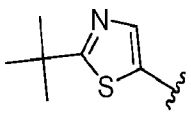
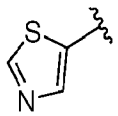
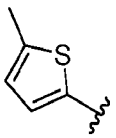
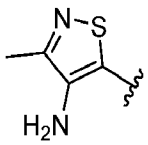
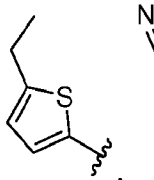
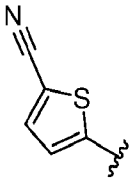
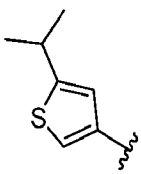
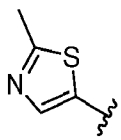
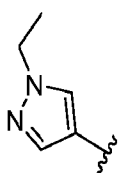
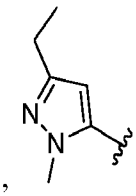
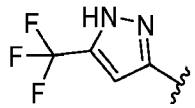
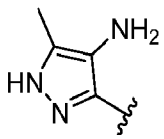
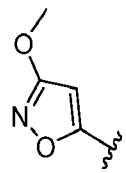
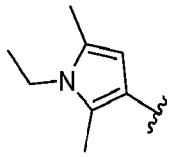
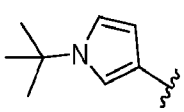
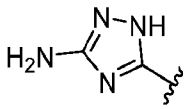
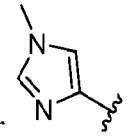
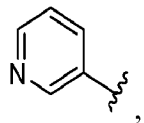
[0725] In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  or  . In certain embodiments, A^1 is  ,  ,  ,  ,  , or  or  .

[0726] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8.

[0727] In certain embodiments, A^1 is naphthyl substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is an 8-10 membered bicyclic

heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8.

[0728] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  , or  . In certain embodiments, A^1 is one of the following:  ,  , or  .

[0729] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . 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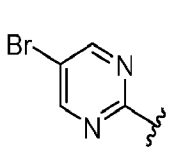
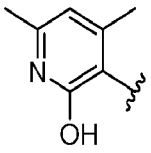
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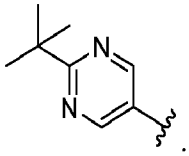
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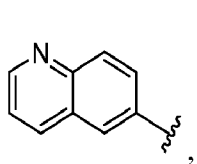
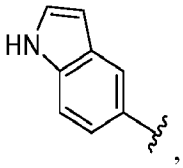
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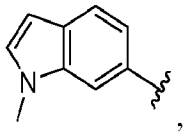
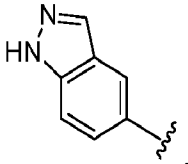
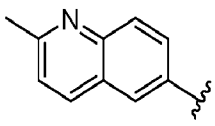
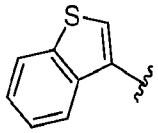
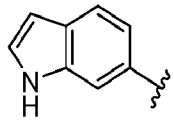
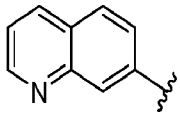
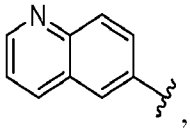
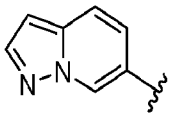
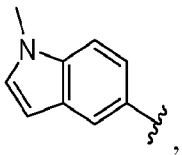
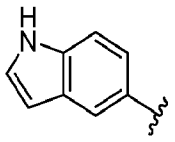
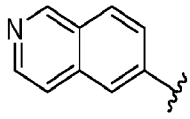
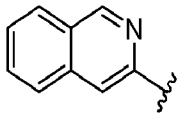
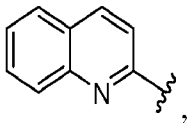
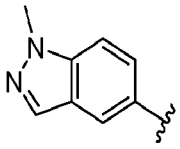
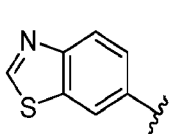
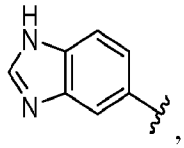
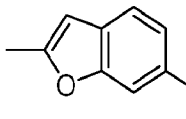
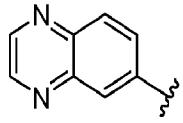
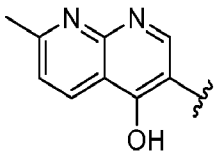
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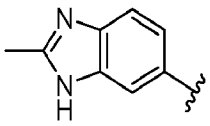
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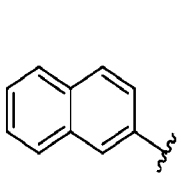
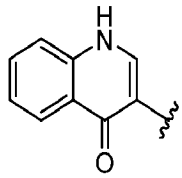
[0731] In certain embodiments, A^1 is one of the following:


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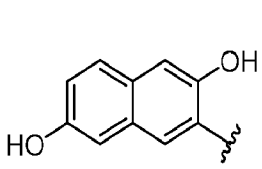
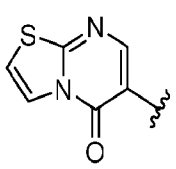
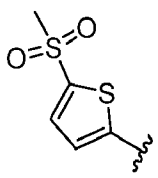
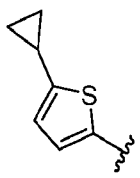
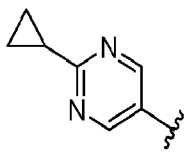
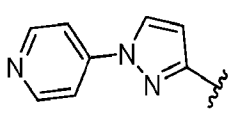
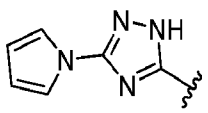
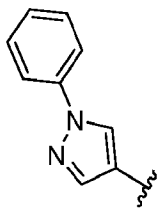
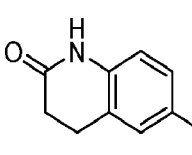
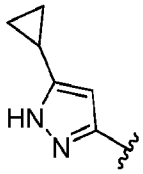
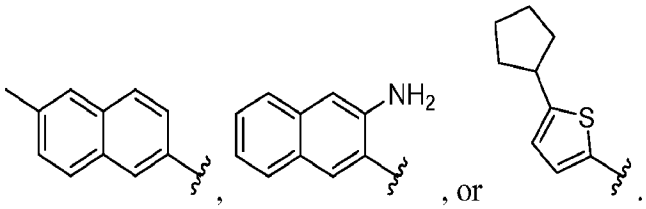













, , or .

[0732] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0733] As defined generally above, n is 1 or 2. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is selected from the values represented in the compounds in Tables A-1, A-2, and A-3, below.

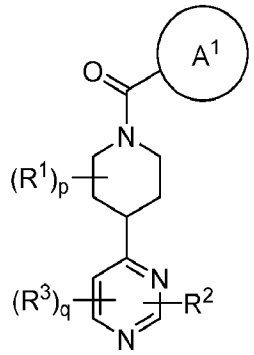
[0734] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Tables A-1, A-2, and A-3, below.

[0735] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 0 or 1. In certain embodiments, p is 1 or 2. In certain embodiments, p is selected from the values represented in the compounds in Tables A-1, A-2, and A-3, below.

[0736] As defined generally above, q is 0, 1, or 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. n certain embodiments, q is 0 or 1. In certain embodiments, q is 1 or 2. In certain embodiments, q is selected from the values represented in the compounds in Tables A-1, A-2, and A-3, below.

[0737] The description above describes multiple embodiments relating to compounds of Formula I-1. The patent application specifically contemplates all combinations of the embodiments.

[0738] Another aspect of the invention provides a compound represented by Formula I-A1:



(I-A1)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^2 is -N(H)C(O)(C_{1-6} alkyl) or -N(H)(R^7);

R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl;

R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic

heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

m is 0, 1, 2, or 3; and

p and q are each independently 0, 1, or 2.

[0739] The definitions of variables in Formula I-A1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0740] In certain embodiments, the compound is a compound of Formula I-A1.

[0741] As defined generally above, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

[0742] In certain embodiments, R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl or C_{1-4} haloalkyl.

[0743] In certain embodiments, R^1 is hydroxyl. In certain embodiments, R^1 is hydroxyl attached at the 4-position of the piperidine ring. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^1 is trifluoromethyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} hydroxyalkyl. In certain embodiments, R^1 is $-CH_2OH$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^1 is methoxy. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^1 is $-OCF_3$.

[0744] In certain embodiments, R^1 is selected from the groups depicted in the compounds in Tables A-1 and A-2, below.

[0745] As defined generally above, R^2 is -N(H)C(O)(C_{1-6} alkyl) or -N(H)(R^7). In certain embodiments, R^2 is -N(H)C(O)(C_{1-6} alkyl). In certain embodiments, R^2 is -N(H)C(O)(C_{1-4} alkyl). In certain embodiments, R^2 is -N(H)C(O)CH_3. In certain embodiments, R^2 is -N(H)(R^7).

[0746] In certain embodiments, R^2 is attached at the 2-position of the pyrimidine. In certain embodiments, R^2 is attached at the 4-position of the pyrimidine.

[0747] In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table A-2, below.

[0748] As defined generally above, R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

[0749] In certain embodiments, R^3 represents independently for each occurrence halo. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} haloalkoxyl. In certain embodiments, R^3 is –OCF_3. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0750] As defined generally above, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 and R^5 are hydrogen. In certain embodiments, R^4 and R^5 each represent independently for each occurrence C_{1-4} alkyl.

[0751] In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 5-6 membered saturated ring having one nitrogen atom. In certain embodiments, R^4 and R^5 are selected from the groups depicted in the compounds in Tables A-1 and A-2, below.

[0752] In certain embodiments, R^4 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Tables A-1 and A-2, below.

[0753] In certain embodiments, R^5 represents independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Tables A-1 and A-2, below.

[0754] As defined generally above, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-6} alkyl or C_{3-6} cycloalkyl.

[0755] In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl; wherein said phenyl is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is C_{3-6} cycloalkyl or phenyl.

[0756] In certain embodiments, R^7 is C_{1-6} alkyl. In certain embodiments, R^7 is C_{1-4} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 is C_{3-6} cycloalkyl. In certain embodiments, R^7 is cyclopropyl. In certain embodiments, R^7 is C_{1-6} haloalkyl. In certain embodiments, R^7 is C_{1-4} haloalkyl. In certain embodiments, R^7 is trifluoromethyl.

[0757] In certain embodiments, R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano. In certain embodiments, R^7 is phenyl.

[0758] In certain embodiments, R^7 is selected from the groups depicted in the compounds in Tables A-1, A-2, and A-3, below.

[0759] As defined generally above, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0760] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0761] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, or C_{1-6} alkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, -$N(R^4)(R^5)$, C_{1-6} haloalkyl, or halo. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^4)(R^5)$. In certain embodiments, R^8 represents independently for each occurrence $–OCF_3$, $–NH_2$, $–CF_3$, fluoro, or chloro. In certain embodiments, R^8 represents independently for each occurrence $–OCF_3$ or $–NH_2$.

[0762] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, halo, or cyano. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, or hydroxyl. In certain embodiments, R^8 represents independently for each occurrence -$N(R^4)(R^5)$, halo, or cyano.

[0763] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl or C_{1-6} haloalkyl.

[0764] In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkoxyl. In certain embodiments, R^8 is $-OCF_3$. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkoxyl. In certain embodiments, R^8 is methoxy. In certain embodiments, R^8 represents independently for each occurrence $-N(R^4)(R^5)$. In certain embodiments, R^8 is $-NH_2$. In certain embodiments, R^8 is hydroxyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} alkyl. In certain embodiments, R^8 is methyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} haloalkyl. In certain embodiments, R^8 is trifluoromethyl. In certain embodiments, R^8 represents independently for each occurrence C_{1-6} hydroxyalkyl. In certain embodiments, R^8 represents independently for each occurrence halo. In certain embodiments, R^8 is fluoro. In certain embodiments, R^8 is cyano.

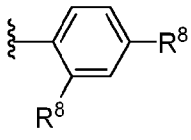
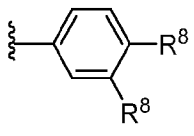
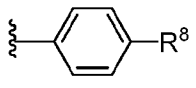
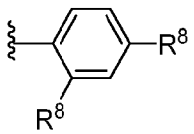
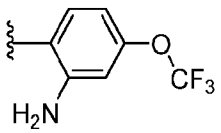
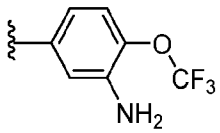
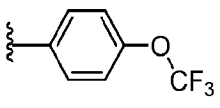
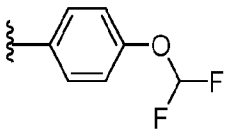
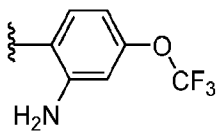
[0765] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0766] In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl. In certain embodiments, two occurrences of R^8 are taken together with the intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl.

[0767] In certain embodiments, R^8 is selected from the groups depicted in the compounds in Tables A-1 and A-2, below.

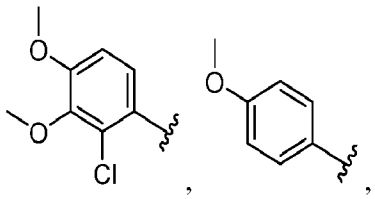
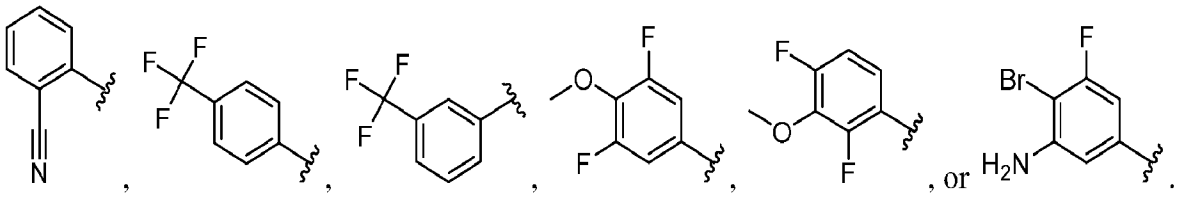
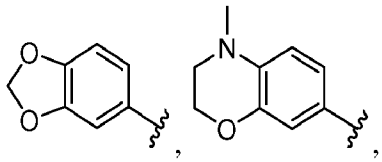
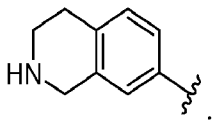
[0768] As defined generally above, A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

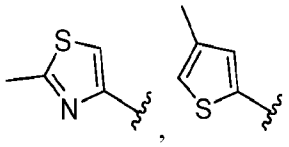
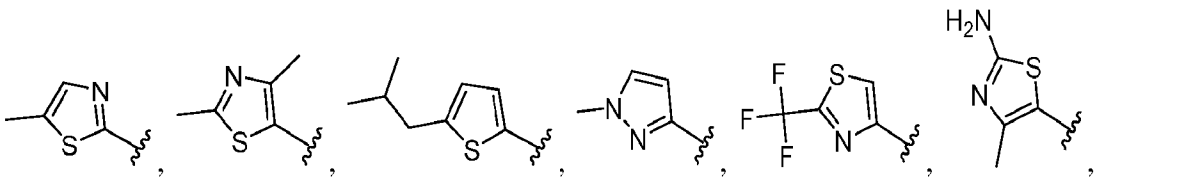
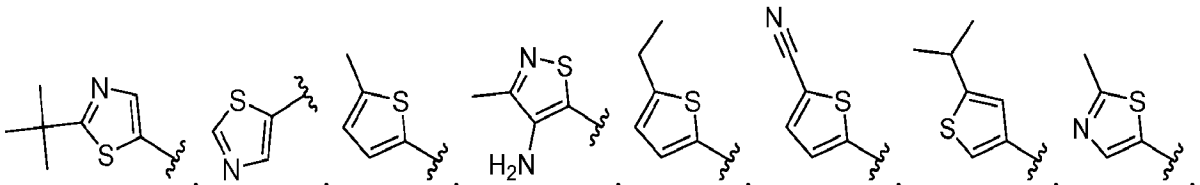
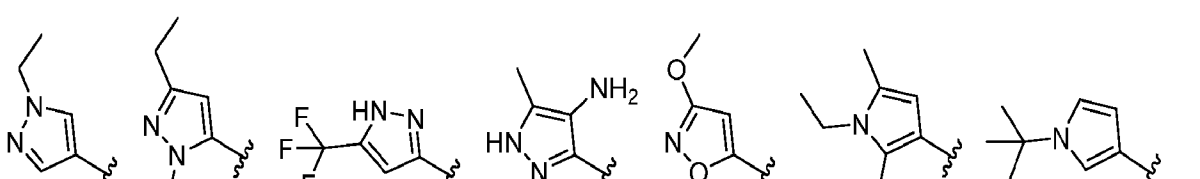
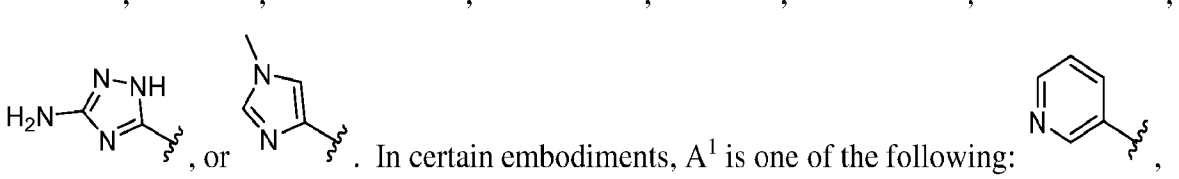
[0769] In certain embodiments, A^1 is phenyl or a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

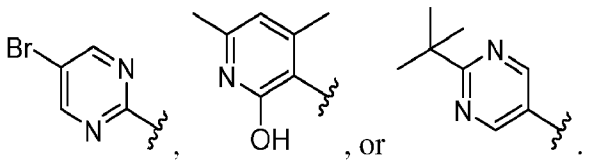
[0770] In certain embodiments, A^1 is phenyl substituted with m occurrences of R^8. In certain embodiments, A^1 is  ,  , or  . In certain embodiments, A^1 is  . In certain embodiments, A^1 is  ,  ,  , or  . In certain embodiments, A^1 is  .

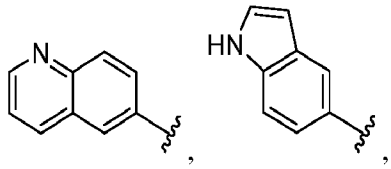
[0771] In certain embodiments, A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is a 6-membered monocyclic heteroaryl having one or two nitrogen atoms; which is substituted with m occurrences of R^8. In certain embodiments, A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms

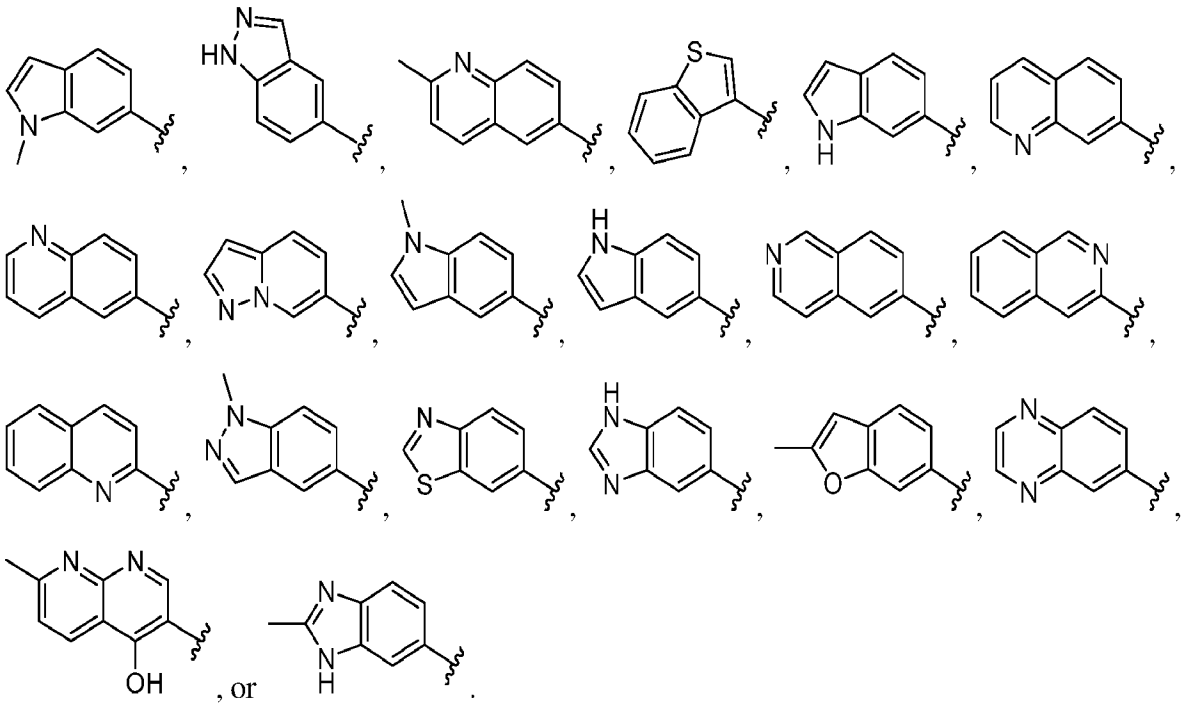
independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^8.

[0772] In certain embodiments, A^1 is one of the following:  ,  , or . In certain embodiments, A^1 is one of the following:  , or  .

[0773] In certain embodiments, A^1 is one of the following:  ,  ,  ,  ,  , or . In certain embodiments, A^1 is one of the following: ,



[0774] In certain embodiments, A^1 is one of the following: 



[0775] In certain embodiments, A^1 is selected from the groups depicted in the compounds in Tables A-1 and A-2, below.

[0776] As defined generally above, m is 0, 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 2 or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 1, 2, or 3. In certain embodiments, m is selected from the values represented in the compounds in Tables A-1 and A-2, below.

[0777] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 0 or 1. In

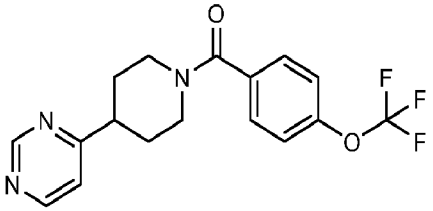
certain embodiments, p is 1 or 2. In certain embodiments, p is selected from the values represented in the compounds in Tables A-1 and A-2, below.

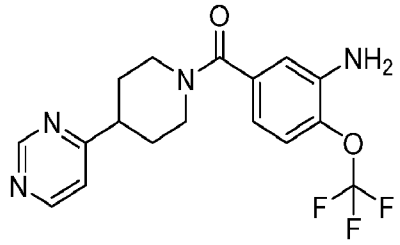
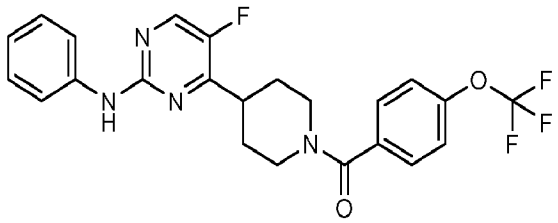
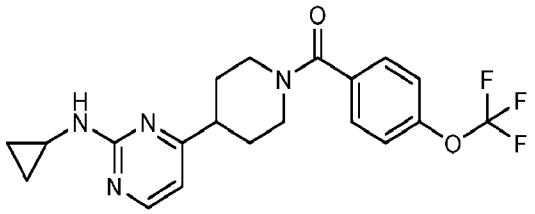
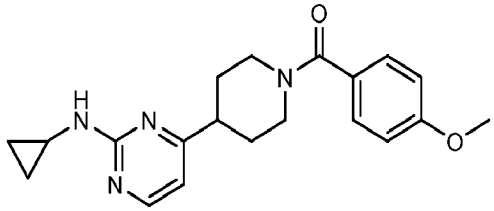
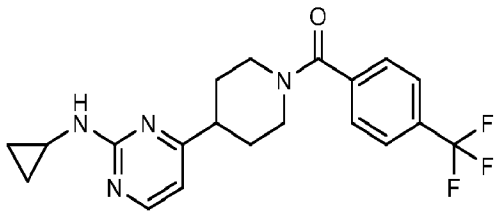
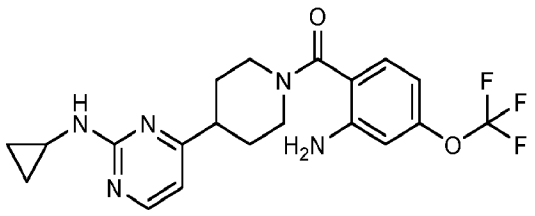
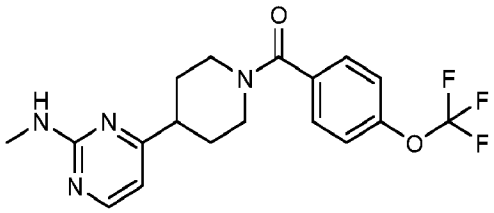
[0778] As defined generally above, q is 0, 1, or 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. n certain embodiments, q is 0 or 1. In certain embodiments, q is 1 or 2. In certain embodiments, q is selected from the values represented in the compounds in Tables A-1 and A-2, below.

[0779] The description above describes multiple embodiments relating to compounds of Formula I-A1. The patent application specifically contemplates all combinations of the embodiments.

[0780] In certain embodiments, the compound is a compound in Table A-1, A-1-A, A-2, or A-3 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table A-1, A-1-A, A-2, or A-3, below. In certain embodiments, the compound is a compound in Table A-1, A-2, or A-3 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table A-1, A-2, or A-3, below. In certain embodiments, the compound is a compound in Table A-1 or A-2 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table A-1 or A-2 below. In certain embodiments, the compound is a compound in Table A-1 or A-1-A below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table A-1 or A-1-A below. In certain embodiments, the compound is a compound in Table A-1 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table A-1 below.

TABLE A-1.

Compound No.	Chemical Structure
I-A-1	

Compound No.	Chemical Structure
I-A-2	
I-A-3	
I-A-4	
I-A-5	
I-A-6	
I-A-7	
I-A-8	

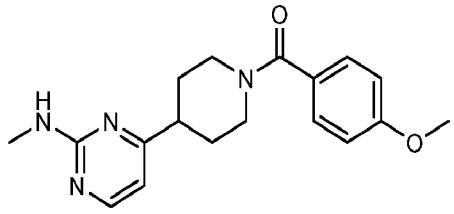
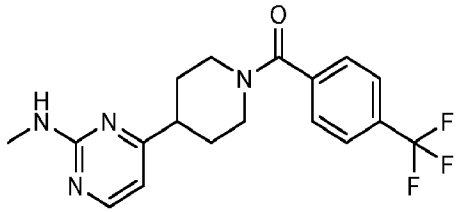
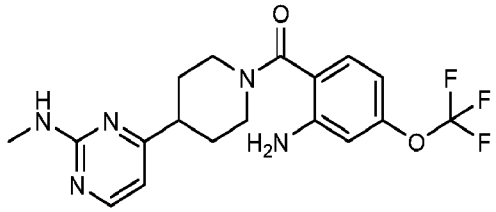
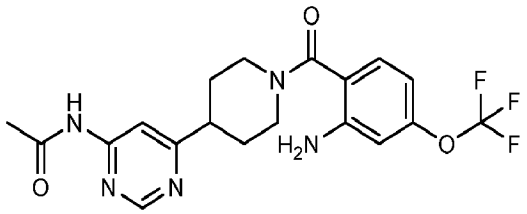
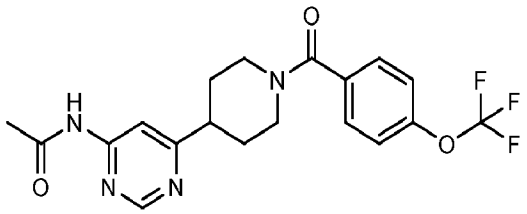
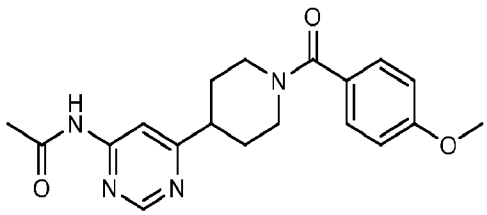
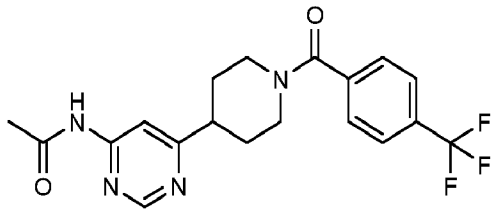
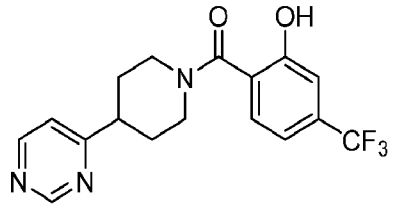
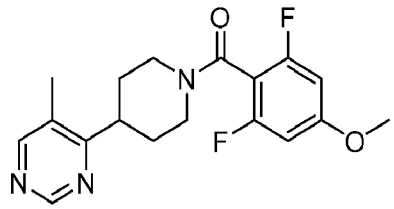
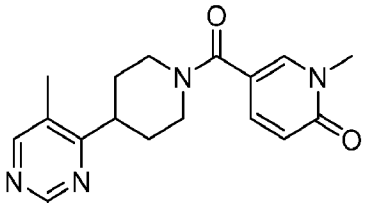
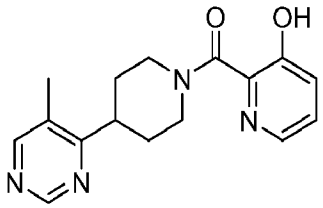
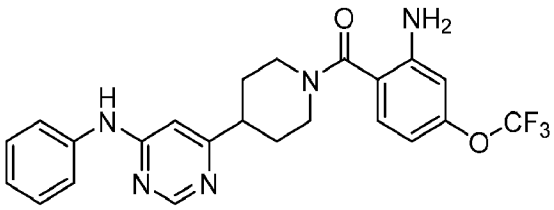
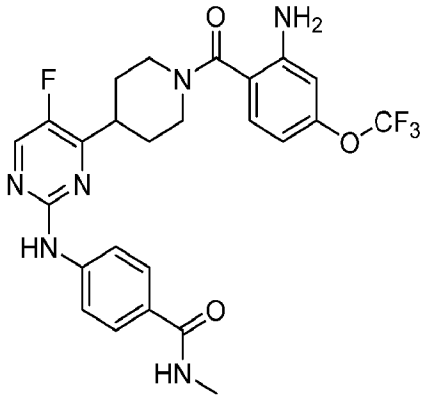
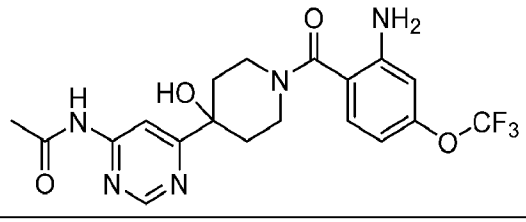
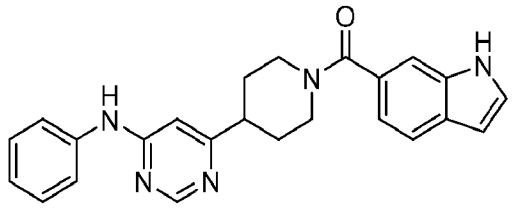
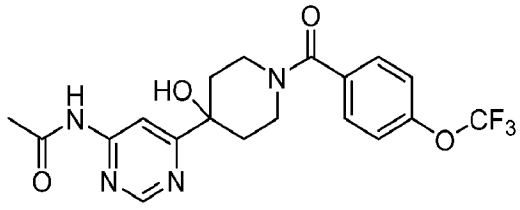
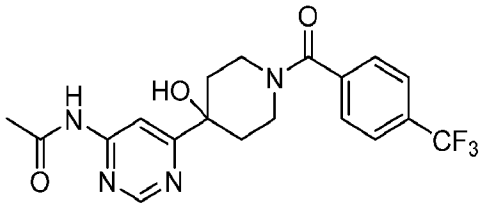
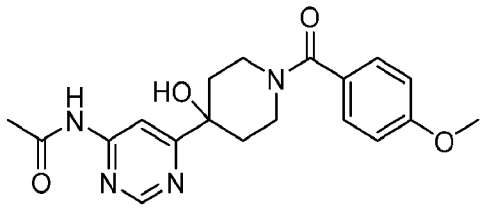
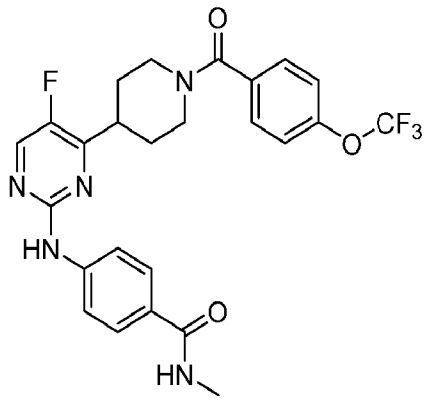
Compound No.	Chemical Structure
I-A-9	
I-A-10	
I-A-11	
I-A-12	
I-A-13	
I-A-14	
I-A-15	

TABLE A-1-A.

Compound No.	Chemical Structure
I-A-16	
I-A-17	
I-A-18	
I-A-19	
I-A-20	
I-A-21	

Compound No.	Chemical Structure
I-A-22	
I-A-23	
I-A-24	
I-A-25	
I-A-26	
I-A-27	

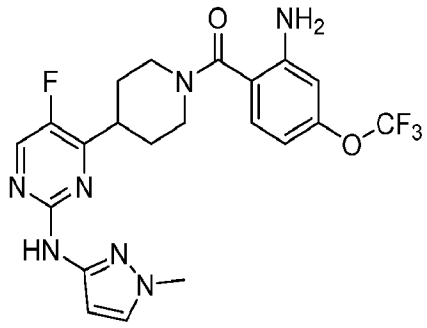
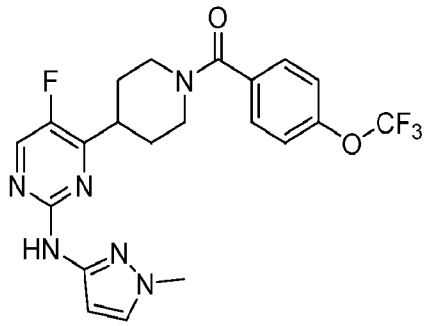
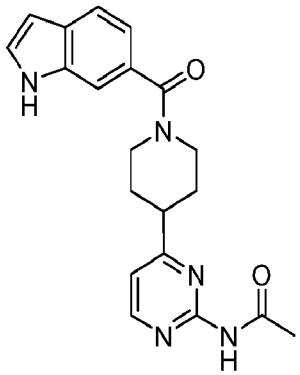
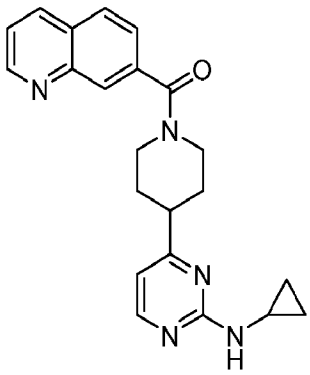
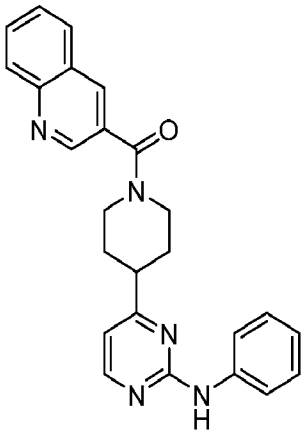
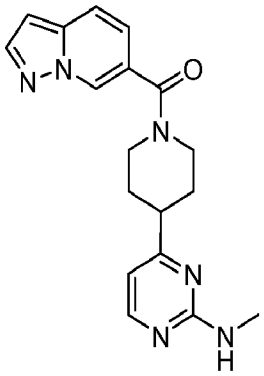
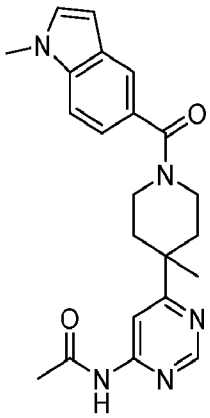
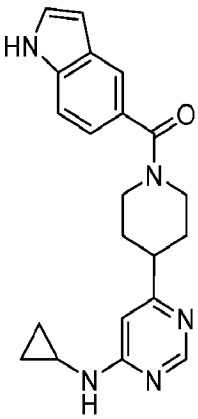
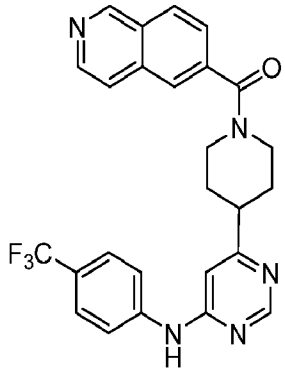
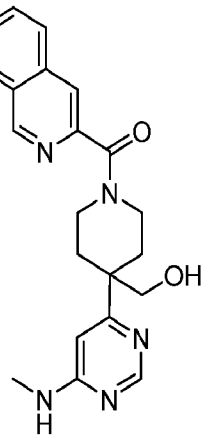
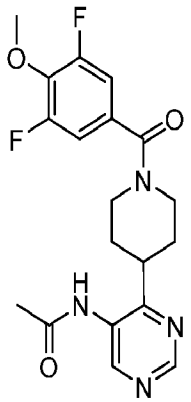
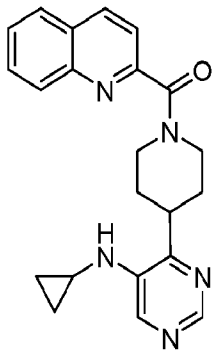
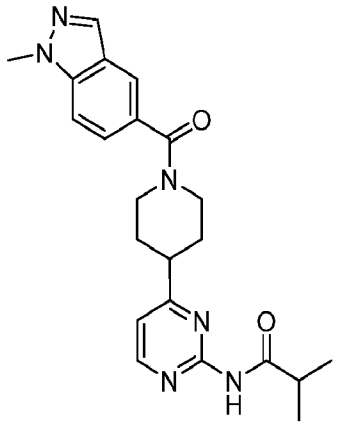
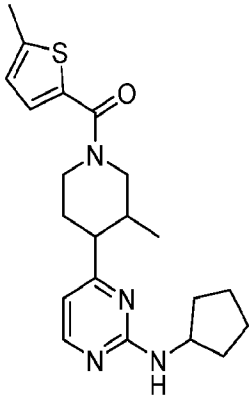
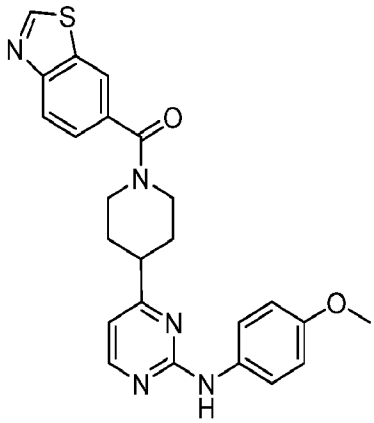
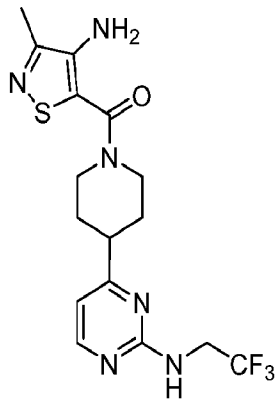
Compound No.	Chemical Structure
I-A-28	
I-A-29	

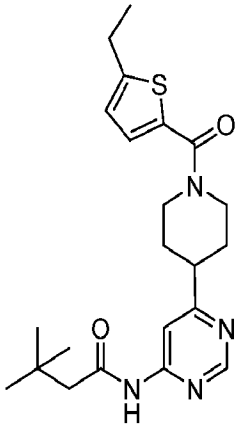
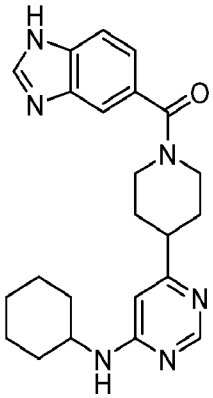
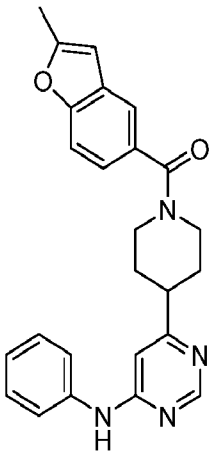
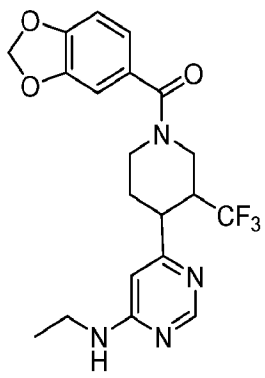
TABLE A-2.

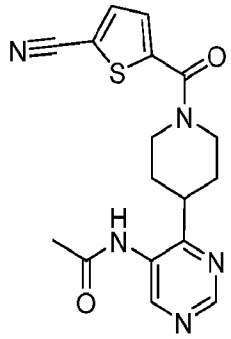
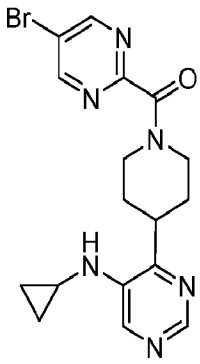
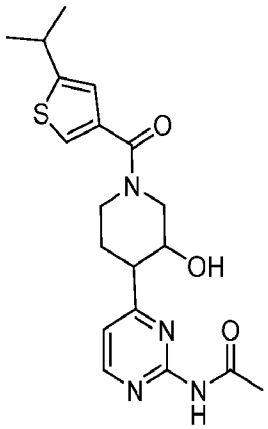
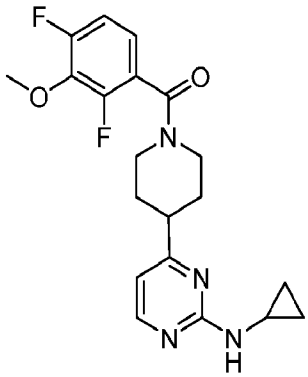
Compound No.	Chemical Structure
II-A-1	
II-A-2	

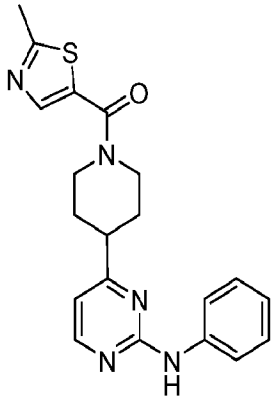
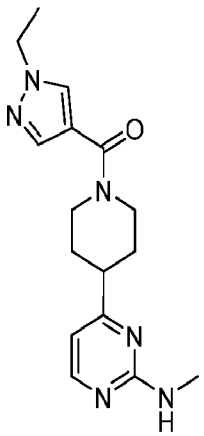
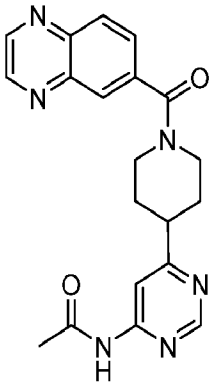
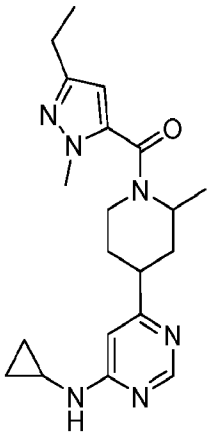
Compound No.	Chemical Structure
II-A-3	
II-A-4	
II-A-5	
II-A-6	

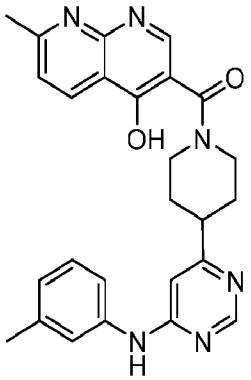
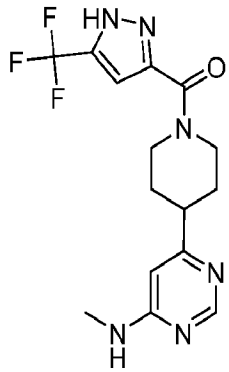
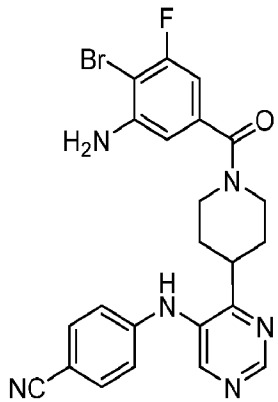
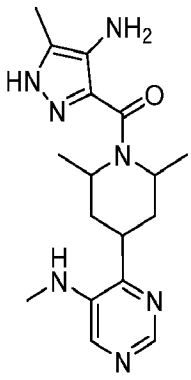
Compound No.	Chemical Structure
II-A-7	
II-A-8	
II-A-9	
II-A-10	

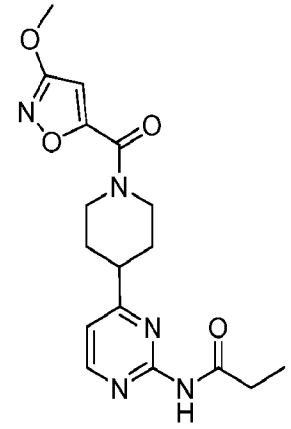
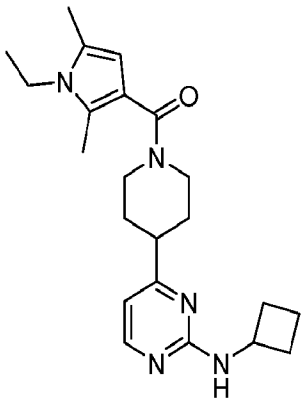
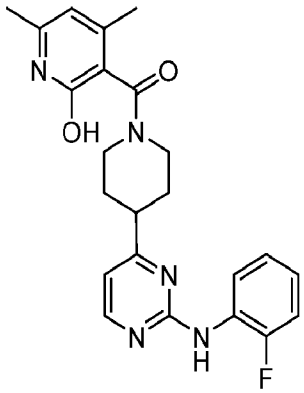
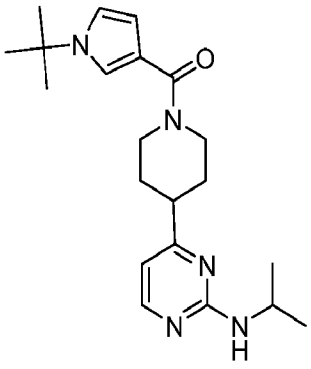
Compound No.	Chemical Structure
II-A-11	
II-A-12	
II-A-13	
II-A-14	

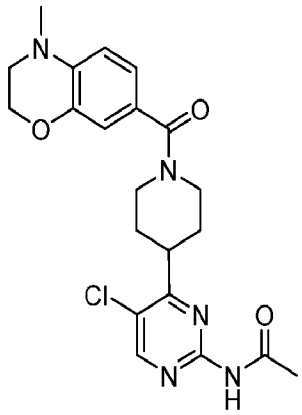
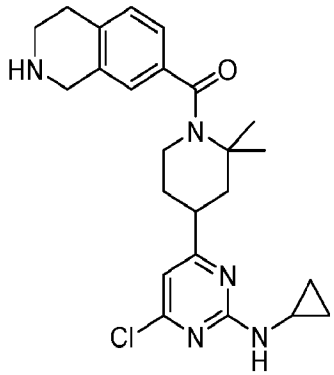
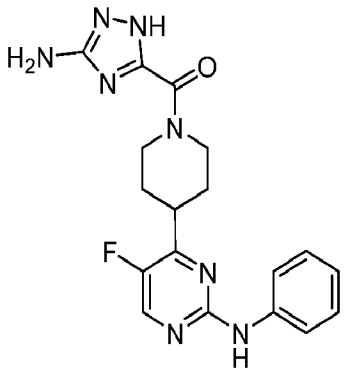
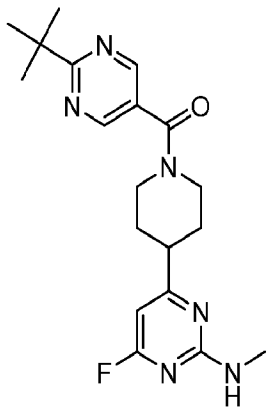
Compound No.	Chemical Structure
II-A-15	
II-A-16	
II-A-17	
II-A-18	

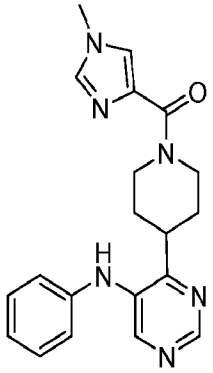
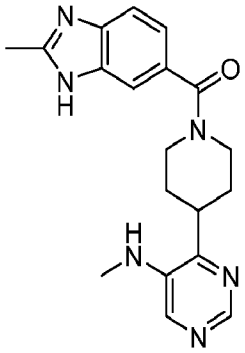
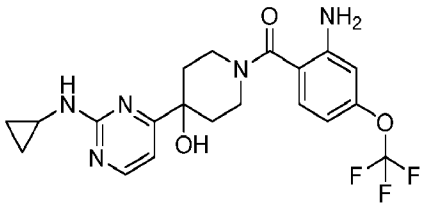
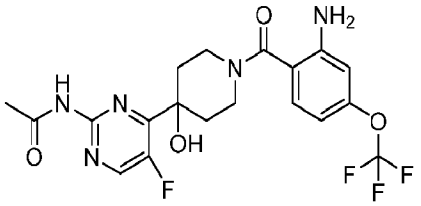
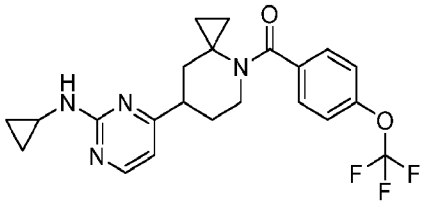
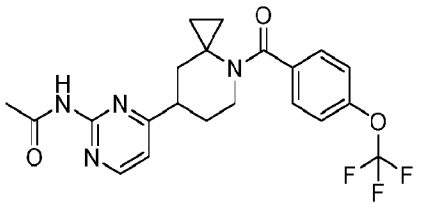
Compound No.	Chemical Structure
II-A-19	
II-A-20	
II-A-21	
II-A-22	

Compound No.	Chemical Structure
II-A-23	
II-A-24	
II-A-25	
II-A-26	

Compound No.	Chemical Structure
II-A-27	
II-A-28	
II-A-29	
II-A-30	

Compound No.	Chemical Structure
II-A-31	
II-A-32	
II-A-33	
II-A-34	

Compound No.	Chemical Structure
II-A-35	
II-A-36	
II-A-37	
II-A-38	

Compound No.	Chemical Structure
II-A-39	
II-A-40	
II-A-41	
II-A-42	
II-A-43	
II-A-44	

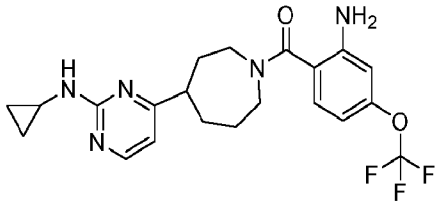
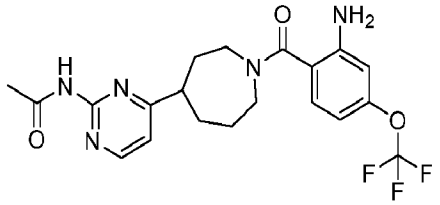
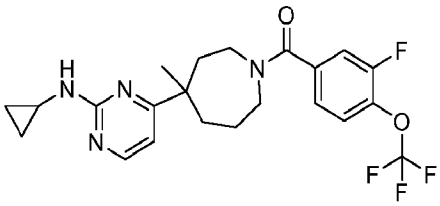
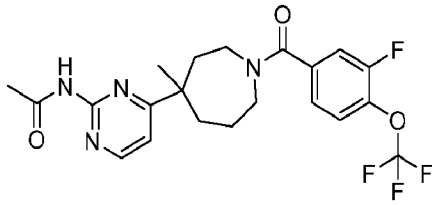
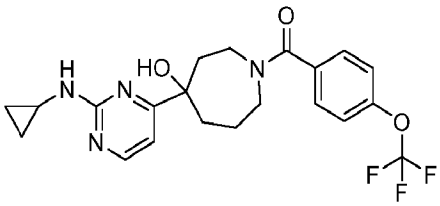
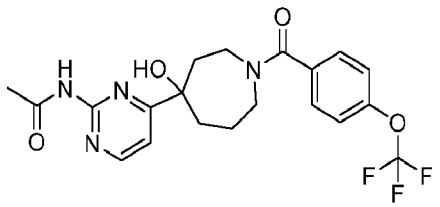
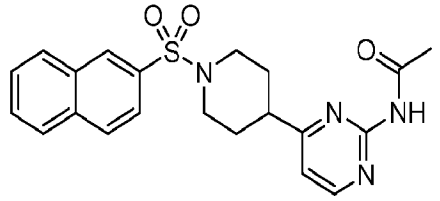
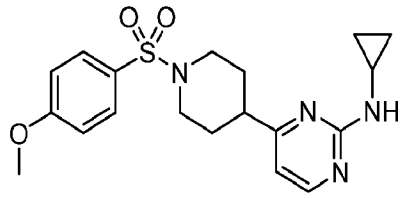
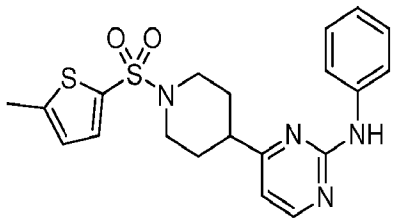
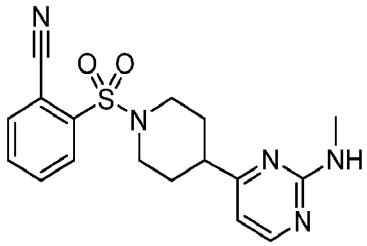
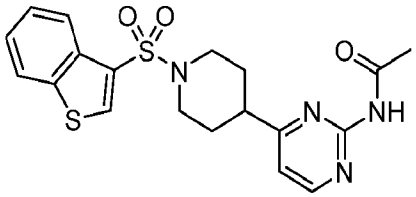
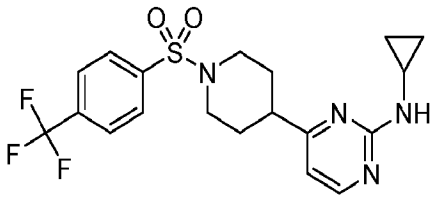
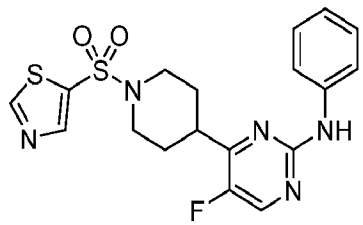
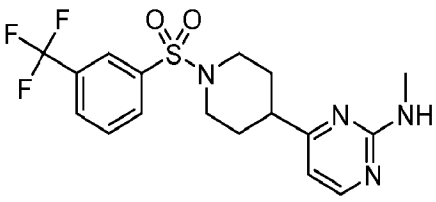
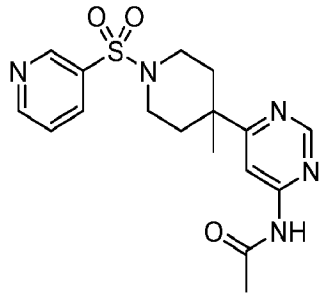
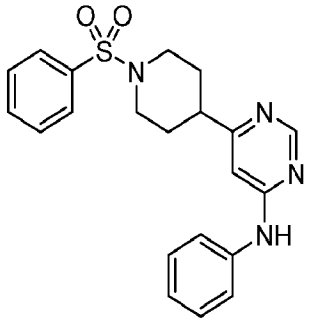
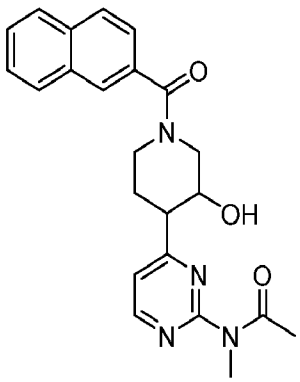
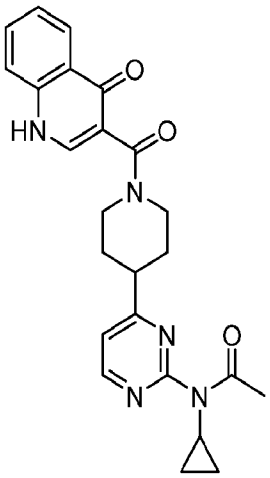
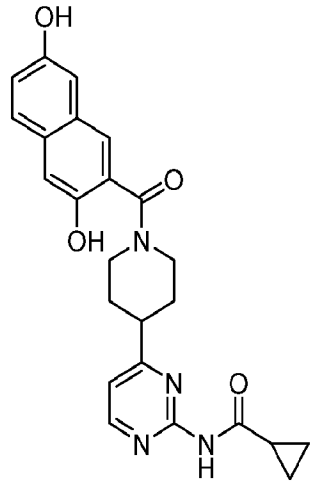
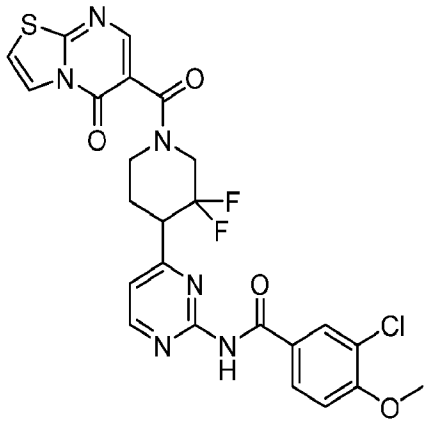
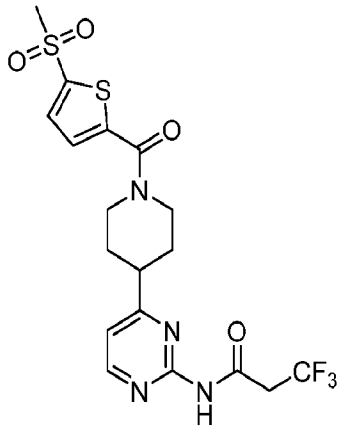
Compound No.	Chemical Structure
II-A-45	
II-A-46	
II-A-47	
II-A-48	
II-A-49	
II-A-50	

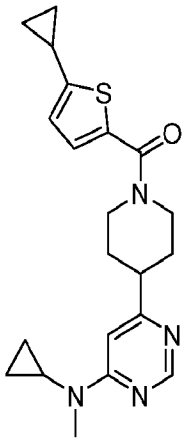
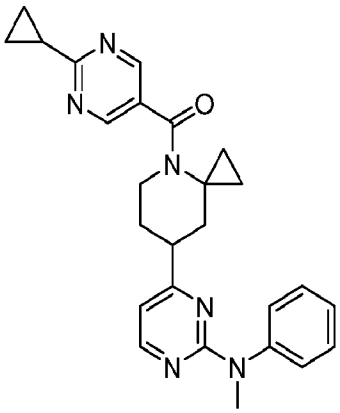
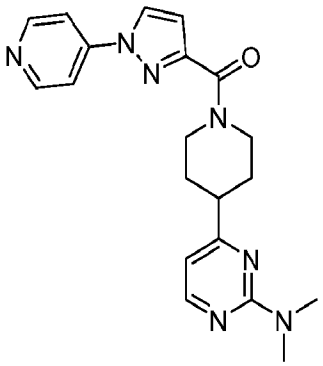
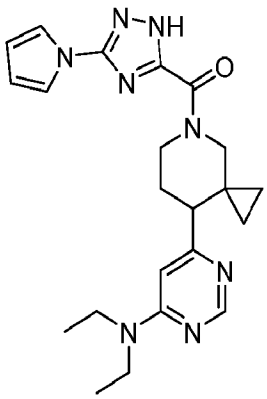
TABLE A-3.

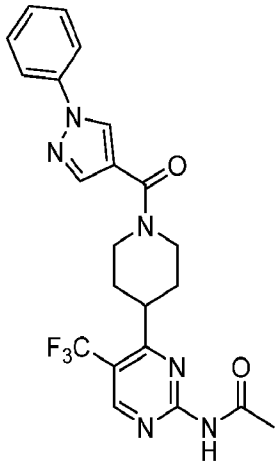
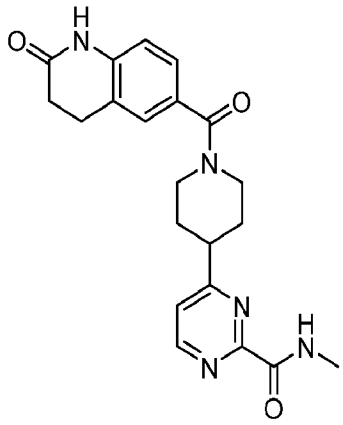
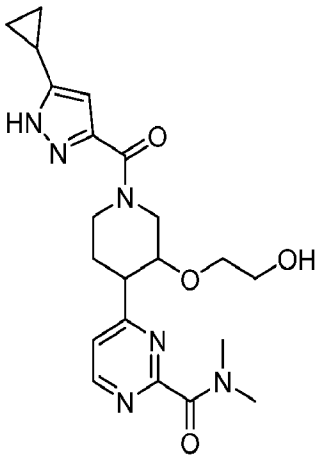
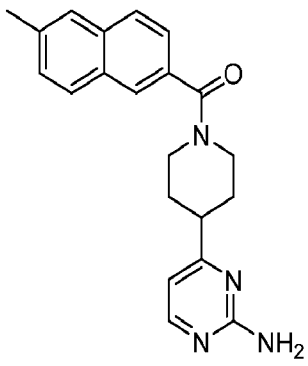
Compound No.	Chemical Structure
III-A-1	

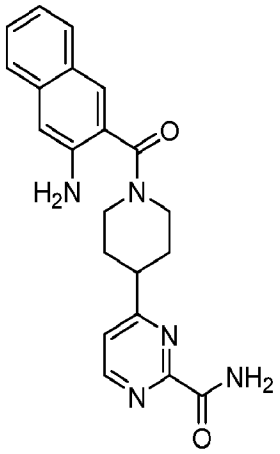
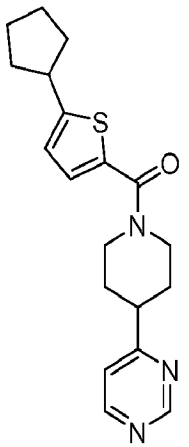
Compound No.	Chemical Structure
III-A-2	
III-A-3	
III-A-4	
III-A-5	
III-A-6	
III-A-7	
III-A-8	

Compound No.	Chemical Structure
III-A-9	
III-A-10	
III-A-11	
III-A-12	

Compound No.	Chemical Structure
III-A-13	
III-A-14	
III-A-15	

Compound No.	Chemical Structure
III-A-16	
III-A-17	
III-A-18	
III-A-19	

Compound No.	Chemical Structure
III-A-20	
III-A-21	
III-A-22	
III-A-23	

Compound No.	Chemical Structure
III-A-24	
III-A-25	

[0781] Compounds may be further characterized according to their inhibitory activity against ERK5. In certain embodiments, a preferred compound has an IC_{50} less than 2 μM against ERK5. In certain embodiments, a more preferred compound has an IC_{50} less than 0.5 μM against ERK5. In certain embodiments, an even more preferred compound has an IC_{50} less than or equal to 0.05 μM against ERK5.

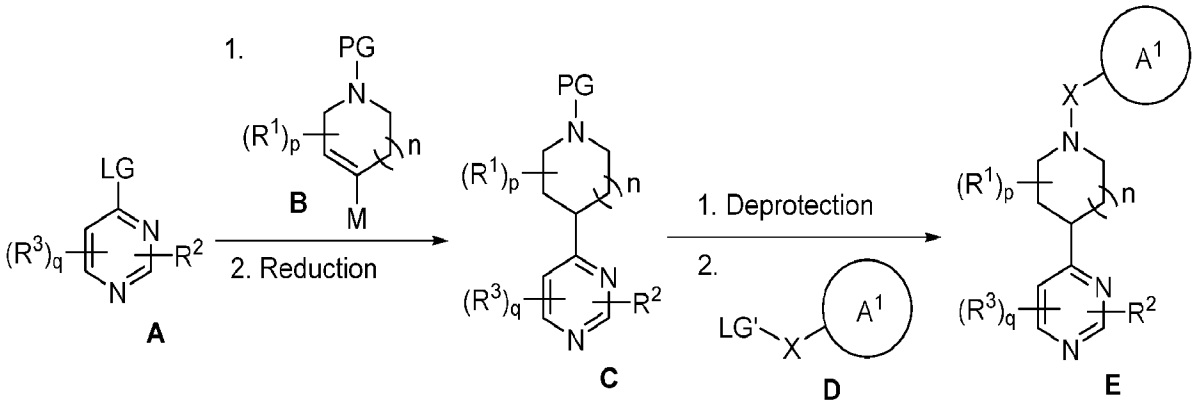
[0782] Methods for preparing compounds described herein are illustrated in the following synthetic Schemes, and in the Examples below. The Schemes are given for the purpose of illustrating the invention, and are not intended to limit the scope or spirit of the invention. Starting materials shown in the Schemes can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[0783] In the Schemes, it is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be

apparent to one skilled in the art, and alternate methods are therefore indicated (for example, use of protecting groups or alternative reactions). Protecting group chemistry and strategy is well known in the art, for example, as described in detail in "Protecting Groups in Organic Synthesis", T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entire contents of which are hereby incorporated by reference.

[0784] The synthetic route illustrated in Scheme 1-A is a general method for preparing substituted 4-piperidinyl-pyrimidine-2-amines and related compounds **E**. Transition-metal-mediated coupling of pyrimidine **A** (wherein LG is a leaving group, such as bromide, chloride, or a sulfonate) with cyclic metal reagent **B** (wherein M is a metal, such as a boronic acid or ester, or a trialkylstannane; and PG is a protecting group, such as Boc), followed by reduction (using, for example, hydrogen and a transition-metal catalyst, such as Pd on carbon), affords protected 4-piperidinyl-pyrimidine **C**. Deprotection (using, for example, an acid, such as HCl or TFA, when PG is Boc), followed by coupling with cyclic compound **D** (wherein LG' is a leaving group, such as a halide, or a hydroxyl group that can be activated using, for example, an amide coupling reagent, such as HATU), affords substituted 4-piperidinyl-pyrimidine-2-amines and related compounds **E**.

SCHEME 1-A.



[0785] The modular synthetic route illustrated in Scheme 1-A can also be readily modified by one of skill in the art to provide additional substituted 4-piperidinyl-pyrimidine-2-amines and related compounds by conducting functional group transformations on the intermediate and final compounds. Such functional group transformations are well known in the art, as described in, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992). For example, the alkene functional group in the coupling product of pyrimidine **A** with cyclic

metal reagent **B** can be oxidized, instead of reduced, to afford, for example, an alcohol (using, for example, Mukaiyama hydration conditions) or a 1,2-diol (using, for example, OsO_4 and a stoichiometric oxidant, such as NMO). The resulting alcohol(s) can be further functionalized, for example, by alkylation (using, for example, a base, such as NaH, and an electrophile, such as an alkyl halide).

II. Therapeutic Applications of Substituted 4-Piperidinyl-quinazolines, 4-Piperidinyl-pyrimidine-2-amines, and Related Compounds

[0786] It is contemplated that the substituted 4-piperidinyl-quinazolines, 4-piperidinyl-pyrimidine-2-amines, and related compounds described herein, such as the compounds in Section I and I-A, provide therapeutic benefits to subjects suffering from cancer and other disorders. Accordingly, one aspect of the invention provides a method of treating a disorder mediated by ERK5 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II in Section I or a compound of Formula I in Section I-A, to a subject in need thereof to treat the disorder. In certain embodiments, the particular compound of Formula I or II in Section I is a compound defined by one of the embodiments described above. In certain embodiments, the particular compound of Formula I, I-A, I-1, or I-A1 in Section I-A, is a compound defined by one of the embodiments described above.

[0787] It is contemplated that the substituted 4-piperidinyl-quinazolines and related compounds described herein, such as a compound of Formula I or II, or other compounds in Section I, provide therapeutic benefits to subjects suffering from cancer and other disorders. Accordingly, one aspect of the invention provides a method of treating a disorder mediated by ERK5 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II in Section I, to a subject in need thereof to treat the disorder. In certain embodiments, the particular compound of Formula I or II in Section I is a compound defined by one of the embodiments described above. In certain embodiments, the compound is a compound of Formula III in Section I defined by one of the embodiments described above.

[0788] It is contemplated that the substituted 4-piperidinyl-pyrimidine-2-amines and related compounds described herein, such as a compound of Formula I, or other compounds in Section

I-A, provide therapeutic benefits to subjects suffering from cancer and other disorders. Accordingly, one aspect of the invention provides a method of treating a disorder mediated by ERK5 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I in Section I-A, to a subject in need thereof to treat the disorder. In certain embodiments, the particular compound of Formula I, I-A, I-1, or I-A1 in Section I-A, is a compound defined by one of the embodiments described above.

[0789] The provided compounds are inhibitors of ERK5 and are therefore useful for treating one or more disorders associated with activity of ERK5. Thus, in certain aspects and embodiments, the present invention provides a method for treating an ERK5-mediated disorder comprising the step of administering to a patient in need thereof a therapeutically effective compound of the present invention, or pharmaceutically acceptable composition thereof.

[0790] As used herein, the term "ERK5-mediated" disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which ERK5, or a variant or mutant thereof, is known to play a role. Accordingly, another aspect or embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which ERK5, or a variant or mutant thereof, are known to play a role.

[0791] In some aspects and embodiments, provided herein are methods of treating, reducing the severity of, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof of a disease or disorder characterized by or associated with increased ERK5 expression and/or increased ERK5 activity, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable composition thereof. In some aspects and embodiments, provided herein are methods of treating, reducing the severity of, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof of a disease or disorder in which inhibition or antagonizing of ERK5 activity is beneficial, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable composition thereof.

[0792] Without wishing to be bound by theory, inhibitor compounds described herein are believed to bind to and inhibit ERK5, leading to reduced translocation of ERK5 to the cell's nucleus and/or reduction of ERK5-mediated gene transcription in the nucleus. The mitogen-activated protein kinases (MAPK) are a group of proteins able to translate environmental signals elicited by a plethora of stimuli, including growth factors and stresses, into different biological responses such as survival, apoptosis, proliferation, migration, and differentiation. The importance of MAPK is underlined by the abnormal signaling conveyed by members of the MAPK family in several human diseases, including Parkinson's disease, inflammatory disorders, and cancer (see, for example, Kim, E.K.; Choi, E.J. *Biochim. Biophys. Acta* (2010), 1802, 396–405; and Kim, S.C. *et al. Blood* (1999) 93, 3893–3899). In mammals, there are more than a dozen MAPK enzymes (Braicu, C. *et al. Cancers* (2019) Cancers (Basel). 11(10):1618). Extracellular signal-regulated kinase 5 (ERK5, also known as Big MAPK 1, BMK1) is a member of this family, and consists of an amino-terminal kinase domain, with a relatively large carboxy-terminus of unique structure and function that makes it distinct from other MAPK members (Drew *et al. Biochim. Biophys. Acta* (2012) 1825(1): 37–48).

[0793] In unstimulated cells and/or in the absence of oncogenic stimuli, cytosolic ERK5 is believed to be in an unphosphorylated inactive folded form, such that the Nuclear Localization Sequence (NLS) is hidden and nuclear translocation is prevented. After stimulus, ERK5 is thought to be activated through a MEK5-dependent phosphorylation at the Thr-Glu-Tyr (TEY) motif of ERK5. This phosphorylation can initiate the ERK5 kinase activity, which can phosphorylate itself in the C-terminus. Following phosphorylation of the C-terminus, ERK5 is understood to assume an open conformation, exposing the NLS sequence that allows ERK5 nuclear translocation. Once in the nucleus, ERK5 is reported to enhance gene transcription either by phosphorylating transcription factors or, in a kinase-independent manner, by interacting with transcription factors through the transactivation domain (TAD) domain (Tubita *et al.*(2020) *Int. J. Mol. Sci.* 21(3), 938). In stimulated cells and/or in the presence of oncogenic stimuli or in response to several targeted therapies, ERK5 is believed to promote tumor growth by, for example, sustaining proliferative signals and evading growth suppressors.

[0794] Accordingly, in some aspects and embodiments, the present invention provides a method for treating one or more disorders, diseases, and/or conditions wherein the disorder, disease, or condition includes, but is not limited to, a cellular proliferative disorder, comprising

administering to a patient in need thereof, an ERK5 inhibitor compound as described herein, or a pharmaceutical salt or composition thereof. In some embodiments, the cellular proliferative disorder is cancer. In some embodiments, the cancer is characterized by increased ERK5 expression and/or increased ERK5 activity, *i.e.*, "increased activated ERK5." In some embodiments, the cancer is characterized by ERK5 genomic amplification and/or constitutively active ERK5 signaling.

[0795] As used herein, the terms "increased," "elevated," or "enhanced," are used interchangeably and encompass any measurable increase in a biological function and/or biological activity and/or a concentration. For example, an increase can be by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to a control or baseline amount of a function, or activity, or concentration.

[0796] As used herein, the terms "increased expression" and/or "increased activity" of a substance, such as ERK5, in a sample or cancer or patient, refers to an increase in the amount of the substance, such as ERK5, of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to the amount of the substance, such as ERK5, in a control sample or control samples, such as an individual or group of individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control, as determined by techniques known in the art. A subject can also be determined to have an "increased expression" or "increased activity" of ERK5 if the expression and/or activity of ERK5 is increased by one standard deviation, two standard deviations, three standard deviations, four standard deviations, five standard deviations, or more, relative to the mean (average) or median amount of ERK5 in a control group of samples or a baseline group of samples or a retrospective analysis of patient samples. As practiced in the art, such control or baseline expression levels can be previously

determined, or measured prior to the measurement in the sample or cancer or subject, or can be obtained from a database of such control samples.

[0797] As used herein, a "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, Cambridge Dictionary of Biology, Cambridge University Press: Cambridge, UK, 1990). A proliferative disease can be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (e.g., metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes, such as the matrix metalloproteinases (e.g., collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis, as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases. Accordingly, in certain aspects and embodiments, the disorder is cancer. The cancer or proliferative disorder or tumor to be treated using the compounds and methods and uses described herein include, but are not limited to, a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, skin cancer, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, a liver cancer, a pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and a vascular cancer.

[0798] In some embodiments of the methods and uses described herein, a cancer is treated by inhibiting or reducing or decreasing or arresting further growth or spread of the cancer or tumor. In some embodiments of the methods and uses described herein, a cancer is treated by inhibiting or reducing the size (e.g., volume or mass) of the cancer or tumor by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, or at least 99% relative to the size of the cancer or tumor prior to treatment. In some embodiments of the methods and uses described herein, a cancer is treated by reducing the quantity of the cancers or tumors in the patient by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, or at least 99% relative to the quantity of the cancers or tumors prior to treatment.

[0799] In some embodiments, the cancer is selected from non-small cell lung cancer (NSCLC), pancreatic cancer, and colorectal cancer.

[0800] In some embodiments, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the cancer is a pancreatic cancer, such as an adenocarcinoma. In some

embodiments, the cancer is colorectal cancer (CRC). In some embodiments, the cancer is a breast cancer, such as ductal breast carcinoma. In some embodiments, the cancer is an ovarian cancer. In some embodiments, the cancer is a brain cancer, such as glioblastoma. In some embodiments, the cancer is a kidney cancer.

[0801] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is a melanoma, carcinoma, or blastoma. In certain embodiments, the cancer is a melanoma. In certain embodiments, the cancer is a carcinoma. In certain embodiments, the cancer is an adenocarcinoma. In certain embodiments, the cancer is a blastoma.

[0802] In certain embodiments, the cancer is breast cancer, lung cancer, pancreatic cancer, cervical cancer, colorectal cancer, prostate cancer, gastric cancer, skin cancer, liver cancer, bile duct cancer, or nervous system cancer. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is pancreatic cancer. In certain embodiments, the cancer is cervical cancer. In certain embodiments, the cancer is colorectal cancer. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is gastric cancer. In certain embodiments, the cancer is skin cancer. In certain embodiments, the cancer is liver cancer. In certain embodiments, the cancer is bile duct cancer. In certain embodiments, the cancer is nervous system cancer.

[0803] In certain embodiments, the cancer is breast adenocarcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, prostate adenocarcinoma, gastric adenocarcinoma, melanoma, lung squamous cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, glioblastoma, or neuroblastoma. In certain embodiments, the cancer is breast adenocarcinoma. In certain embodiments, the cancer is lung adenocarcinoma. In certain embodiments, the cancer is pancreatic adenocarcinoma. In certain embodiments, the cancer is cervical adenocarcinoma. In certain embodiments, the cancer is prostate adenocarcinoma. In certain embodiments, the cancer is gastric adenocarcinoma.

[0804] In certain embodiments, the cancer is melanoma.

[0805] In certain embodiments, the cancer is lung squamous cell carcinoma, hepatocellular carcinoma, or cholangiocarcinoma. In certain embodiments, the cancer is lung squamous cell carcinoma. In certain embodiments, the cancer is hepatocellular carcinoma. In certain embodiments, the cancer is cholangiocarcinoma.

[0806] In certain embodiments, the cancer is glioblastoma or neuroblastoma. In certain embodiments, the cancer is glioblastoma. In certain embodiments, the cancer is neuroblastoma.

[0807] In certain embodiments, the cancer is lung cancer, pancreatic cancer, or colorectal cancer. In certain embodiments, the cancer is non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is non-small cell lung cancer.

[0808] In certain embodiments, the cancer has elevated ERK5 activity. In certain embodiments, the cancer overexpresses ERK5. In certain embodiments, the cancer has genomically amplified ERK5. In certain embodiments, the cancer has constitutively active ERK5 signaling.

[0809] In some embodiments, the cancer is a KRAS mutant cancer. In some embodiments, the KRAS mutant cancer harbors the KRAS G12C mutation. In some embodiments, the KRAS mutant cancer harbors the KRAS G12D mutation. In some embodiments, the KRAS mutant cancer harbors the KRAS G12V mutation. In some embodiments, the KRAS mutant cancer harbors the KRAS G13 mutation. In some embodiments, the KRAS mutant cancer harbors one or more KRAS mutations selected from a KRAS G12C, a KRAS G12D mutation, a KRAS G12V mutation, and a KRAS G13 mutation.

[0810] In some embodiments, the cancer is a KRAS mutant lung cancer.

[0811] In certain embodiments, the cancer is a leukemia (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (e.g., Hodgkin's disease or non-Hodgkin's disease), Waldenstrom's macroglobulinemia, multiple myeloma, heavy chain disease, or a solid tumor such as a sarcoma or carcinoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas,

cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

[0812] In some embodiments, the cancer is glioma, astrocytoma, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

[0813] In some embodiments, the cancer is acoustic neuroma, astrocytoma (e.g. Grade I – Pilocytic Astrocytoma, Grade II – Low-grade Astrocytoma, Grade III – Anaplastic Astrocytoma, or Grade IV – Glioblastoma (GBM)), chordoma, CNS lymphoma, craniopharyngioma, brain stem glioma, ependymoma, mixed glioma, optic nerve glioma, subependymoma, medulloblastoma, meningioma, metastatic brain tumor, oligodendroglioma, pituitary tumors, primitive neuroectodermal (PNET) tumor, or schwannoma. In some embodiments, the cancer is a type found more commonly in children than adults, such as brain stem glioma, craniopharyngioma, ependymoma, juvenile pilocytic astrocytoma (JPA), medulloblastoma, optic nerve glioma, pineal tumor, primitive neuroectodermal tumors (PNET), or rhabdoid tumor.

[0814] In some embodiments, the cancer is mesothelioma, hepatobilliary (hepatic and billiary duct), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell

carcinoma, carcinoma of the renal pelvis, non-Hodgkins's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

[0815] In some embodiments, the cancer is hepatocellular carcinoma, ovarian cancer, ovarian epithelial cancer, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), prostate cancer, testicular cancer, gallbladder cancer, hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, Ewing sarcoma, anaplastic thyroid cancer, adrenocortical adenoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, gastrointestinal/stomach (GIST) cancer, lymphoma, squamous cell carcinoma of the head and neck (SCCHN), salivary gland cancer, glioma, or brain cancer, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0816] In some embodiments, the cancer is hepatocellular carcinoma (HCC), hepatoblastoma, colon cancer, rectal cancer, ovarian cancer, ovarian epithelial cancer, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, anaplastic thyroid cancer, adrenocortical adenoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, glioma, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0817] In some embodiments, the cancer is selected from renal cell carcinoma, or kidney cancer; hepatocellular carcinoma (HCC) or hepatoblastoma, or liver cancer; melanoma; breast cancer; colorectal carcinoma, or colorectal cancer; colon cancer; rectal cancer; anal cancer; lung cancer, such as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC); ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, or fallopian tube cancer; papillary serous cystadenocarcinoma or uterine papillary serous carcinoma (UPSC); prostate cancer; testicular cancer; gallbladder cancer; hepatocholangiocarcinoma; soft tissue and bone synovial sarcoma; rhabdomyosarcoma; osteosarcoma; chondrosarcoma; Ewing sarcoma; anaplastic thyroid cancer;

adrenocortical carcinoma; pancreatic cancer; pancreatic ductal carcinoma or pancreatic adenocarcinoma; gastrointestinal/stomach (GIST) cancer; lymphoma; squamous cell carcinoma of the head and neck (SCCHN); salivary gland cancer; glioma, or brain cancer; neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST); Waldenstrom's macroglobulinemia; and medulloblastoma.

[0818] In some embodiments, the cancer is renal cell carcinoma, hepatocellular carcinoma (HCC), hepatoblastoma, colorectal carcinoma, colorectal cancer, colon cancer, rectal cancer, anal cancer, ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, anaplastic thyroid cancer, adrenocortical carcinoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, glioma, brain cancer, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0819] In some embodiments, the cancer is hepatocellular carcinoma (HCC), hepatoblastoma, colon cancer, rectal cancer, ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, anaplastic thyroid cancer, adrenocortical carcinoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, glioma, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0820] In some embodiments, the cancer is hepatocellular carcinoma (HCC). In some embodiments, the cancer is hepatoblastoma. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is rectal cancer. In some embodiments, the cancer is ovarian cancer, or ovarian carcinoma. In some embodiments, the cancer is ovarian epithelial cancer. In some embodiments, the cancer is fallopian tube cancer. In some embodiments, the cancer is papillary serous cystadenocarcinoma. In some embodiments, the cancer is uterine papillary serous carcinoma (UPSC). In some embodiments, the cancer is hepatocholangiocarcinoma. In some embodiments, the cancer is soft tissue and bone synovial sarcoma. In some embodiments,

the cancer is rhabdomyosarcoma. In some embodiments, the cancer is osteosarcoma. In some embodiments, the cancer is anaplastic thyroid cancer. In some embodiments, the cancer is adrenocortical carcinoma. In some embodiments, the cancer is pancreatic cancer, or pancreatic ductal carcinoma. In some embodiments, the cancer is pancreatic adenocarcinoma. In some embodiments, the cancer is glioma. In some embodiments, the cancer is malignant peripheral nerve sheath tumors (MPNST). In some embodiments, the cancer is neurofibromatosis-1 associated MPNST. In some embodiments, the cancer is Waldenstrom's macroglobulinemia. In some embodiments, the cancer is medulloblastoma.

[0821] In certain embodiments, the subject is a human. In certain embodiments, the subject is an adult human. In certain embodiments, the subject is a pediatric human. In certain embodiments, the subject is a companion animal. In certain embodiments, the subject is a canine, feline, or equine.

[0822] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I or II, or other compounds in Section I) in the manufacture of a medicament. In certain embodiments, the medicament is for treating a disorder described herein, such as cancer.

[0823] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I or II, or other compounds in Section I) for treating a medical disorder, such as a medical disorder described herein (for example, cancer).

[0824] Further, it is contemplated that the compounds described herein, such as a compound of Formula I or II, or other compounds in Section I, can inhibit ERK5 activity. Accordingly, another aspect of the invention provides a method of inhibiting ERK5 activity. The method comprises contacting ERK5 with an effective amount of a substituted 4-piperidinyl-quinazoline or related compound described herein, such as a compound of Formula I or II, or other compounds in Section I, to inhibit ERK5 activity. In certain embodiments, the particular compound of Formula I or II is the compound defined by one of the embodiments described above. In certain embodiments, the compound is a compound of Formula III defined by one of the embodiments described above.

[0825] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I, or other compounds in Section I-A) in the manufacture of a

medicament. In certain embodiments, the medicament is for treating a disorder described herein, such as cancer.

[0826] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I, or other compounds in Section I-A) for treating a medical disorder, such as a medical disorder described herein (for example, cancer).

[0827] Further, it is contemplated that the compounds described herein, such as a compound of Formula I, or other compounds in Section I-A, can inhibit ERK5 activity. Accordingly, another aspect of the invention provides a method of inhibiting ERK5 activity. The method comprises contacting ERK5 with an effective amount of a substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein, such as a compound of Formula I, or other compounds in Section I-A, to inhibit ERK5 activity. In certain embodiments, the particular compound of Formula I, I-A, I-1, or I-A1 is the compound defined by one of the embodiments described above.

III. Combination Therapy

[0828] Another aspect of the invention provides for combination therapy. Substituted 4-piperidinyl-quinazoline or related compounds described herein (*e.g.*, a compound of Formula I or II, or other compounds in Section I) or their pharmaceutically acceptable salts may be used in combination with additional therapeutic agents to treat medical disorders, such as a cancer. Substituted 4-piperidinyl-pyrimidine-2-amine or related compounds described herein (*e.g.*, a compound of Formula I, or other compounds in Section I-A) or their pharmaceutically acceptable salts may be used in combination with additional therapeutic agents to treat medical disorders, such as a cancer.

[0829] In some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents. In some embodiments, the combination of the disclosed compound and the additional therapeutic agent or agents acts synergistically.

[0830] One or more other therapeutic agents may be administered separately from a compound or composition of the invention, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent and a compound or composition of the invention may be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, or 24 hours from one another. In some embodiments, one or more other therapeutic agent and a compound or composition of the invention are administerd as a multiple dosage regimen more than 24 hours aparts.

[0831] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention can be administered with one or more other therapeutic agent(s) simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, one or more other therapeutic agent(s), and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0832] The amount of a compound of the invention and one or more other therapeutic agent(s) (in those compositions which comprise an additional therapeutic agent, such as a second anti-cancer agent, as described above) that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Preferably, a composition of the invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of a compound of the invention can be administered.

[0833] In those compositions which comprise one or more other therapeutic agent(s), the one or more other therapeutic agent(s) and a compound of the invention can act synergistically. Therefore, the amount of the one or more other therapeutic agent(s) in such compositions may be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 1,000 g/kg body weight/day of the one or more other therapeutic agent(s) can be administered.

[0834] The amount of one or more other therapeutic agent(s) present in the compositions of this invention is preferably no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of one or more other therapeutic agent(s) in the presently disclosed compositions ranges from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent. In some embodiments, one or more other therapeutic agent(s) is administered at a dosage of about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the amount normally administered for that agent. As used herein, the phrase "normally administered" means the amount an FDA-approved therapeutic agent is approved for dosing per the FDA label insert.

[0835] Accordingly, another aspect of the invention provides a method of treating cancer in a subject. The method comprises administering to a subject in need thereof (i) a therapeutically effective amount of a substituted 4-piperidinyl-quinazoline or related compound described herein and (ii) a second anti-cancer agent, in order to treat the cancer.

[0836] Accordingly, another aspect of the invention provides a method of treating cancer in a subject. The method comprises administering to a subject in need thereof (i) a therapeutically effective amount of a substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein and (ii) a second anti-cancer agent, in order to treat the cancer.

[0837] In certain embodiments, the second anti-cancer agent is an ALK Inhibitor, an ATR Inhibitor, an A2A Antagonist, a Base Excision Repair Inhibitor, a Bcr-Abl Tyrosine Kinase Inhibitor, a Bruton's Tyrosine Kinase Inhibitor, a CDC7 Inhibitor, a CHK1 Inhibitor, a Cyclin-Dependent Kinase Inhibitor, a DNA-PK Inhibitor, an Inhibitor of both DNA-PK and mTOR, a DNMT1 Inhibitor, a DNMT1 Inhibitor plus 2-chloro-deoxyadenosine, an HDAC Inhibitor, a Hedgehog Signaling Pathway Inhibitor, an IDO Inhibitor, a JAK Inhibitor, a mTOR Inhibitor, a MEK Inhibitor, a MELK Inhibitor, a MTH1 Inhibitor, a PARP Inhibitor, a Phosphoinositide 3-Kinase Inhibitor, an Inhibitor of both PARP1 and DHODH, a Proteasome Inhibitor, a Topoisomerase-II Inhibitor, a Tyrosine Kinase Inhibitor, a VEGFR Inhibitor, or a WEE1 Inhibitor.

[0838] In certain embodiments, the second anti-cancer agent is an ALK Inhibitor. In certain embodiments, the second anti-cancer agent is an ALK Inhibitor comprisng ceritinib, crizotinib,

or alectinib. In certain embodiments, the second anti-cancer agent is an ALK Inhibitor comprisng ceritinib or crizotinib.

[0839] In certain embodiments, the second anti-cancer agent is an ATR Inhibitor. In certain embodiments, the second anti-cancer agent is an ATR Inhibitor comprising AZD6738 or VX-970.

[0840] In certain embodiments, the second anti-cancer agent is an A2A Antagonist. In certain embodiments, the second anti-cancer agent is a Base Excision Repair Inhibitor comprising methoxyamine. In certain embodiments, the second anti-cancer agent is a Base Excision Repair Inhibitor, such as methoxyamine.

[0841] In certain embodiments, the second anti-cancer agent is a Bcr-Abl Tyrosine Kinase Inhibitor. In certain embodiments, the second anti-cancer agent is a Bcr-Abl Tyrosine Kinase Inhibitor such as imatinib (GLEEVEC®, Novartis); nilotinib (TASIGNA®, Novartis); dasatinib (SPRYCEL®, BristolMyersSquibb); bosutinib (BOSULIF®, Pfizer); and ponatinib (INCLUSIG®, Ariad Pharmaceuticals). In certain embodiments, the second anti-cancer agent is a Bcr-Abl Tyrosine Kinase Inhibitor comprising dasatinib or nilotinib.

[0842] In certain embodiments, the second anti-cancer agent is a Bruton's Tyrosine Kinase Inhibitor. In certain embodiments, the second anti-cancer agent is a Bruton's Tyrosine Kinase Inhibitor comprising ibrutinib or AVL-292. In certain embodiments, the second anti-cancer agent is a Bruton's Tyrosine Kinase Inhibitor comprising ibrutinib. Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention, can be found in WO2008/039218 and WO2011/090760, the entirety of which are incorporated herein by reference.

[0843] In certain embodiments, the second anti-cancer agent is a CDC7 Inhibitor. In certain embodiments, the second anti-cancer agent is a CDC7 Inhibitor comprising RXDX-103 or AS-141.

[0844] In certain embodiments, the second anti-cancer agent is a CHK1 Inhibitor. In certain embodiments, the second anti-cancer agent is a CHK1 Inhibitor comprising MK-8776, ARRY-575, or SAR-020106.

[0845] In certain embodiments, the second anti-cancer agent is a Cyclin-Dependent Kinase Inhibitor. In certain embodiments, the second anti-cancer agent is a Cyclin-Dependent Kinase Inhibitor, such as a CDK4/CDK6 inhibitor. In certain embodiments, the second anti-cancer agent is a Cyclin-Dependent Kinase Inhibitor selected from palbociclib (IBRANCE®, Pfizer); ribociclib (KISQALI®, Novartis); abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics). In certain embodiments, the second anti-cancer agent is a Cyclin-Dependent Kinase Inhibitor comprising palbociclib.

[0846] In certain embodiments, the second anti-cancer agent is a DNA-PK Inhibitor. In certain embodiments, the second anti-cancer agent is a DNA-PK Inhibitor comprising MSC2490484A. In certain embodiments, the second anti-cancer agent is Inhibitor of both DNA-PK and mTOR. In certain embodiments, the second anti-cancer agent comprises CC-115.

[0847] In certain embodiments, the second anti-cancer agent is a DNMT1 Inhibitor. In certain embodiments, the second anti-cancer agent is a DNMT1 Inhibitor comprising decitabine, RX-3117, guadecitabine, NUC-8000, or azacytidine. In certain embodiments, the second anti-cancer agent comprises a DNMT1 Inhibitor and 2-chloro-deoxyadenosine. In certain embodiments, the second anti-cancer agent comprises ASTX-727.

[0848] In certain embodiments, the second anti-cancer agent is a histone deacetylase (HDAC) Inhibitor. In certain embodiments, the second anti-cancer agent is a HDAC Inhibitor comprising OBP-801, CHR-3996, etinostate, resminostate, pracinostat, CG-200745, panobinostat, romidepsin, mocetinostat, belinostat, AR-42, ricolinostat, KA-3000, or ACY-241.

[0849] In certain embodiments, the second anti-cancer agent is a Hedgehog Signaling Pathway Inhibitor. In certain embodiments, the second anti-cancer agent is a Hedgehog Signaling Pathway Inhibitor comprising sonidegib (ODOMZO®, Sun Pharmaceuticals) or vismodegib (ERIVEDGE®, Genentech).

[0850] In certain embodiments, the second anti-cancer agent is an IDO Inhibitor. In certain embodiments, the second anti-cancer agent is an IDO Inhibitor comprising INCB024360.

[0851] In certain embodiments, the second anti-cancer agent is a JAK Inhibitor. In certain embodiments, the second anti-cancer agent is a JAK Inhibitor comprising ruxolitinib or tofacitinib.

[0852] In certain embodiments, the second anti-cancer agent is a mTOR Inhibitor. In certain embodiments, the second anti-cancer agent is a mTOR Inhibitor comprising everolimus or temsirolimus.

[0853] In certain embodiments, the second anti-cancer agent is a MEK Inhibitor. In certain embodiments, the second anti-cancer agent is a MEK Inhibitor comprising cobimetinib or trametinib.

[0854] In certain embodiments, the second anti-cancer agent is a MELK Inhibitor. In certain embodiments, the second anti-cancer agent is a MELK Inhibitor comprising ARN-7016, APTO-500, or OTS-167.

[0855] In certain embodiments, the second anti-cancer agent is a MTH1 Inhibitor. In certain embodiments, the second anti-cancer agent is a MTH1 Inhibitor comprising (*S*)-crizotinib, TH287, or TH588.

[0856] In certain embodiments, the second anti-cancer agent is a Poly ADP ribose polymerase (PARP) Inhibitor. In certain embodiments, the second anti-cancer agent is a PARP Inhibitor comprising MP-124, olaparib (LYNPARZA®, AstraZeneca), BGB-290 (BeiGene, Inc.), talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin), veliparib (ABT-888, AbbVie), niraparib (ZEJULA®, Tesaro), E7449, rucaparib (RUBRACA®, Clovis Oncology), or ABT-767.

[0857] In certain embodiments, the second anti-cancer agent is a Phosphoinositide 3-Kinase (PI3 Kinase) Inhibitor. In certain embodiments, the second anti-cancer agent is a Phosphoinositide 3-Kinase Inhibitor comprising idelalisib (ZYDELIG®, Gilead), alpelisib (BYL719, Novartis), taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity Pharmaceuticals); PQR309 (Piqur Therapeutics, Switzerland); or TGR1202 (formerly RP5230, TG Therapeutics). In certain embodiments, the second anti-cancer agent is a Phosphoinositide 3-Kinase Inhibitor comprising idelalisib. In certain embodiments, the second anti-cancer agent is an inhibitor of both PARP1 and DHODH (*i.e.*, an agent that inhibits both poly ADP ribose polymerase 1 and dihydroorotate dehydrogenase).

[0858] In certain embodiments, the second anti-cancer agent is a Proteasome Inhibitor. In certain embodiments, the second anti-cancer agent is a Proteasome Inhibitor comprising bortezomib (VELCADE®, Takeda), carfilzomib (KYPROLIS®, Amgen), or ixazomib (NINLARO®, Takeda). In certain embodiments, the second anti-cancer agent is a Proteasome Inhibitor comprising bortezomib or carfilzomib.

[0859] In certain embodiments, the second anti-cancer agent is a Topoisomerase-II Inhibitor. In certain embodiments, the second anti-cancer agent is a Topoisomerase-II Inhibitor comprising vosaroxin.

[0860] In some embodiments, the second anti-cancer agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present invention include irinotecan (ONIVYDE®, Merrimack Pharmaceuticals) and topotecan (HYCAMTIN®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present invention include pixantrone (PIXUVRI®, CTI Biopharma).

[0861] In certain embodiments, the second anti-cancer agent is a Tyrosine Kinase Inhibitor. In certain embodiments, the second anti-cancer agent is a Tyrosine Kinase Inhibitor comprising bosutinib (BOSULIF®, Pfizer), cabozantinib (COMETRIQ®, Exelexis), imatinib (GLEEVEC®, Novartis), or ponatinib (INCLUSIG®, Ariad Pharmaceuticals). In certain embodiments, the Tyrosine Kinase Inhibitor is an inhibitor of ROS1 and/or NTRK, such as taletrectinib (DS-6051b, AB-106, AnHeart Therapeutics Co., Ltd.).

[0862] In certain embodiments, the second anti-cancer agent is a VEGFR Inhibitor. In certain embodiments, the second anti-cancer agent is a VEGFR Inhibitor comprising regorafenib (STIVARGA®, Bayer). In certain embodiments, the second anti-cancer agent is a WEE1 Inhibitor. In certain embodiments, the second anti-cancer agent is a WEE1 Inhibitor comprising AZD1775.

[0863] In some embodiments, the second anti-cancer agent is a compound targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine;

llmofosine; RO 318220 and RO 320432; GO 6976; lsis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor).

[0864] In some embodiments, the second anti-cancer agent is a KRAS inhibitor. In some embodiments, the second anti-cancer agent is a KRAS inhibitor, such as adagrasib (MRTX849, Mirati Therapeutics) or sotorasib (Amgen). In some embodiments, the KRAS inhibitor is a KRAS G12C inhibitor, such as adagrasib (MRTX849, Mirati Therapeutics), sotorasib (AMG510, Amgen), D-1553 (InventisBio Inc.), GDC-6036, or JNJ-74699157/ARS-3248 (Janssen Biotech and Wellspring Biosciences). In some embodiments, the KRAS inhibitor is a KRAS G12D inhibitor, such as MRTX1133 (Mirati Therapeutics), RM-030/031 (Revolution Medicines), STX200 (SyntheX), JAB-22000 (JacoBio). In some embodiments, the KRAS inhibitor is a KRAS G12V inhibitor, such as JAB-23000 (JacoBio). In some embodiments, the KRAS inhibitor is a pan-KRAS inhibitor, such as BI-1701963 (Boehringer Ingelheim). Non-limiting examples of KRAS inhibitors for use as the second anti-cancer agent in the methods and uses described herein include, but are not limited to, those described in WO2020/097537, WO2020/132597, WO2020/035031, WO2020/243103, WO2020/212895, WO2021/041671, WO2021/081212, WO2021/106231, WO2021/107160, WO2021/108683, WO2021/119343, and WO2021/127404, the contents of each of which are herein incorporated by reference in their entireties.

[0865] In some embodiments, the second anti-cancer agent is a SOS1 inhibitor, such as BI-3406.

[0866] In certain embodiments, the second anti-cancer agent is an agonist of OX40, CD137, CD40, GITR, CD27, HVEM, TNFRSF25, or ICOS. In certain embodiments, the second anti-cancer agent is an agonist of OX40, CD137, CD40, or GITR. In certain embodiments, the second anti-cancer agent is an agonist of CD27, HVEM, TNFRSF25, or ICOS.

[0867] In certain embodiments, the second anti-cancer agent is a therapeutic antibody. In certain embodiments, the therapeutic antibody targets one of the following: CD20, CD30, CD33, CD52, EpCAM, CEA, gpA33, a mucin, TAG-72, CAIX, PSMA, a folate-binding protein, a ganglioside, Le, VEGF, VEGFR, VEGFR2, integrin $\alpha V\beta 3$, integrin $\alpha 5\beta 1$, EGFR, ERBB2, ERBB3, MET, IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, FAP, tenascin, CD19, KIR,

NKG2A, CD47, CEACAM1, c-MET, VISTA, CD73, CD38, BAFF, interleukin-1 beta, B4GALNT1, interleukin-6, and interleukin-6 receptor.

[0868] In certain embodiments, the second anti-cancer agent is a therapeutic antibody selected from the group consisting of rituximab, ibritumomab tiuxetan, tositumomab, obinutuzumab, ofatumumab, brentuximab vedotin, gemtuzumab ozogamicin, alemtuzumab, IGN101, adecatumumab, labetuzumab, huA33, pemtumomab, oregovomab, minetumomab, cG250, J591, Mov18, farletuzumab, 3F8, ch14.18, KW-2871, hu3S193, lgN311, bevacizumab, IM-2C6, pazopanib, sorafenib, axitinib, CDP791, lenvatinib, ramucirumab, etaracizumab, volociximab, cetuximab, panitumumab, nimotuzumab, 806, afatinib, erlotinib, gefitinib, osimertinib, vandetanib, trastuzumab, pertuzumab, MM-121, AMG 102, METMAB, SCH 900105, AVE1642, IMC-A12, MK-0646, R1507, CP 751871, KB004, IIIA-4, mapatumumab, HGS-ETR2, CS-1008, denosumab, sibrotuzumab, F19, 81C6, MEDI551, lirilumab, MEDI9447, daratumumab, belimumab, canakinumab, dinutuximab, siltuximab, and tocilizumab.

[0869] In certain embodiments, the second anti-cancer agent is a cytokine. In certain embodiments, the cytokine is IL-12, IL-15, GM-CSF, or G-CSF.

[0870] In certain embodiments, the second anti-cancer agent is sipuleucel-T, aldesleukin (a human recombinant interleukin-2 product having the chemical name des-alanyl-1, serine-125 human interleukin-2), dabrafenib (a kinase inhibitor having the chemical name *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide), vemurafenib (a kinase inhibitor having the chemical name propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide), or 2-chloro-deoxyadenosine.

[0871] In certain embodiments, the second anti-cancer agent is a placental growth factor, an antibody-drug conjugate, an oncolytic virus, or an anti-cancer vaccine. In certain embodiments, the second anti-cancer agent is a placental growth factor. In certain embodiments, the second anti-cancer agent is a placental growth factor comprising ziv-aflibercept. In certain embodiments, the second anti-cancer agent is an antibody-drug conjugate. In certain embodiments, the second anti-cancer agent is an antibody-drug conjugate selected from the group consisting of brentoxumab vedotin and trastuzumab emtransine.

[0872] In certain embodiments, the second anti-cancer agent is an oncolytic virus. In certain embodiments, the second anti-cancer agent is the oncolytic virus talimogene laherparepvec. In certain embodiments, the second anti-cancer agent is an anti-cancer vaccine. In certain embodiments, the second anti-cancer agent is an anti-cancer vaccine selected from the group consistint of a GM-CSF tumor vaccine, a STING/GM-CSF tumor vaccine, and NY-ESO-1. In certain embodiments, the second anti-cancer agent is a cytokine selected from IL-12, IL-15, GM-CSF, and G-CSF.

[0873] In certain embodiments, the second anti-cancer agent is an immune checkpoint inhibitor (also referred to as immune checkpoint blockers). Immune checkpoint inhibitors are a class of therapeutic agents that have the effect of blocking immune checkpoints. See, for example, Pardoll in *Nature Reviews Cancer* (2012) vol. 12, pages 252-264. In certain embodiments, the immune checkpoint inhibitor is an agent that inhibits one or more of (i) cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), (ii) programmed cell death protein 1 (PD1), (iii) PDL1, (iv) LAB3, (v) B7-H3, (vi) B7-H4, and (vii) TIM3.

[0874] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab. In certain embodiments, the immune checkpoint inhibitor is ipilumumab. In certain embodiments, the immune checkpoint inhibitor is pembrolizumab. In certain embodiments, the immune checkpoint inhibitor is nivolumab.

[0875] In certain embodiments, the second anti-cancer agent is a monoclonal antibody that targets a non-checkpoint target (e.g., herceptin). In certain embodiments, the second anti-cancer agent is a non-cytoxic agent (e.g., a tyrosine-kinase inhibitor).

[0876] In certain embodiments, the second anti-cancer agent is selected from mitomycin, ribomustin, vincristine, tretinoin, etoposide, cladribine, gemcitabine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, cytarabine, bicalutamide, vinorelbine, vesnarinone, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride,

oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, leutinizing hormone releasing factor, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma.

[0877] In certain embodiments, the second anti-cancer agent is radiation therapy.

[0878] In certain embodiments, the second anti-cancer agent is a MEK Inhibitor. In certain embodiments, the second anti-cancer agent is binimetinib (MEK162, ARRY-438162, ARRAY BIOPHARMA INC.), cobimetinib (COTELLIC®, Exelexis/Genentech/Roche), refametinib (BAY 86–9766, RDEA119; Bayer AG), selumetinib (AZD6244, ARRY-142886; ASTRAZENECA), trametinib (MEKINIST®, Novartis), mirdametinib (PD-0325901, Spring Works Therapeutics), pimasertib (AS703026, MSC1936369B, Merck KGaA) or a pharmaceutically acceptable salt and/or solvate of any of the foregoing. In certain embodiments, the second anti-cancer agent is binimetinib, cobimetinib, selumetinib, trametinib, mirdametinib, pimasertib, or a pharmaceutically acceptable salt and/or solvate of any of the foregoing.

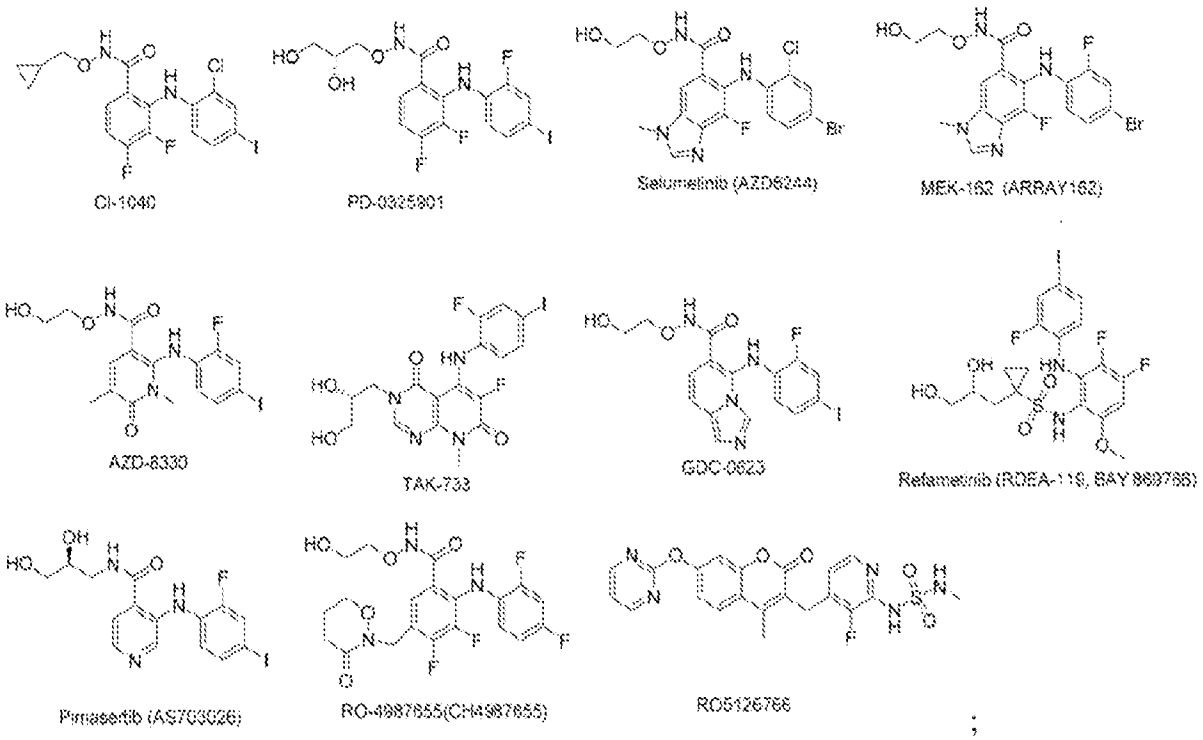
[0879] In certain embodiments, the second anti-cancer agent is binimetinib, cobimetinib, refametinib, selumetinib, trametinib, or a pharmaceutically acceptable salt and/or solvate of any of the foregoing. In certain embodiments, the second anti-cancer agent is binimetinib, cobimetinib, selumetinib, trametinib, or a pharmaceutically acceptable salt and/or solvate of any of the foregoing.

[0880] In certain embodiments, the second anti-cancer agent is trametinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second anti-cancer agent is trametinib or a pharmaceutically acceptable solvate thereof. In certain embodiments, the second anti-cancer agent is trametinib dimethylsulfoxide. In certain embodiments, the second anti-cancer agent is trametinib.

[0881] In certain embodiments, the second anti-cancer agent is binimetinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second anti-cancer agent is cobimetinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second anti-cancer agent is refametinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second anti-cancer agent is selumetinib or a pharmaceutically acceptable salt and/or solvate thereof.

[0882] In certain embodiments, the second anti-cancer agent is binimetinib. In certain embodiments, the second anti-cancer agent is cobimetinib. In certain embodiments, the second anti-cancer agent is refametinib. In certain embodiments, the second anti-cancer agent is selumetinib.

[0883] In some embodiments, the second anti-cancer agent is selected from:



;

or a pharmaceutically acceptable salt and/or solvate thereof.

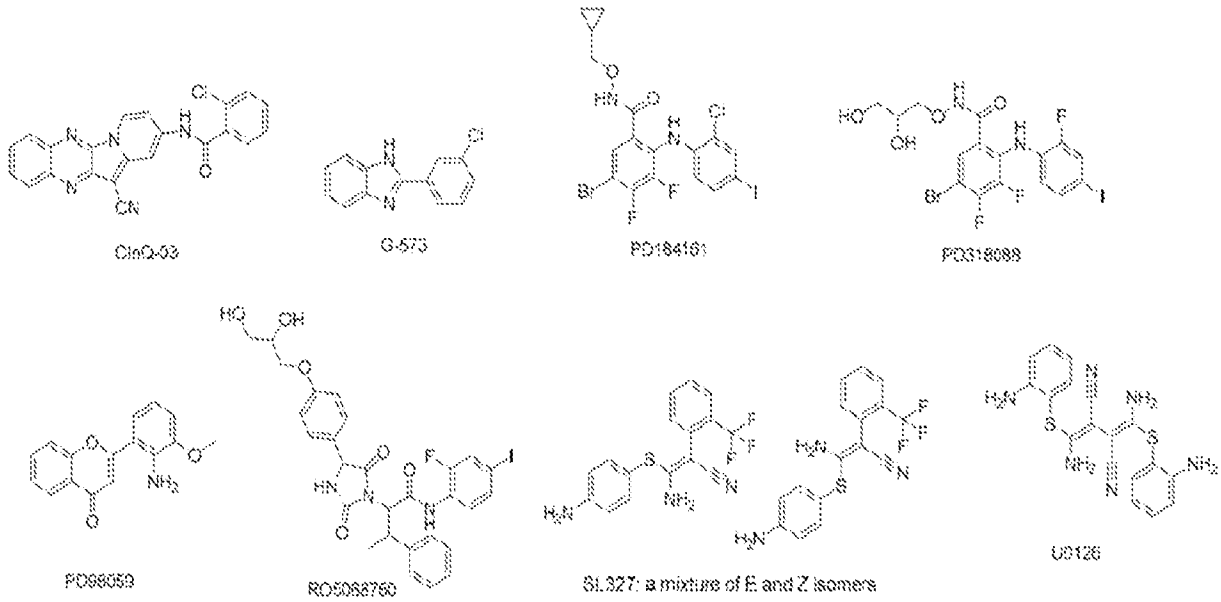
[0884] Other examples of MEK inhibitors for use as a second anti-cancer agent in the methods described herein include, but are not limited to, E6201 (Eisai Co Ltd./Strategia Theraputics), GDC-0623 (RG 7421, Genentech, Inc.), CH5126766 (RO5126766, Chugai Pharmaceutical Co., Roche), HL-085 (Shanghai Kechow Pharma, Inc.), SHR7390 (HENGRUI MEDICINE), TQ-B3234 (CHIATAI TIANQING), CS-3006 (CSTONE Pharmaceuticals), FCN-159 (Fosun Pharmaceuticals), VS-6766 (Verastem Oncology), and IMM-1-104 (Immuneering Corp.). Other examples of MEK inhibitors for use as second anti-cancer agents in the methods and uses described herein include, but are not limited to, those described in WO2005/121142, WO2014/169843, WO2016/035008, WO2016/168704, WO2020/125747, WO2021/142144, WO2021/142345, WO2021/149776, the contents of each of which are herein incorporated by reference in their entireties.

[0885] In some embodiments, the second anti-cancer agent is WX-554. WX-554 is a selective, noncompetitive MEK1/2 inhibitor, which has been tested in dose-escalation phase I/II studies (ClinicalTrials.gov: NCT01859351, NCT01581060).

[0886] In some embodiments, the second anti-cancer agent is HL-085 (Shanghai Kechow Pharma, Inc.). HL-085 is an orally active, selective MEK inhibitor, which has been tested in phase I clinical study.

[0887] In some embodiments, the second anti-cancer agent is FCN-159 (Fosun Pharmaceuticals).

[0888] In some embodiments, the second anti-cancer agent is selected from:



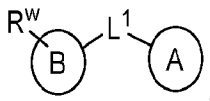
or a pharmaceutically acceptable salt and/or solvate thereof.

[0889] In certain embodiments, the second anti-cancer agent is a TEAD inhibitor.

TEAD Inhibitors of Formulae A, and A-1 to A-50

[0890] In certain embodiments, a TEAD inhibitor is selected from those described in WO 2020/243415, the contents of which are herein incorporated by reference in their entirety.

[0891] In certain embodiments, a TEAD inhibitor is a compound of **Formula A**



, or a pharmaceutically acceptable salt thereof, wherein

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –

$CH(N(R)_2)$-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2$-, $-SO_2N(R)$-, $-(R)NSO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

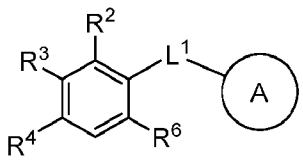
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^W is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R is independently -H or optionally substituted $-C_{1-6}$ aliphatic.

[0892] In certain embodiments, a TEAD inhibitor is a compound of **Formula A-1:**



, or a pharmaceutically acceptable salt thereof, wherein

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)$-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2$-, $-SO_2N(R)$-, $-(R)NSO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

Ring A is a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Ring A is optionally substituted 1-2 times by -halogen, -CN, $-NO_2$, or $-C_{1-6}$ aliphatic substituted 0-6 times by -halogen, -CN, or $-NO_2$;

R^2 is -H, or an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is -H;

R^4 is -H, halogen, $-S(O)_2N(R)_2$, $-S(O)N(R)_2$, or $-C(O)N(R)_2$;

R^6 is -H or $-C_{1-6}$ aliphatic substituted 0-6 times by -halogen, -CN, or $-NO_2$; and

each R is independently -H or optionally substituted $-C_{1-6}$ aliphatic.

[0893] As defined generally above, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)-$, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-.

[0894] In some embodiments, L^1 is a covalent bond, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)-$, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-.

[0895] In some embodiments, L^1 is a covalent bond.

[0896] In some embodiments, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, $-CH(N(R)_2)-$, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, or -N(R)C(O)N(R)-. In some embodiments, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are optionally replaced with -CH(SR)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-. In some embodiments, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are

independently and optionally replaced with -O-, -S-, or -N(R)-. In some embodiments, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -CH(OR)-, -CH(SR)-, or –CH(N(R)$_2$)-. In some embodiments, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -C(O)-, -C(O)O-, -OC(O)-, -SO-, -SO_2-, -C(S)-, -C(S)O-, or -OC(S)-.

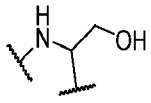
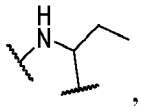
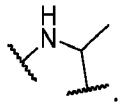
[0897] In some embodiments, L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -SO_2N(R)-, -(R)NSO_2-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-. In some embodiments, L^1 is -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-. In some embodiments, L^1 is -O-, -CH(OR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, or -N(R)C(O)N(R)-. In some embodiments, L^1 is -CH(SR)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-.

[0898] In some embodiments, L^1 is -O-, -S-, or -N(R)-. In some embodiments, L^1 is -O-. In some embodiments, L^1 is -S-. In some embodiments, L^1 is -N(R)-. In some embodiments, L^1 is -NH-. In some embodiments, L^1 is -CH(OR)-, -CH(SR)-, or –CH(N(R)$_2$)-. In some embodiments, L^1 is -CH(OR)-. In some embodiments, L^1 is -CH(SR)-. In some embodiments, L^1 is –CH(N(R)$_2$)-.

[0899] In some embodiments, L^1 is -C(O)-, -C(O)O-, -OC(O)-, -SO-, -SO_2-, -C(S)-, -C(S)O-, or -OC(S)-. In some embodiments, L^1 is -C(O)-. In some embodiments, L^1 is -C(O)O-. In some embodiments, L^1 is -OC(O)-. In some embodiments, L^1 is -SO-. In some embodiments, L^1 is -SO_2-. In some embodiments, L^1 is -C(S)-. In some embodiments, L^1 is -C(S)O-. In some embodiments, L^1 is -OC(S)-.

[0900] In some embodiments, L^1 is -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -SO_2N(R)-, -(R)NSO_2-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-. In some embodiments, L^1 is -C(O)N(R)-. In some embodiments, L^1 is -(R)NC(O)-. In some embodiments, L^1 is -OC(O)N(R)-. In some embodiments, L^1 is -(R)NC(O)O-. In some

embodiments, L^1 is -N(R)C(O)N(R)-. In some embodiments, L^1 is -SO_2N(R)-. In some embodiments, L^1 is -(R)NSO_2-. In some embodiments, L^1 is -C(S)N(R)-. In some embodiments, L^1 is -(R)NC(S)-. or In some embodiments, L^1 is -(R)NC(S)N(R)-.

[0901] In some embodiments, L^1 is –CH_2-, -$CH(CH_3)$-, -NH-CH_2-, -NH-$CH(CH_3)$-, -C(O)-NH-, or –$N(CH_3)$-. In some embodiments, L^1 is  ,  , or  .

[0902] In some embodiments, L^1 is selected from those depicted in Table A, below.

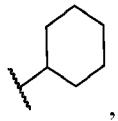
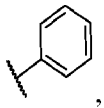
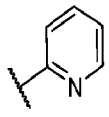
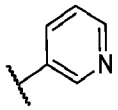
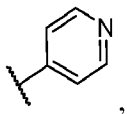
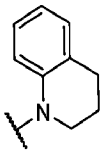
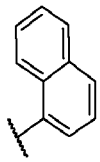
[0903] As defined generally above, Ring A is a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Ring A is optionally substituted 1-2 times by halogen, -CN, –NO_2, or -C_{1-6} aliphatic substituted 0-6 times by halogen, -CN, or –NO_2.

[0904] In some embodiments, Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0905] In some embodiments, Ring A is optionally substituted phenyl. In some embodiments, Ring A is optionally substituted 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring A is optionally substituted 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is optionally substituted 8-10 membered bicyclic aromatic ring. In

some embodiments, Ring A is optionally substituted 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0906] In some embodiments, Ring A is optionally substituted phenyl, a 6-membered monocyclic heteroaromatic ring having 1 or 2 nitrogen, or a 10-membered bicyclic heteroaromatic ring having 1-2 nitrogen.

[0907] In some embodiments, Ring A is optionally substituted  ,  ,  ,  ,  ,  , or  .

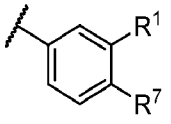
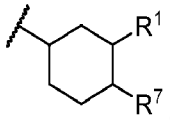
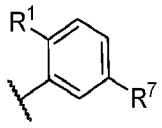
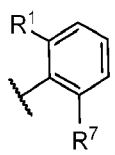
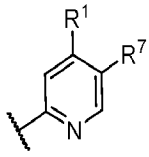
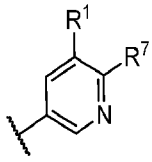
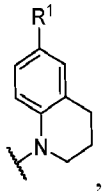
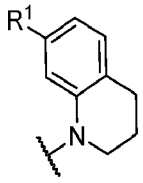
[0908] In some embodiments, Ring A is optionally substituted 1-2 times by -halogen, -CN, $-NO_2$, $-C_{1-6}$ aliphatic, or $-O-C_{1-6}$ aliphatic, wherein each of $-C_{1-6}$ aliphatic and $-O-C_{1-6}$ aliphatic is independently substituted 0-6 times by -halogen, -CN, or $-NO_2$. In some embodiments, Ring A is optionally substituted 1-2 times by halogen, -CN, $-NO_2$, $-C_{1-6}$ aliphatic, or $-O-C_{1-6}$ aliphatic, wherein each of $-C_{1-6}$ aliphatic and $-O-C_{1-6}$ aliphatic is independently substituted 0, 1, 2, 3, 4, 5, or 6 times by halogen, -CN, or $-NO_2$. In some embodiments, Ring A is optionally substituted 1-2 times by halogen, $-C_{1-6}$ aliphatic, or $-O-C_{1-6}$ aliphatic, wherein each of $-C_{1-6}$ aliphatic and $-O-C_{1-6}$ aliphatic is independently substituted 1, 2, 3, 4, 5, or 6 times by halogen.

[0909] In some embodiments, Ring A is a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring A is cyclohexyl. In some embodiments, Ring A is phenyl. In some embodiments, Ring A is a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0910] In some embodiments, Ring A is a 8-10 membered bicyclic aromatic ring. In some embodiments, Ring A is a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0911] In some embodiments, Ring A is optionally substituted 1-2 times by halogen, -CN, $-NO_2$, or $-C_{1-6}$ aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by halogen, -CN, or $-NO_2$. In some

embodiments, Ring A is optionally substituted 1-2 times by halogen, or -C_{1-6} aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by halogen.

[0912] In some embodiments, Ring A is selected from  and  , wherein each of R^1 and R^7 is independently as described herein. In some embodiments, Ring A is selected from  ,  ,  ,  ,  , or  .

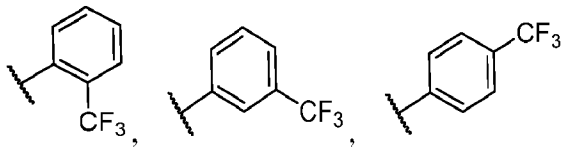
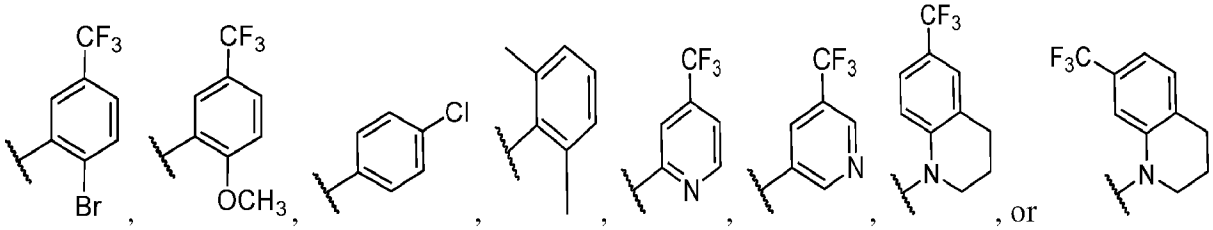
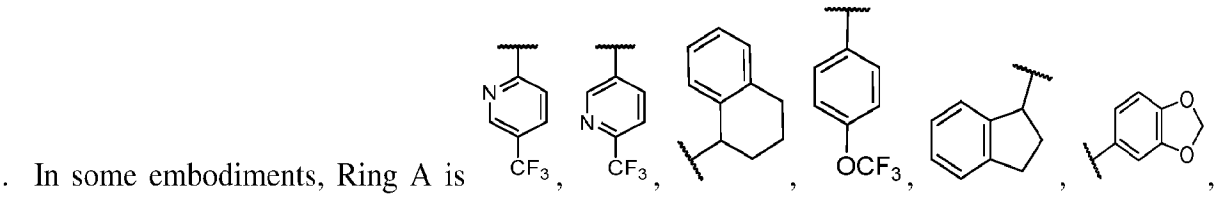
[0913] In some embodiments, R^1 is -H, -halogen, -CN, $-NO_2$, -C_{1-6} aliphatic, or $-O-C_{1-6}$ aliphatic, wherein each of -C_{1-6} aliphatic and $-O-C_{1-6}$ aliphatic is substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or $-NO_2$. In some embodiments, R^1 is unsubstituted $-O-C_{1-6}$ aliphatic. In some embodiments, R^1 is $-OCH_3$. In some embodiments, R^1 is $-O-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^1 is $-O-C_{1-3}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^1 is $-O-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^1 is $-OCF_3$. In some embodiments, R^1 is .

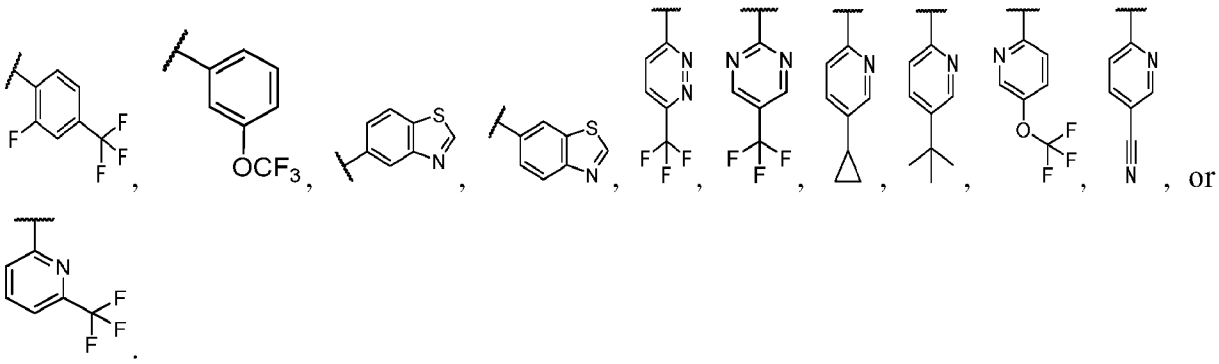
[0914] In some embodiments, R^1 is -H, -halogen, -CN, $-NO_2$, or -C_{1-6} aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or $-NO_2$. In some embodiments, R^1 is –H. In some embodiments, R^1 is –halogen. In some embodiments, R^1 is –F. In some embodiments, R^1 is –Cl. In some embodiments, R^1 is –Br. In some embodiments, R^1 is –CN. In some embodiments, R^1 is $-NO_2$. In some embodiments, R^1 is unsubstituted -C_{1-6} aliphatic. In some embodiments, R^1 is $-CH_3$. In some embodiments, R^1 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^1 is -C_{1-3} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^1 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^1 is -C_{1-3} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^1 is $-CF_3$. In some embodiments, R^1 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –CN. In some embodiments, R^1 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by $-NO_2$.

[0915] In some embodiments, R^7 is -H, -halogen, -CN, $-NO_2$, -C_{1-6} aliphatic, or $-O-C_{1-6}$ aliphatic, wherein each of -C_{1-6} aliphatic and $-O-C_{1-6}$ aliphatic is substituted 0, 1, 2, 3, 4, 5, or 6

times by -halogen, -CN, or $-NO_2$. In some embodiments, R^7 is unsubstituted $-O-C_{1-6}$ aliphatic. In some embodiments, R^7 is $-OCH_3$. In some embodiments, R^7 is $-O-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^7 is $-O-C_{1-3}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^7 is $-O-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^7 is $-OCF_3$. In some embodiments, R^7 is .

[0916] In some embodiments, R^7 is -H, -halogen, -CN, $-NO_2$, or $-C_{1-6}$ aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or $-NO_2$. In some embodiments, R^7 is –H. In some embodiments, R^7 is –halogen. In some embodiments, R^7 is –F. In some embodiments, R^7 is –Cl. In some embodiments, R^7 is –Br. In some embodiments, R^7 is –CN. In some embodiments, R^7 is $-NO_2$. In some embodiments, R^7 is unsubstituted $-C_{1-6}$ aliphatic. In some embodiments, R^1 is $-CH_3$. In some embodiments, R^7 is $-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^7 is $-C_{1-3}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –halogen. In some embodiments, R^7 is $-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^7 is $-C_{1-3}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^7 is $-CF_3$. In some embodiments, R^7 is $-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –CN. In some embodiments, R^7 is $-C_{1-6}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by $-NO_2$.

[0917] In some embodiments, Ring A is  ,  , or  . In some embodiments, Ring A is

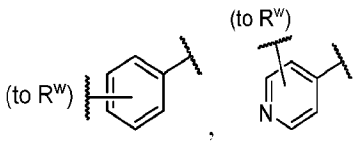
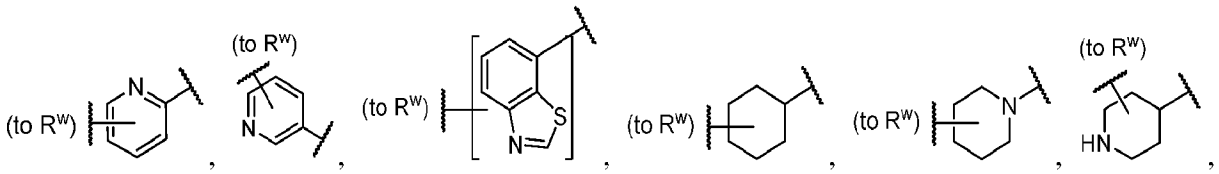
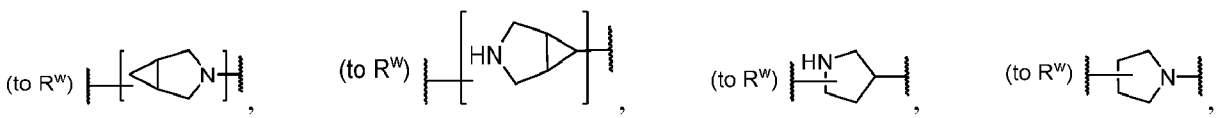
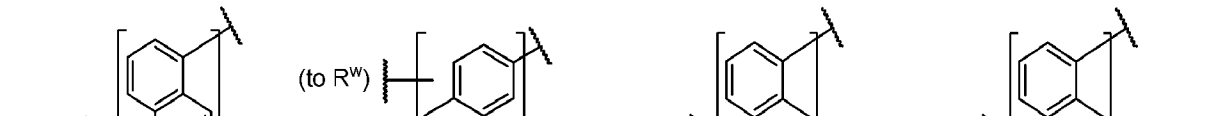
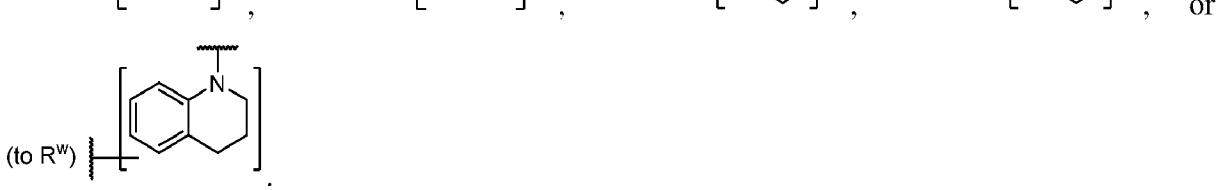


[0918] In some embodiments, Ring A is selected from those depicted in Table A, below.

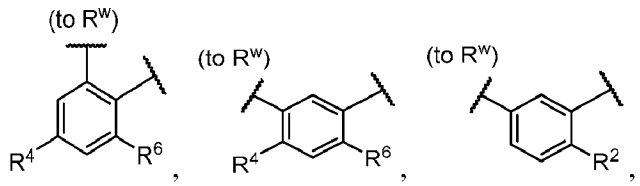
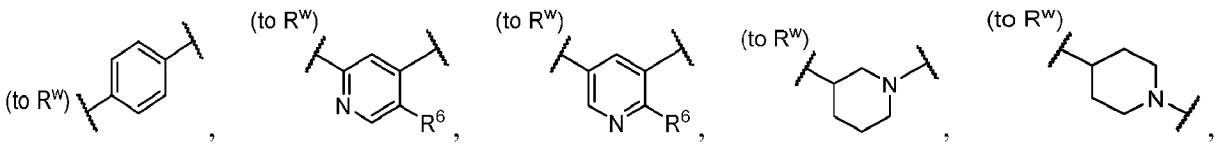
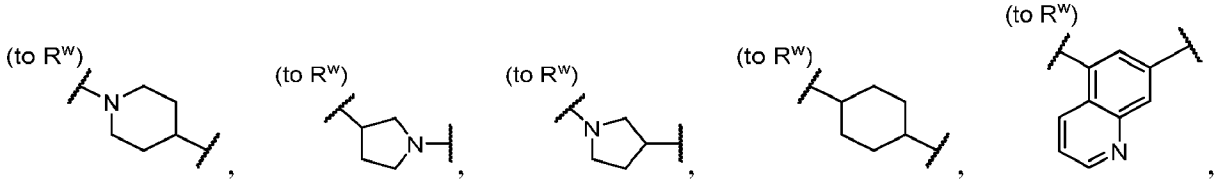
[0919] As defined generally above, Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

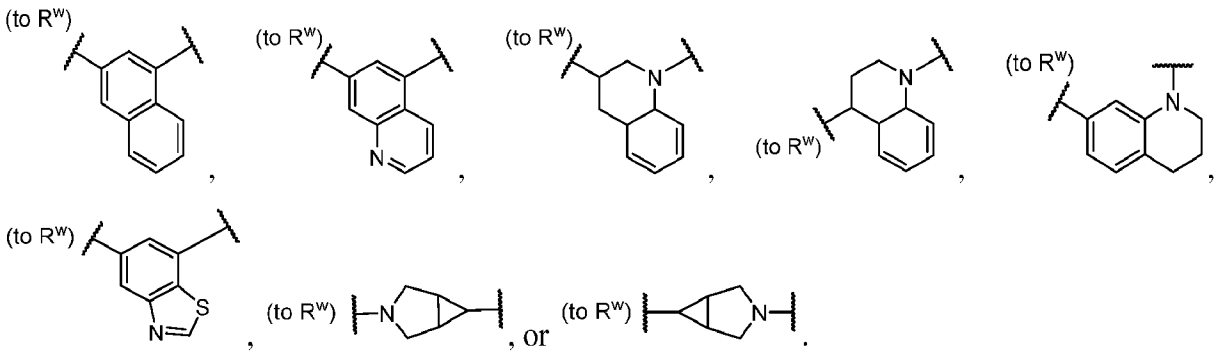
[0920] In some embodiments, Ring B is optionally substituted phenyl. In some embodiments, Ring B is optionally substituted 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring B is optionally substituted 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is optionally substituted 8-10 membered bicyclic aromatic ring. In some embodiments, Ring B is optionally substituted 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0921] In some embodiments, Ring B is optionally substituted phenyl or a 6-membered monocyclic heteroaromatic ring having 1 or 2 nitrogen.

[0922] In some embodiments, Ring B is optionally substituted  ,  ,  ,  ,  , , , , or .

[0923] In some embodiments, Ring B is optionally substituted 1-4 times by halogen, -$S(O)_2N(R)_2$, -$S(O)N(R)_2$, -$C(O)N(R)_2$, -C(O)OR, -C_{1-6} aliphatic, or –O-C_{1-6} aliphatic, wherein each of -C_{1-6} aliphatic and –O-C_{1-6} aliphatic is independently substituted 0-6 times by halogen, -CN, or –NO_2. In some embodiments, Ring B is optionally substituted 1-4 times by –F, -Cl, -Br-, -$S(O)_2NHCH_3$, -$S(O)NHCH_3$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_3$, -C(O)OH, -$C(O)OCH_3$, -CH_3, –OCH_3, or -$C(CH_3)_3$.

[0924] In some embodiments, Ring B is  ,  ,  .

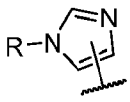
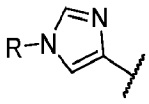


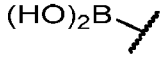
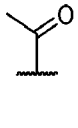
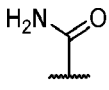
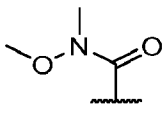
[0925] In some embodiments, Ring B is selected from those depicted in Table A, below.

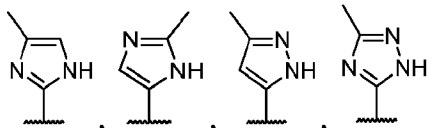
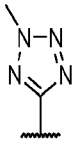
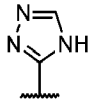
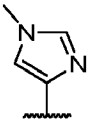
[0926] As defined generally above, R^2 is -H, or an optionally substituted 4-, 5-, or 6-membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

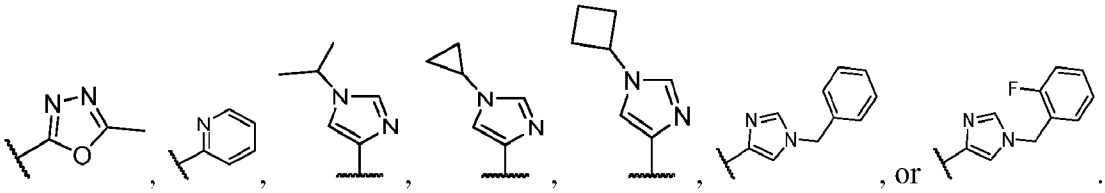
[0927] In some embodiments, R^2 is –H.

[0928] In some embodiments, R^2 is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^2 is a 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted 1-3 times by -C_{1-6} alkyl.

[0929] In some embodiments, R^2 is  , wherein R is as described herein. In some embodiments, R^2 is  , wherein R is as described herein.

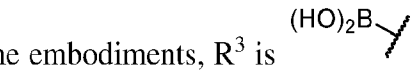
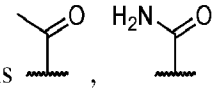
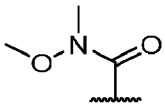
[0930] In some embodiments, R^2 is  . In some embodiments, R^2 is  ,  , or  .

[0931] In some embodiments, R^2 is an optionally substituted 5-membered ring having 1, 2, 3, or 4 nitrogen. In some embodiments, R^2 is selected from  , and  . In some embodiments, R^2 is  or  . In some embodiments, R^2 is



[0932] In some embodiments, R^2 is selected from those depicted in Table A, below.

[0933] As defined generally above, in some embodiments, R^3 is –H.

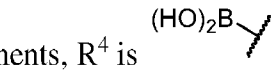
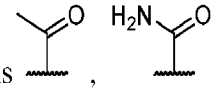
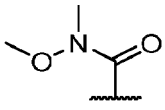
[0934] In some embodiments, R^3 is  . In some embodiments, R^3 is  ,  , or .

[0935] In some embodiments, R^3 is selected from those depicted in Table A, below.

[0936] As defined generally above, R^4 is -H, halogen, $-S(O)_2N(R)_2$, $-S(O)N(R)_2$, or $-C(O)N(R)_2$.

[0937] In some embodiments, R^4 is -H, halogen, $-S(O)_2N(R)_2$, $-S(O)N(R)_2$, $-C(O)N(R)_2$, or -C(O)OR. In some embodiments, R^4 is –H. In some embodiments, R^4 is halogen. In some embodiments, R^4 is -F. In some embodiments, R^4 is -Cl. In some embodiments, R^4 is -Br.

[0938] In some embodiments, R^4 is $-S(O)_2N(R)_2$, $-S(O)N(R)_2$, or $-C(O)N(R)_2$. In some embodiments, R^4 is $-S(O)_2N(R)_2$. In some embodiments, R^4 is $-S(O)N(R)_2$. In some embodiments, R^4 is $-C(O)N(R)_2$. In some embodiments, R^4 is $-S(O)_2NHCH_3$. In some embodiments, R^4 is $-S(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)NHCH_3$, -C(O)OH, or $-C(O)OCH_3$.

[0939] In some embodiments, R^4 is  . In some embodiments, R^4 is  ,  , or .

[0940] In some embodiments, R^4 is selected from those depicted in Table A, below.

[0941] As defined generally above, R^6 is -H or $-C_{1-6}$ aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or $–NO_2$.

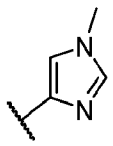
[0942] In some embodiments, R^6 is –H, -halogen, -CN, $–NO_2$, $-C_{1-6}$ aliphatic, $-OC_{1-6}$ aliphatic, or a 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur optionally substituted 1-3 times by $-C_{1-6}$ aliphatic or $-OC_{1-6}$

aliphatic, wherein each of -C_{1-6} aliphatic and -OC_{1-6} aliphatic is independently substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2.

[0943] In some embodiments, R^6 is –H. In some embodiments, R^6 is –F. In some embodiments, R^6 is –Cl. In some embodiments, R^6 is –Br. In some embodiments, R^6 is –CN. In some embodiments, R^6 is –NO_2.

[0944] In some embodiments, R^6 is -C_{1-6} aliphatic, substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2. In some embodiments, R^6 is unsubstituted -C_{1-6} aliphatic. In some embodiments, R^6 is –CH_3. In some embodiments, R^6 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2. In some embodiments, R^6 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -F. In some embodiments, R^6 is -C_{1-3} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^6 is –CF_3.

[0945] In some embodiments, R^6 is -OC_{1-6} aliphatic, substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2. In some embodiments, R^6 is unsubstituted -OC_{1-6} aliphatic. In some embodiments, R^6 is –OCH_3. In some embodiments, R^6 is -OC_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2. In some embodiments, R^6 is -OC_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -F. In some embodiments, R^6 is -OC_{1-3} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R^6 is –OCF_3.

[0946] In some embodiments, R^6 is a 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur optionally substituted 1-3 times by -C_{1-6} aliphatic or -OC_{1-6} aliphatic, wherein each of -C_{1-6} aliphatic and -OC_{1-6} aliphatic is independently substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2. In some embodiments, R^6 is a 5-membered ring having 1, 2, 3, or 4 nitrogen optionally substituted 1-3 times by -C_{1-6} aliphatic. In some embodiments, R^6 is 

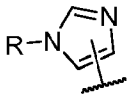
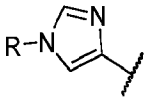
.

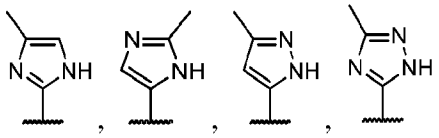
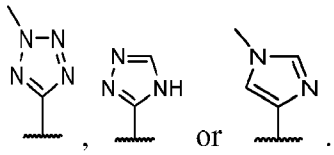
[0947] In some embodiments, R^6 is selected from those depicted in Table A, below.

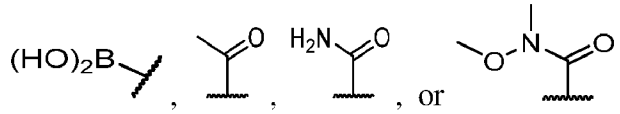
[0948] As defined generally above, R^w is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

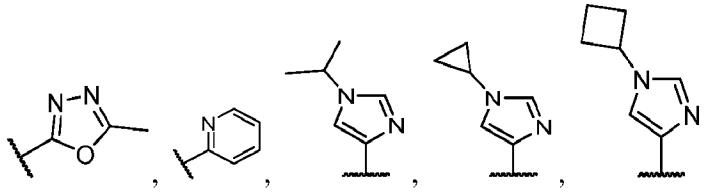
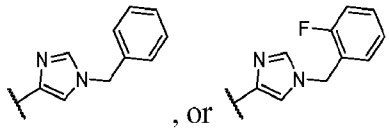
[0949] In some embodiments, R^w is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^w is a 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, optionally substituted 1-3 times by -C_{1-6} alkyl.

[0950] In some embodiments, R^W is  , wherein R is as described herein. In some embodiments, R^W is  , wherein R is as described herein.

[0951] In some embodiments, R^W is a 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted 1-3 times by -C_{1-6} alkyl. In some embodiments, R^W is an optionally substituted 5-membered ring having 1, 2, 3, or 4 nitrogen. In some embodiments, R^W is  ,  , or .

[0952] In some embodiments, R^W is  .

[0953] In some embodiments, R^W is  ,  , or .

[0954] In some embodiments, R^W is selected from those depicted in Table A, below.

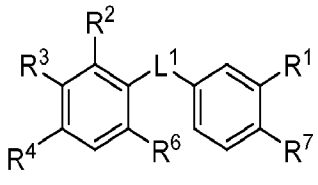
[0955] As defined generally above, R is independently -H or optionally substituted -C_{1-6} aliphatic.

[0956] In some embodiments, R is –H. In some embodiments, R is optionally substituted -C_{1-6} aliphatic. In some embodiments, R is unsubstituted -C_{1-6} aliphatic. In some embodiments, R is –CH_3. In some embodiments, R is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or –NO_2. In some embodiments, R is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –

F. In some embodiments, R is -C_{1-3} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F. In some embodiments, R is –CF_3.

[0957] In some embodiments, R is selected from those depicted in Table A, below.

[0958] In some embodiments, a TEAD inhibitor is a compound of **Formula A-2**:



, or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^6, R^7, and L^1 is independently as defined and described in embodiments in Section of TEAD Inhibitors of Formulae A, and A-1 to A-50.

[0959] In some embodiments, the present invention provides a compound of **Formula A-2**, or a pharmaceutically acceptable salt thereof, wherein:

(a):

L^1 is -O- or -S-;

R^1 is -C_{1-6} aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by halogen;

R^2 is an optionally substituted 5-membered aromatic ring having 1, 2, 3, or 4 nitrogen;

R^3 is -H;

R^4 is -$S(O)_2N(R)_2$; -$S(O)N(R)_2$, or -$C(O)N(R)_2$, each R independently is selected -H and optionally substituted -C_{1-6} aliphatic;

R^6 is -H or -C_{1-6} aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by halogen; and

R^7 is -H; or

(b):

L^1 is -NH-;

R^1 is -C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen;

R^2 is an optionally substituted 5-membered aromatic ring having 1, 2, 3, or 4 nitrogen;

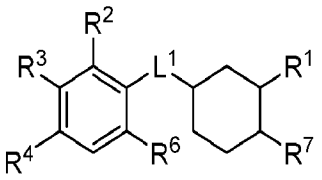
R^3 is -H;

R^4 is -$S(O)_2N(R)_2$, -$S(O)N(R)_2$, or -$C(O)N(R)_2$, each R independently is selected from -H and optionally substituted -C_{1-6} aliphatic;

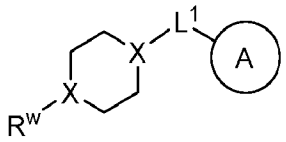
R^6 is -C_{1-6} aliphatic; and

R^7 is -H.

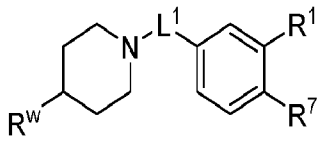
[0960] In some embodiments, a TEAD inhibitor is a compound of **Formula**:



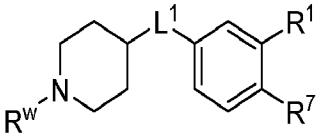
A-3



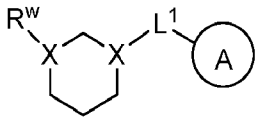
A-4



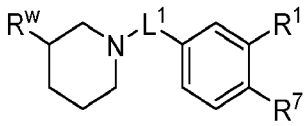
A-5



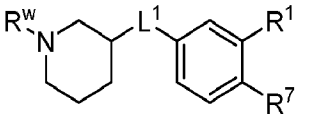
A-6



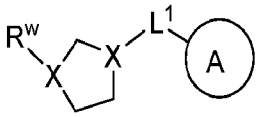
A-7



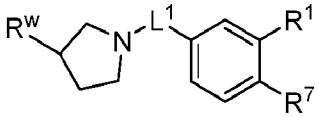
A-8



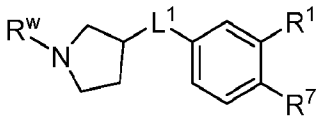
A-9



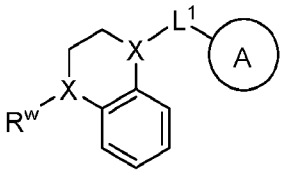
A-10



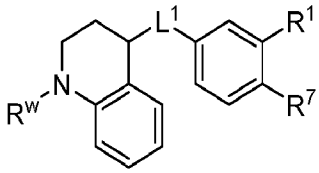
A-11



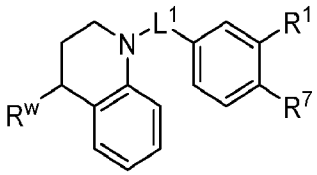
A-12



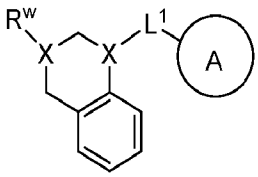
A-13



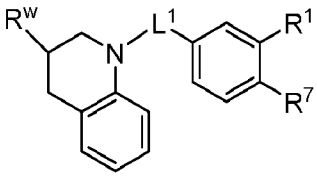
A-14



A-15

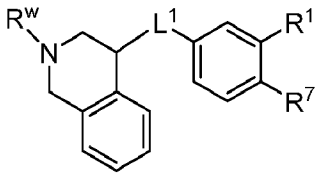


A-16



A-17

or



A-18

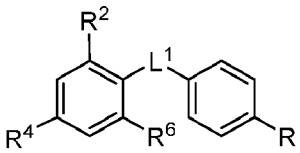
or a pharmaceutically acceptable salt thereof, wherein each of X is independently C or N, and each of Ring A, R^w, R^1, R^2, R^3, R^4, R^6, R^7, and L^1 is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50.

[0961] In some embodiments, a TEAD inhibitor is a compound of Formula **A**, or a pharmaceutically acceptable salt thereof, wherein Ring A is phenyl, a 6-membered monocyclic

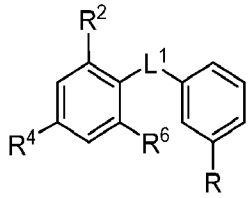
heteroaromatic ring having 1 or 2 nitrogen, or a 10-membered bicyclic heteroaromatic ring having 1-2 nitrogen; Ring B is phenyl or a 6-membered monocyclic heteroaromatic ring having 1 or 2 nitrogen; and each of R^w and L^1 is as defined above and described in embodiments herein, both singly and in combination.

[0962] In some embodiments, a TEAD inhibitor is a compound selected from the following:

i. Formula (**A-19**) or (**A-20**):



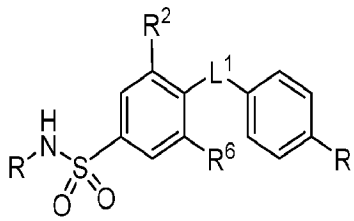
A-19



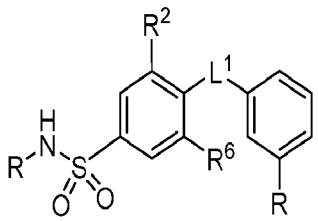
A-20

wherein L^1 is a C_{2-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -N(R)-, and each of R^2, R^4, R^6, and R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

ii. Formula (**A-21**) or (**A-22**):



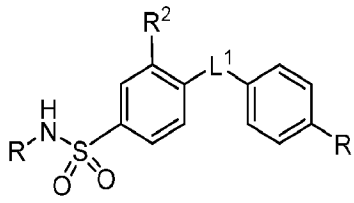
A-21



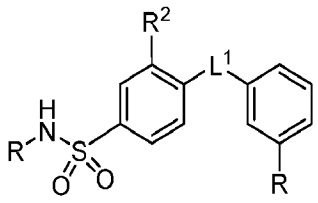
A-22

wherein L^1 is a C_{2-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -N(R)-, and each of R^2, R^6, and R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

iii. Formula (**A-23**) or (**A-24**):



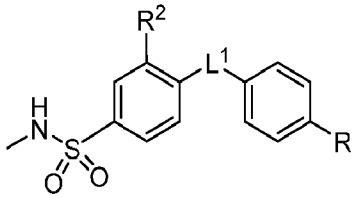
A-23



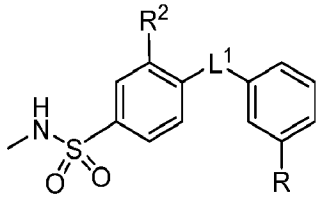
A-24

wherein L^1 is a C_{2-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, each of R^2 and R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

iv. Formula (**A-25**) or (**A-26**):



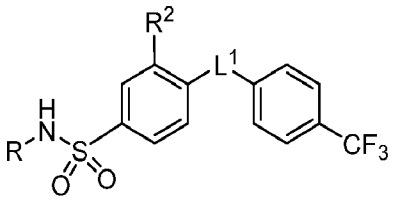
A-25



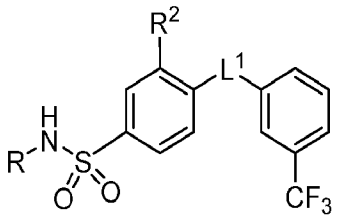
A-26

wherein L^1 is a C_{2-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, R is $-C_{1-3}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F, and R^2 is as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

v. Formula (**A-27**) or (**A-28**):



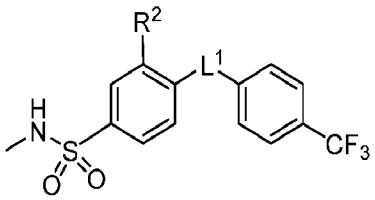
A-27



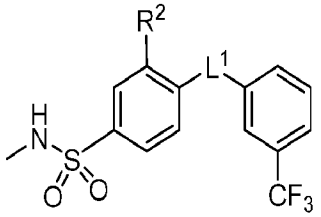
A-28

wherein L^1 is a C_{2-6} bivalent straight hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, R is optionally substituted $-C_{1-6}$ aliphatic, and R^2 is as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

vi. Formula (**A-29**) or (**A-30**):



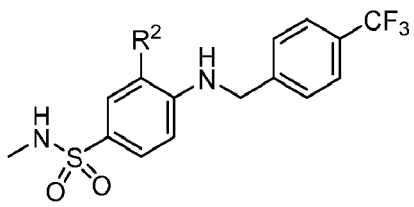
A-29



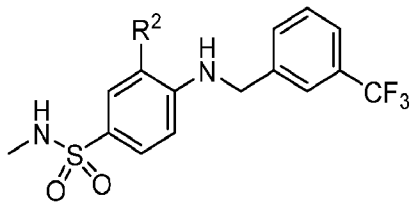
A-30

wherein L^1 is a C_{2-6} bivalent straight hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, and R^2 is as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

vii. Formula (**A-31**) or (**A-32**):



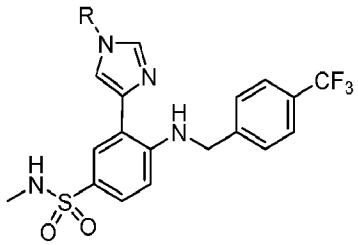
A-31



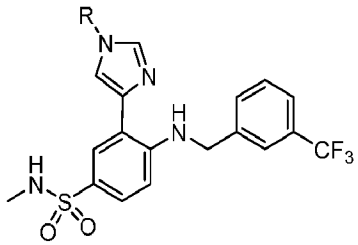
A-32

wherein R^2 is an optionally substituted 5-membered ring having 1, 2, 3, or 4 nitrogen;

viii. Formula (**A-33**) or (**A-34**):



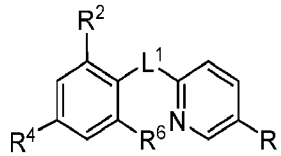
(A-33)



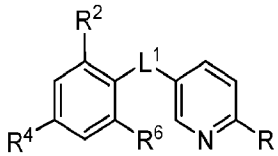
(A-34)

wherein R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

ix. Formula (**A-35**) or (**A-36**):



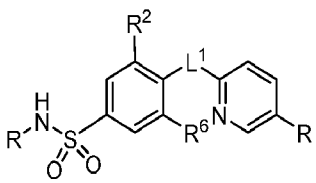
A-35

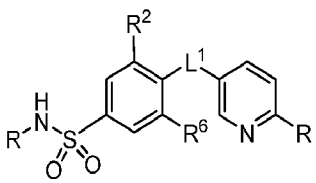


A-36

wherein L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -N(R)-, and each of R^2, R^4, R^6, and R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

x. Formula (**A-37**) or (**A-38**):

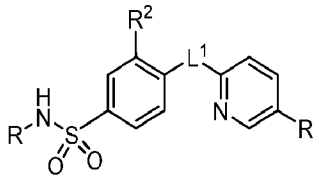




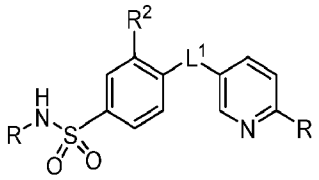
A-37 **A-38**

wherein L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -N(R)-, and each of R^2, R^6, and R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

xi. Formula **(A-39)** or **(A-40)**:



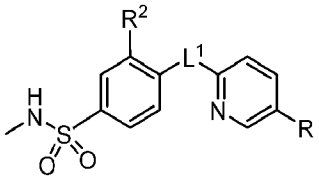
A-39



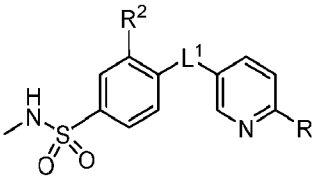
A-40

wherein L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, each of R^2 and R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

xii. Formula **(A-41)** or **(A-42)**:



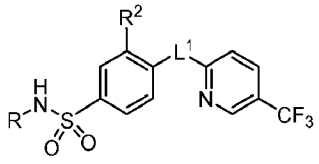
A-41



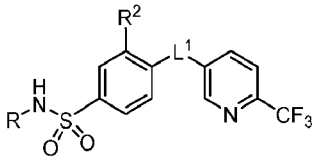
A-42

wherein L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, R is $-C_{1-3}$ aliphatic substituted 1, 2, 3, 4, 5, or 6 times by –F, and R^2 is as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

xiii. Formula **(A-43)** or **(A-44)**:



A-43

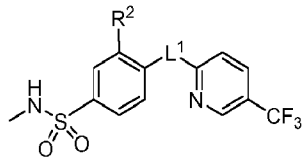


A-44

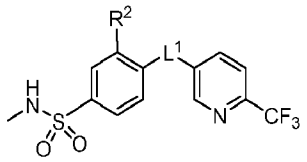
wherein L^1 is a C_{1-6} bivalent straight hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, R is optionally substituted $-C_{1-6}$ aliphatic, and R^2 is as

defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

xiv. Formula (**A-45**) or (**A-46**):



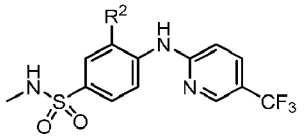
A-45



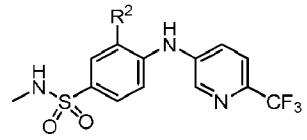
A-46

wherein L^1 is a C_{1-6} bivalent straight hydrocarbon chain wherein 1 methylene unit of the chain is replaced with -NH-, and R^2 is as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50;

xv. Formula (**A-47**) or (**A-48**):



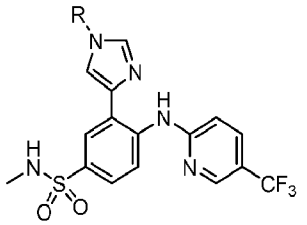
A-47



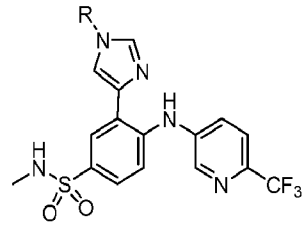
A-48

wherein R^2 is an optionally substituted 5-membered ring having 1, 2, 3, or 4 nitrogen; or

xvi. Formula (**A-49**) or (**A-50**):



A-49

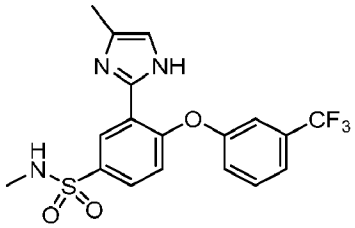
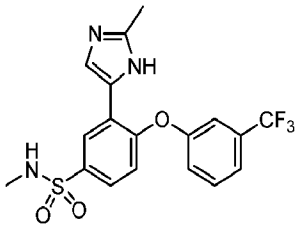
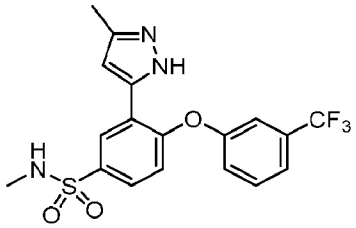
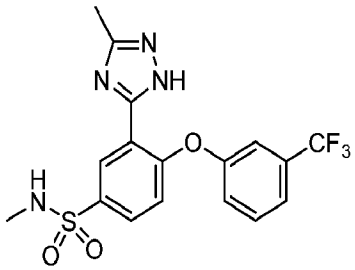
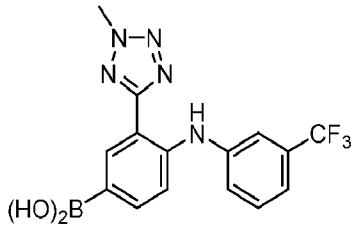
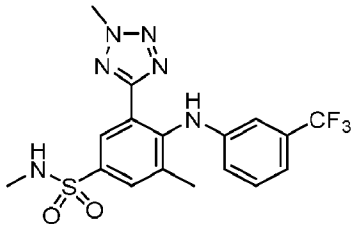
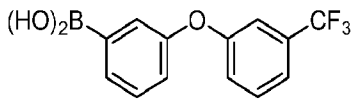
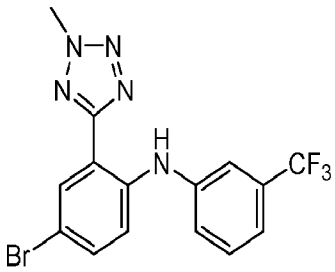
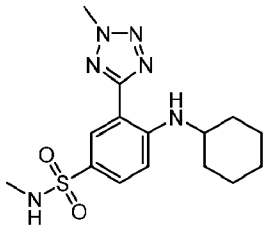
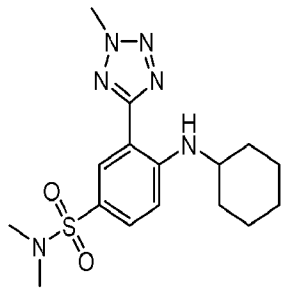
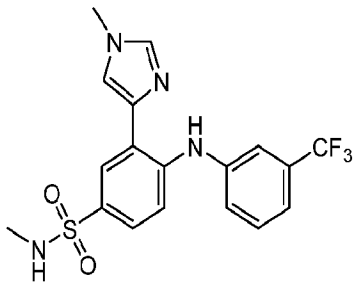
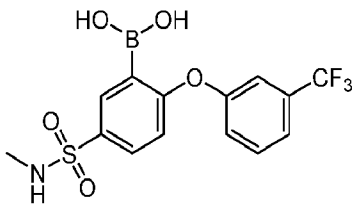
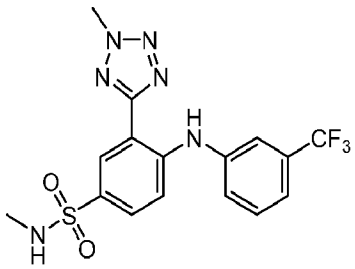
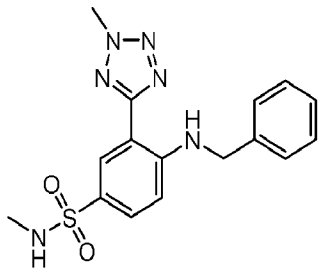
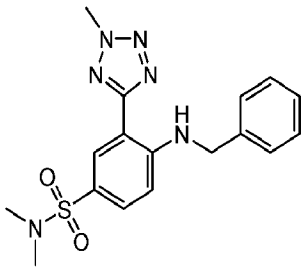


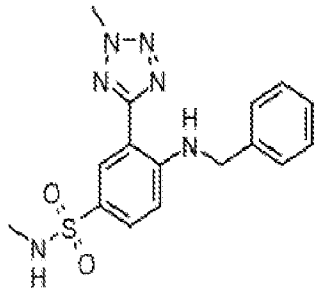
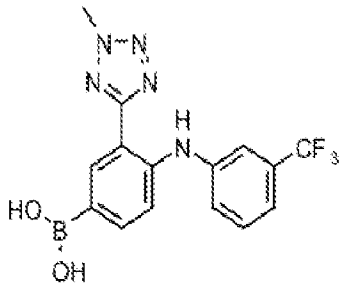
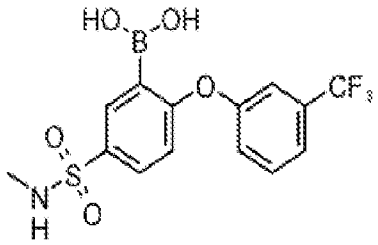
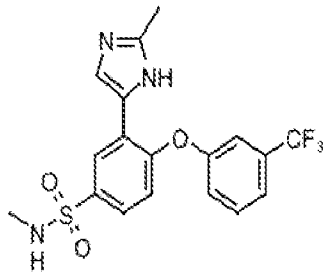
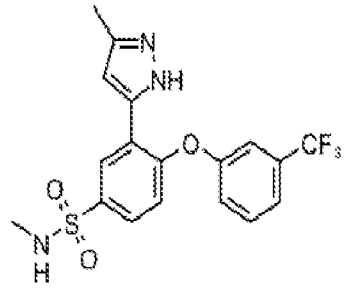
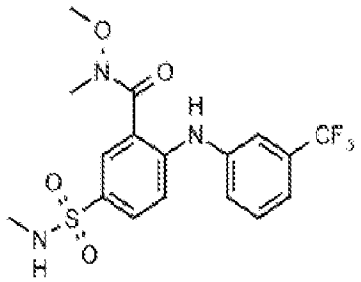
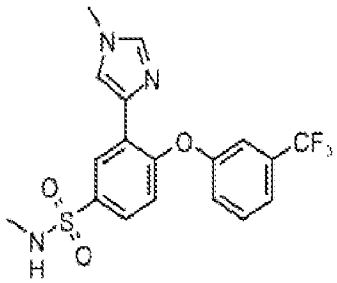
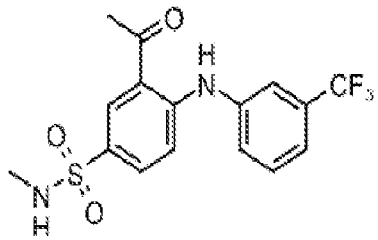
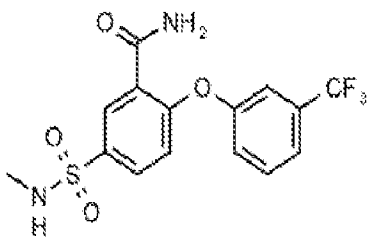
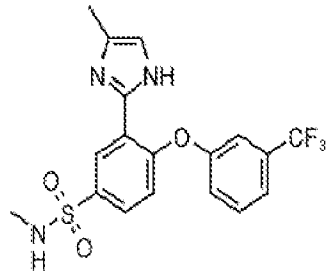
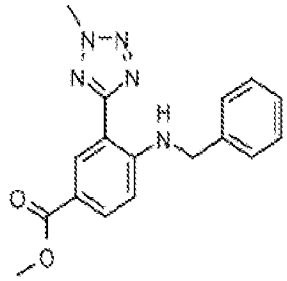
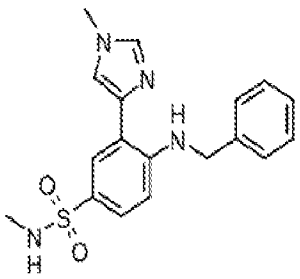
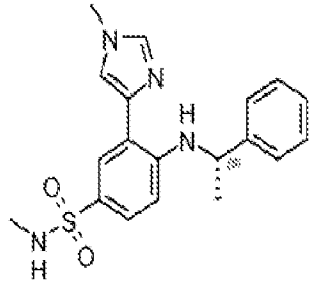
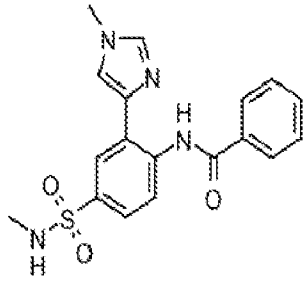
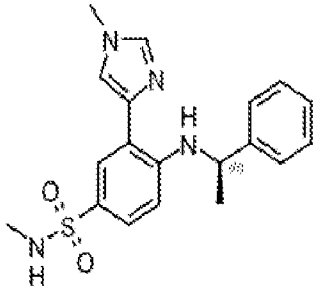
A-50

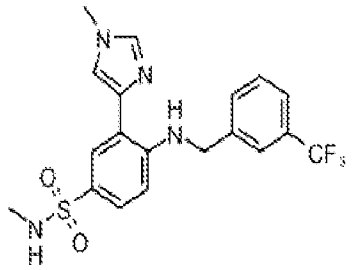
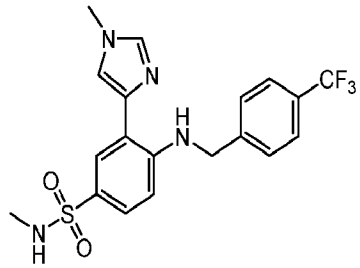
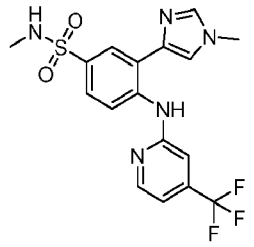
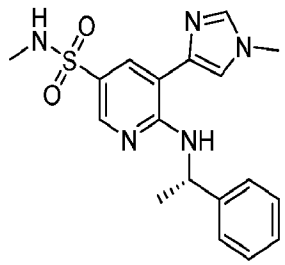
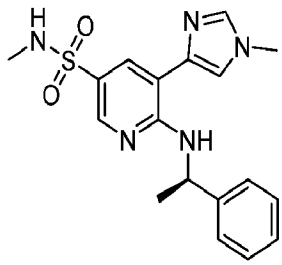
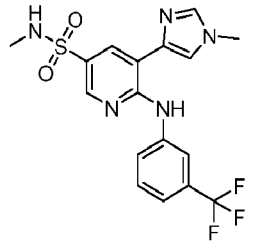
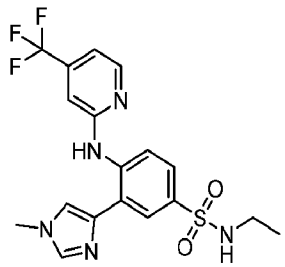
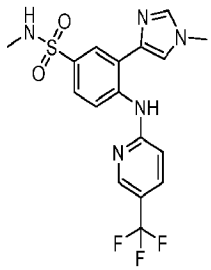
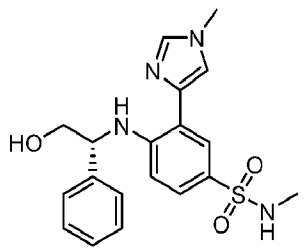
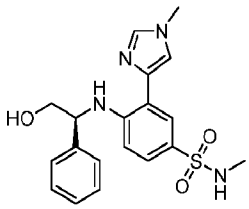
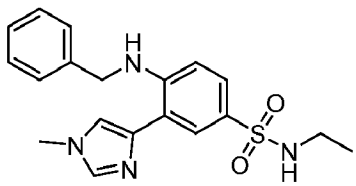
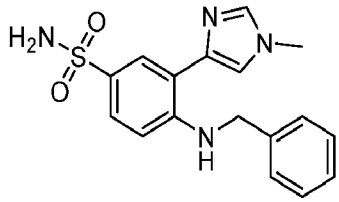
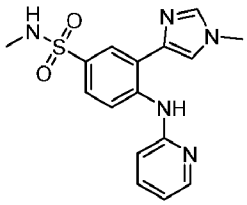
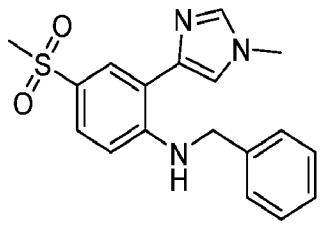
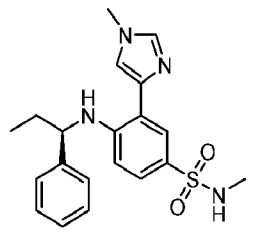
wherein R is independently as defined and described in embodiments in the section of TEAD Inhibitors of Formulae A, and A-1 to A-50.

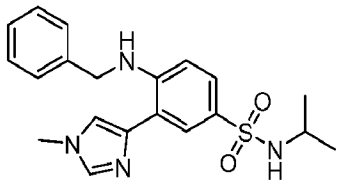
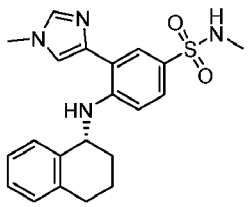
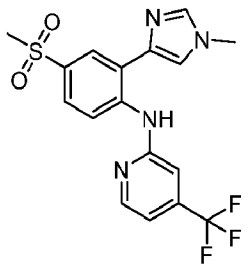
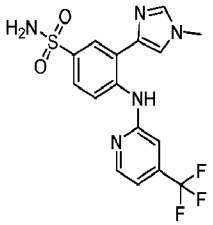
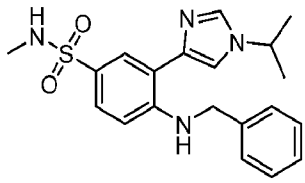
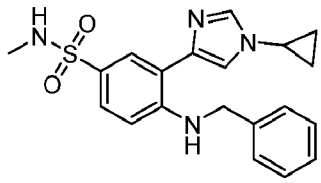
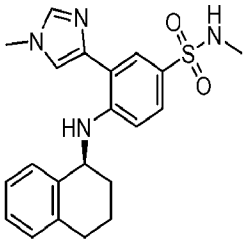
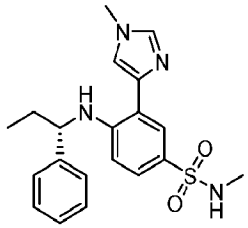
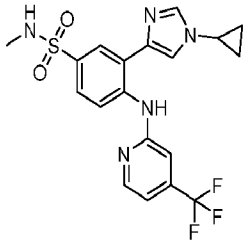
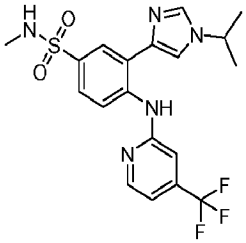
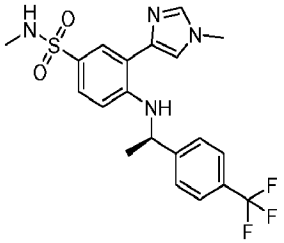
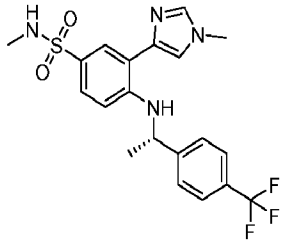
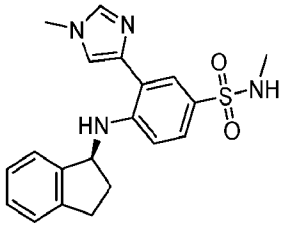
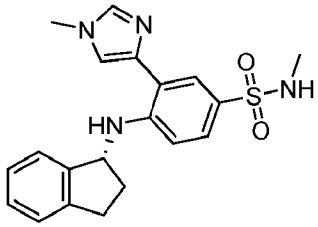
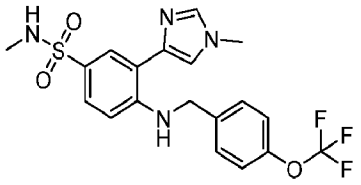
[0963] In some embodiments, a TEAD inhibitor is selected from those listed in **Table A**, or a pharmaceutically acceptable salt thereof.

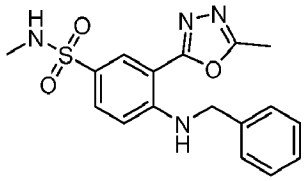
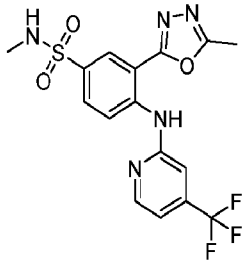
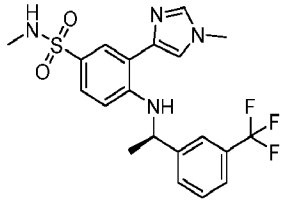
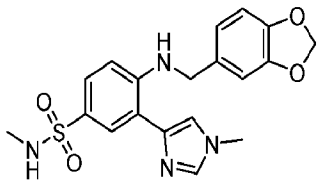
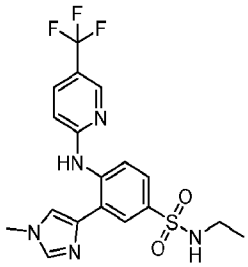
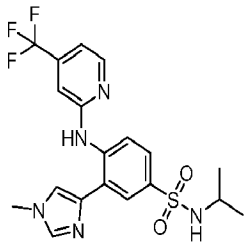
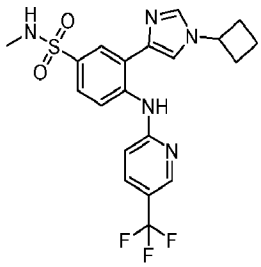
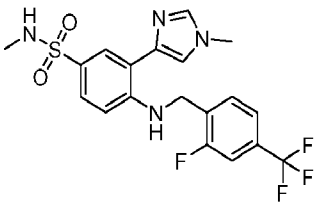
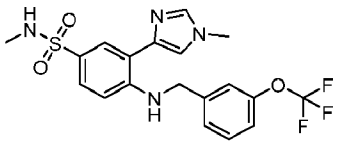
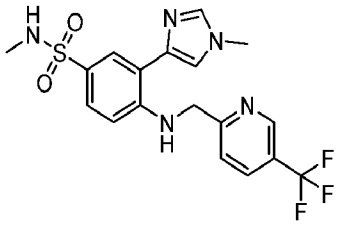
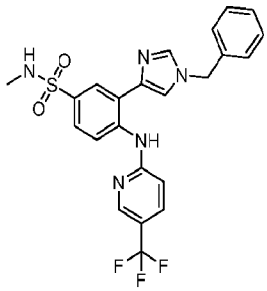
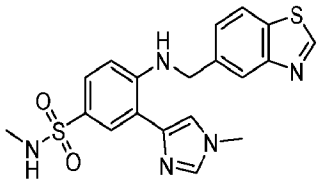
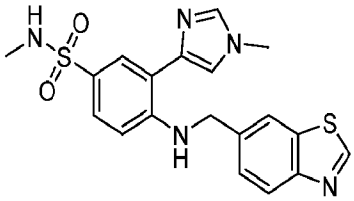
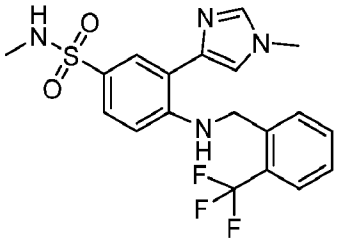
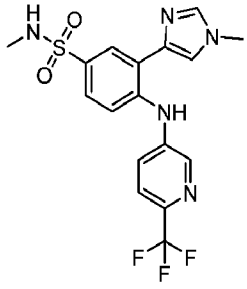
Table A. Exemplary TEAD Inhibitors

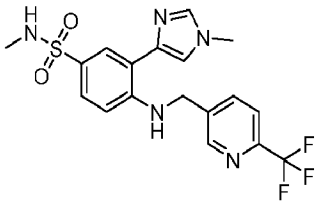
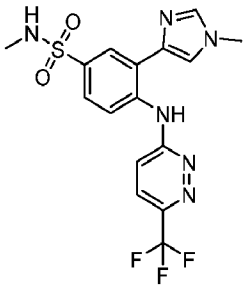
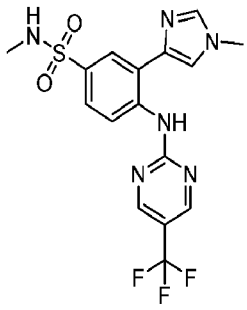
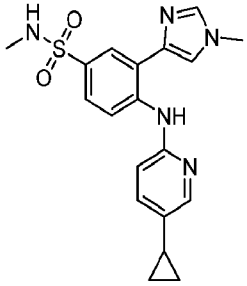
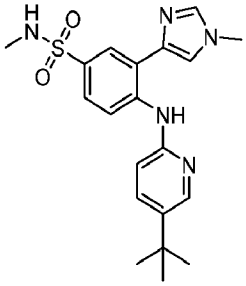
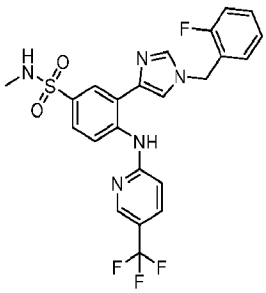
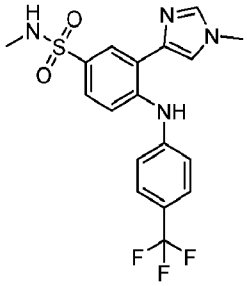
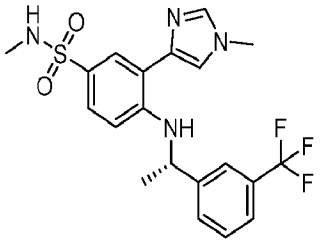
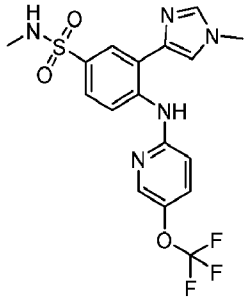
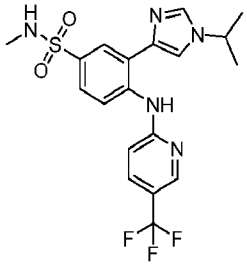
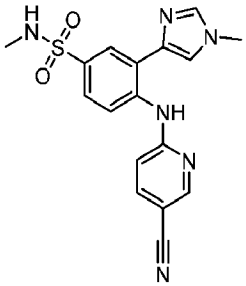
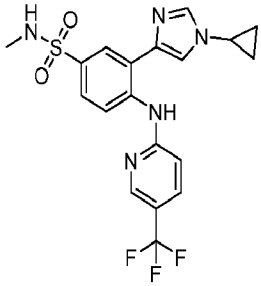
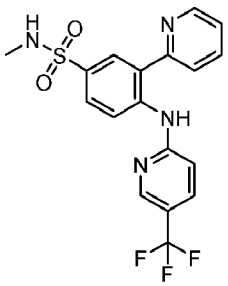
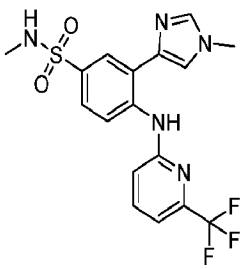
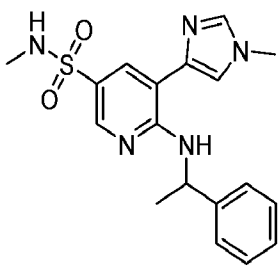
T-A-1 	**T-A-2** 	**T-A-3** 
T-A-4 	**T-A-5** 	**T-A-6** 
T-A-7 	**T-A-8** 	**T-A-9** 
T-A-10 	**T-A-11** 	**T-A-12** 
T-A-13 	**T-A-14** 	**T-A-15** 

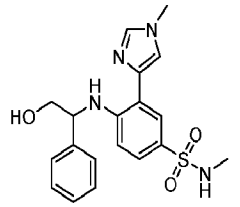
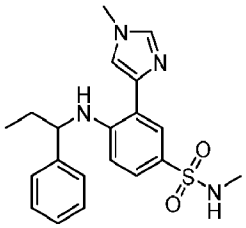
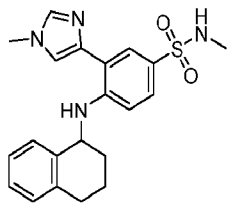
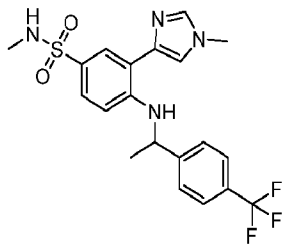
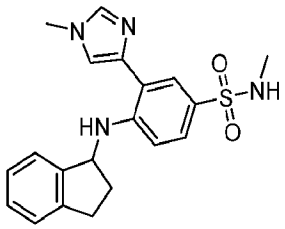
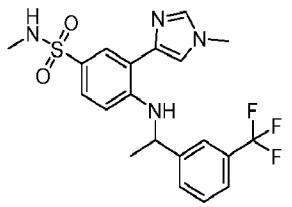
T-A-16 	**T-A-17** 	**T-A-18** 
T-A-19 	**T-A-20** 	**T-A-21** 
T-A-22 	**T-A-23** 	**T-A-24** 
T-A-25 	**T-A-26** 	**T-A-27** 
T-A-28 	**T-A-29** 	**T-A-30** 

T-A-31 	**T-A-32** 	**T-A-33** 
T-A-34 	**T-A-35** 	**T-A-36** 
T-A-37 	**T-A-38** 	**T-A-39** 
T-A-40 	**T-A-41** 	**T-A-42** 
T-A-43 	**T-A-44** 	**T-A-45** 

T-A-46 	**T-A-47** 	**T-A-48** 
T-A-49 	**T-A-50** 	**T-A-51** 
T-A-52 	**T-A-53** 	**T-A-54** 
T-A-55 	**T-A-56** 	**T-A-57** 
T-A-58 	**T-A-59** 	**T-A-60** 

T-A-61 	**T-A-62** 	**T-A-63** 
T-A-64 	**T-A-65** 	**T-A-66** 
T-A-67 	**T-A-68** 	**T-A-69** 
T-A-70 	**T-A-71** 	**T-A-72** 
T-A-73 	**T-A-74** 	**T-A-75** 

T-A-76 	**T-A-77** 	**T-A-78** 
T-A-79 	**T-A-80** 	**T-A-81** 
T-A-82 	**T-A-83** 	**T-A-84** 
T-A-85 	**T-A-86** 	**T-A-87** 
T-A-88 	**T-A-89** 	**T-A-90** 

T-A-91 	**T-A-92** 	**T-A-93** 
T-A-94 	**T-A-95** 	**T-A-96** 

[0964] In certain embodiments, a TEAD inhibitor is T-A-31, T-A-32, T-A-56, T-A- 57, T-A-60, T-A-63, T-A-68, T-A-74, T-A-83, T-A-94, T-A-96, or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-31 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-32 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-56 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A- 57 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-60 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-63 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-68 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-74 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-83 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-94 or a pharmaceutically acceptable salt thereof. In certain embodiments, a TEAD inhibitor is T-A-96 or a pharmaceutically acceptable salt thereof.

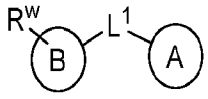
[0965] In certain embodiments, a TEAD inhibitor is T-A-31, T-A-32, T-A-56, T-A- 57, T-A-60, T-A-63, T-A-68, T-A-74, T-A-83, T-A-94, or T-A-96. In certain embodiments, a TEAD inhibitor is T-A-31. In certain embodiments, a TEAD inhibitor is T-A-32. In certain embodiments, a TEAD inhibitor is T-A-56. In certain embodiments, a TEAD inhibitor is T-A-57. In certain embodiments, a TEAD inhibitor is T-A-60. In certain embodiments, a TEAD inhibitor is T-A-63. In certain embodiments, a TEAD inhibitor is T-A-68. In certain

embodiments, a TEAD inhibitor is T-A-74. In certain embodiments, a TEAD inhibitor is T-A-83. In certain embodiments, a TEAD inhibitor is T-A-94. In certain embodiments, a TEAD inhibitor is T-A-96.

TEAD Inhibitors of Formulae B and B-1

[0966] In certain embodiments, a TEAD inhibitor is selected from those described in WO 2020/243423, the contents of which are herein incorporated by reference in their entirety.

[0967] In certain embodiments, a TEAD inhibitor is a compound of **Formula B**:



, or a pharmaceutically acceptable salt thereof, wherein

L^1 is a covalent bond, or a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

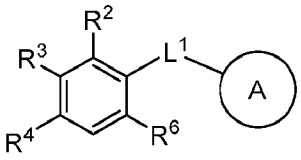
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^w is a warhead group; wherein when R^w is a saturated or partially unsaturated monocyclic carbocyclic or heterocyclic ring, it optionally forms a spiro bicyclic ring with Ring B; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic.

[0968] In certain embodiments, a TEAD inhibitor is a compound of formula **B-1**



, or a pharmaceutically acceptable salt thereof, wherein

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

Ring A is a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Ring A is optionally substituted 1-2 times by halogen, -CN, –NO_2, or -C_{1-6} aliphatic substituted 0-6 times by halogen, -CN, or –NO_2;

R^2 is -H, or a warhead group;

R^3 is -H or a warhead group;

R^4 is -H, halogen, -S(O)$_2$N(R)$_2$, -S(O)N(R)$_2$, -C(O)N(R)$_2$, or a warhead group;

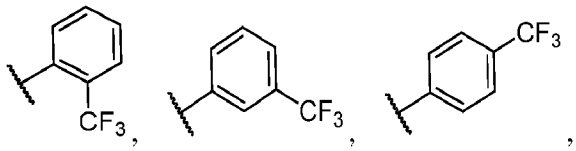
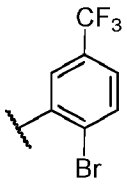
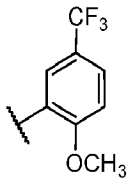
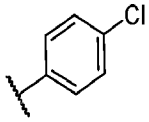
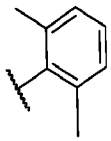
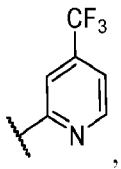
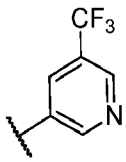
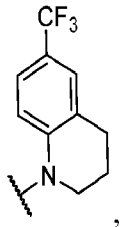
R^6 is -H or -C_{1-6} aliphatic substituted 0-6 times by halogen, -CN, or –NO_2; and

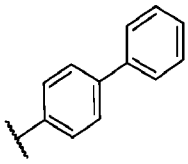
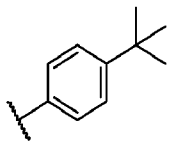
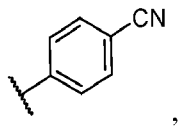
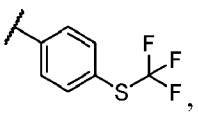
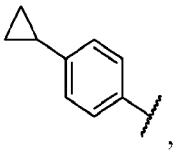
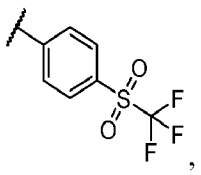
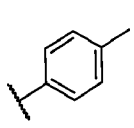
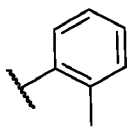
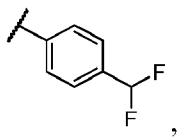
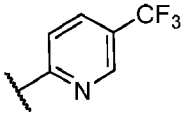
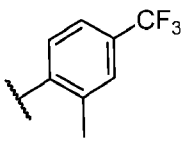
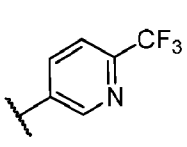
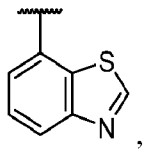
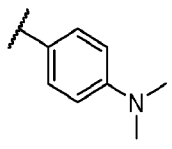
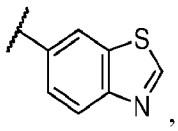
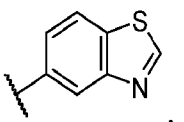
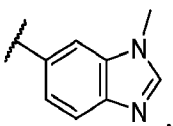
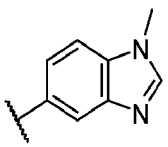
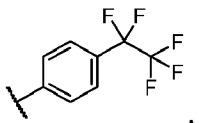
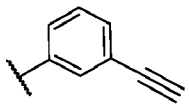
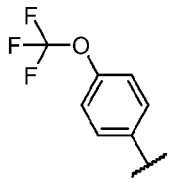
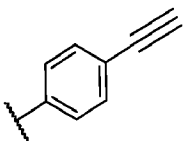
each R is independently -H or optionally substituted -C_{1-6} aliphatic.

[0969] In some embodiments, L^1 is -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-. In some embodiments, L^1 is -O-, -S-, or -N(R)-. In some embodiments, L^1 is -O-. In some embodiments, L^1 is -S-. In some embodiments, L^1 is -N(R)-. In some embodiments, L^1 is -NH-. In some embodiments, L^1 is selected from those depicted in Table B, below.

[0970] In some embodiments, Ring A is optionally substituted phenyl. In some embodiments, Ring A is optionally substituted 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring A is optionally

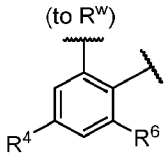
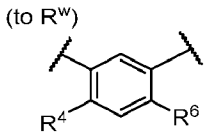
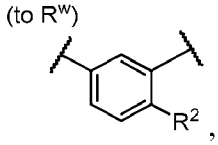
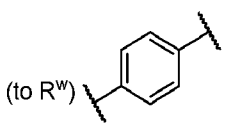
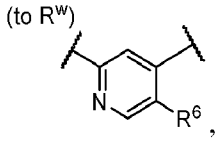
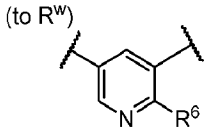
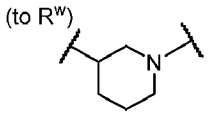
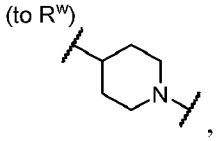
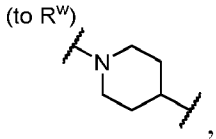
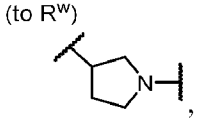
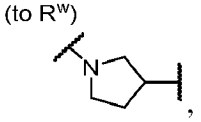
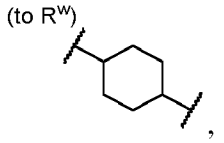
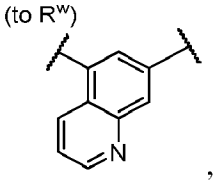
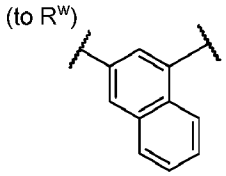
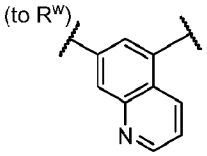
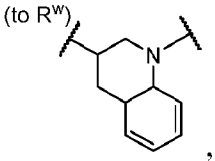
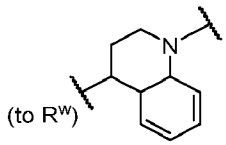
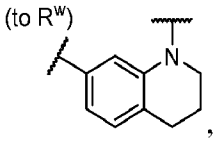
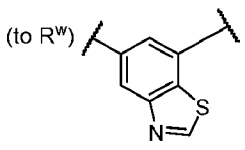
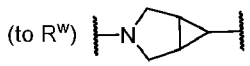
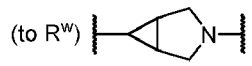
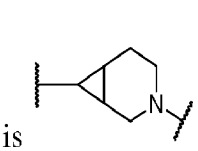
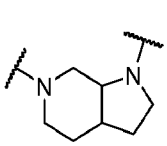
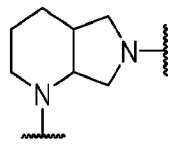
substituted 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is optionally substituted 8-10 membered bicyclic aromatic ring. In some embodiments, Ring A is optionally substituted 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0971] In some embodiments, Ring A is  , , ,  ,  ,  ,  ,  ,  ,  , or .

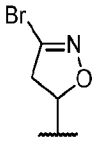
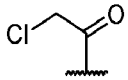
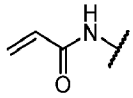
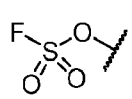
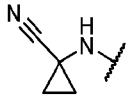
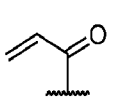
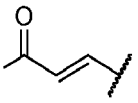
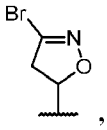
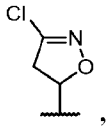
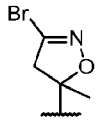
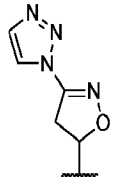
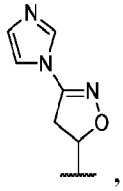
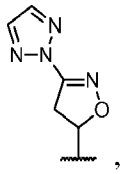
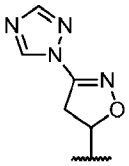
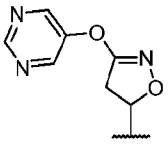
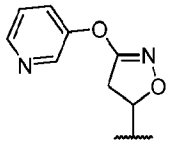
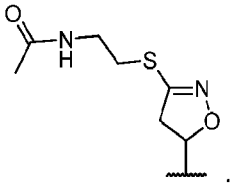
[0972] In some embodiments, Ring A is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0973] In some embodiments, Ring A is selected from those depicted in Table B, below.

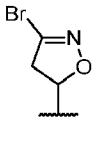
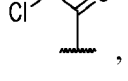
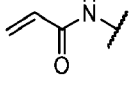
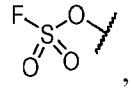
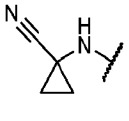
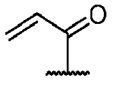
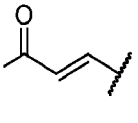
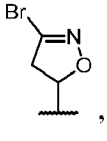
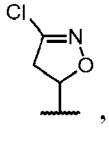
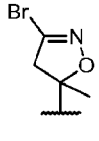
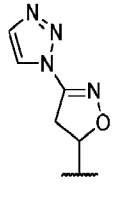
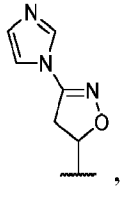
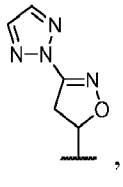
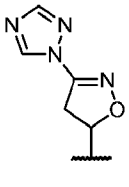
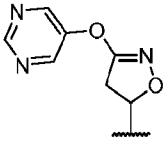
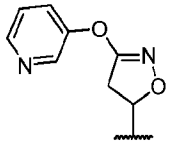
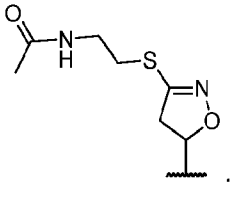
[0974] In some embodiments, Ring B is optionally substituted phenyl. In some embodiments, Ring B is optionally substituted 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring B is optionally substituted 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is optionally substituted 8-10 membered bicyclic aromatic ring. In some embodiments, Ring B is optionally substituted 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0975] In some embodiments, Ring B is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, Ring B is  ,  , or  .

[0976] In some embodiments, Ring B is selected from those depicted in Table B, below.

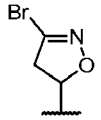
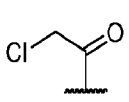
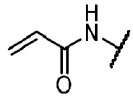
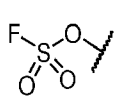
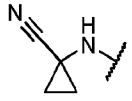
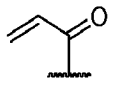
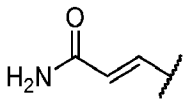
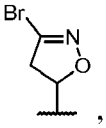
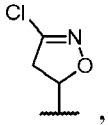
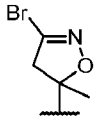
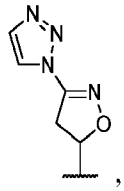
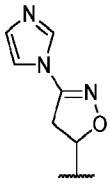
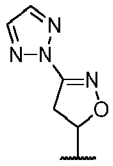
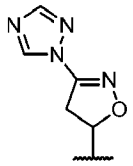
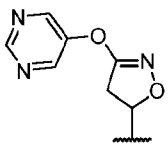
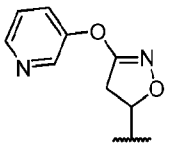
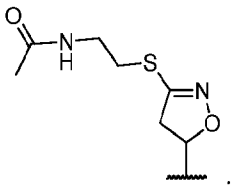
[0977] In some embodiments, R^2 is –H. In some embodiments, R^2 is a warhead group. In some embodiments, R^2 is  ,  ,  ,  , or  . In some embodiments, R^2 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0978] In some embodiments, R^2 is selected from those depicted in Table B, below.

[0979] In some embodiments, R^3 is –H. In some embodiments, R^3 is a warhead group. In some embodiments, R^3 is  ,  ,  ,  , or  . In some embodiments, R^3 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

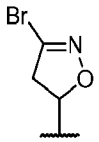
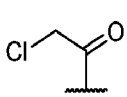
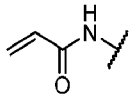
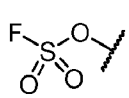
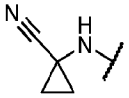
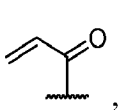
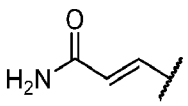
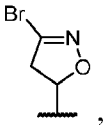
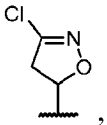
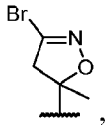
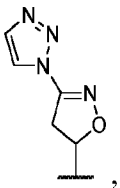
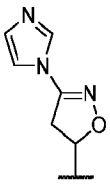
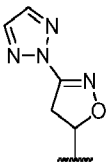
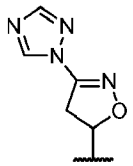
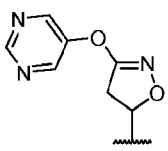
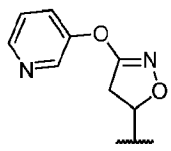
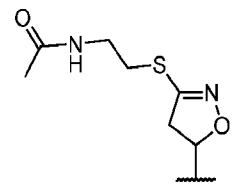
[0980] In some embodiments, R^3 is selected from those depicted in Table B, below.

[0981] In some embodiments, R^4 is –H. In some embodiments, R^4 is halogen. In some embodiments, R^4 is -F. In some embodiments, R^4 is -Cl. In some embodiments, R^4 is -Br. In some embodiments, R^4 is $-S(O)_2N(R)_2$. In some embodiments, R^4 is $-S(O)N(R)_2$. In some embodiments, R^4 is $-C(O)N(R)_2$. In some embodiments, R^4 is $-S(O)_2NHCH_3$.

[0982] In some embodiments, R^4 is a warhead group. In some embodiments, R^4 is  ,  ,  ,  , or  . In some embodiments, R^4 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0983] In some embodiments, R^4 is selected from those depicted in Table B, below.

[0984] In some embodiments, R^6 is -H. In some embodiments, R^6 is -C_{1-6} aliphatic substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or $-NO_2$. In some embodiments, R^6 is selected from those depicted in Table B, below.

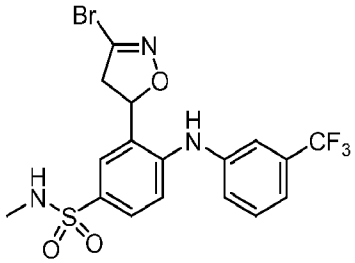
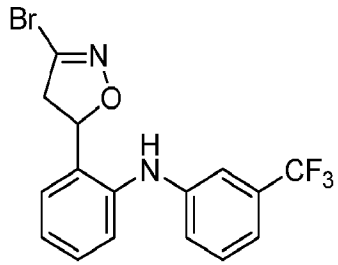
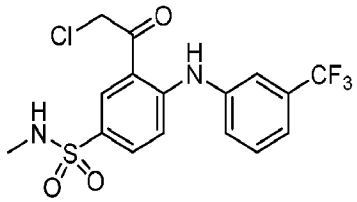
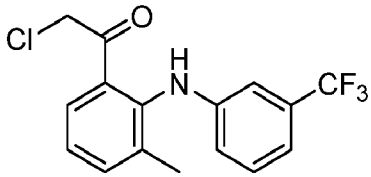
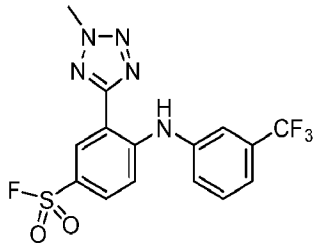
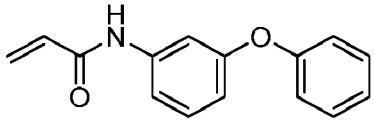
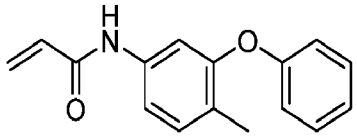
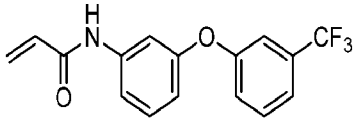
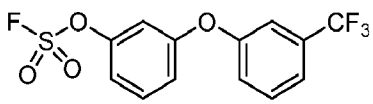
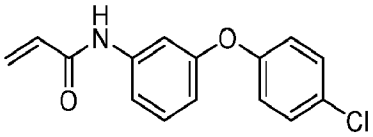
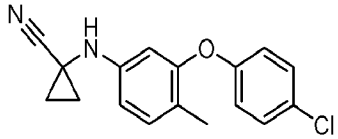
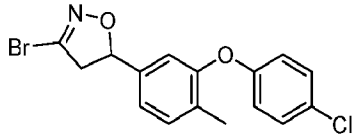
[0985] In some embodiments, R^w is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^w is selected from those depicted in Table B, below.

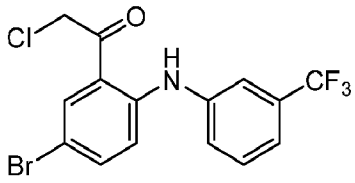
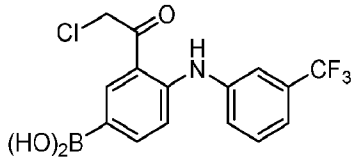
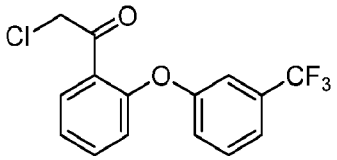
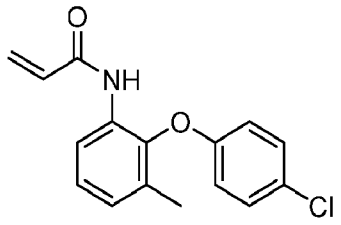
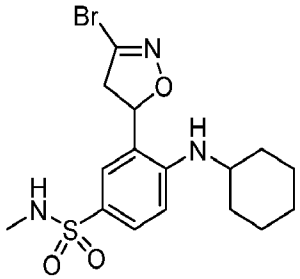
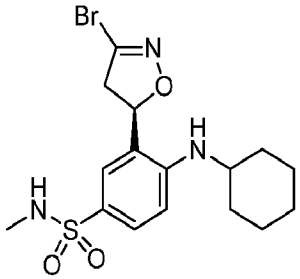
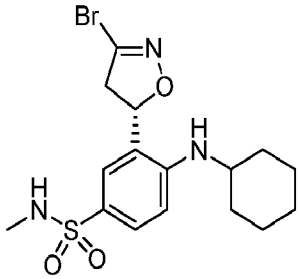
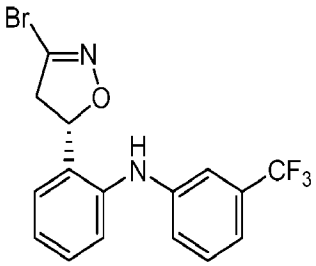
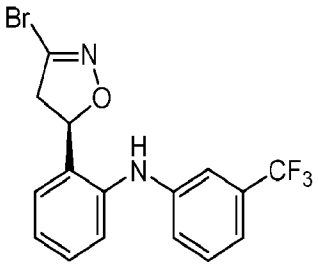
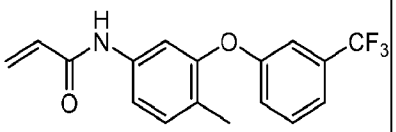
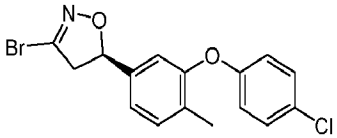
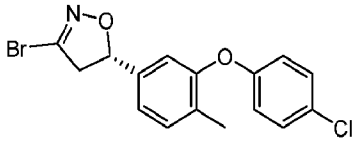
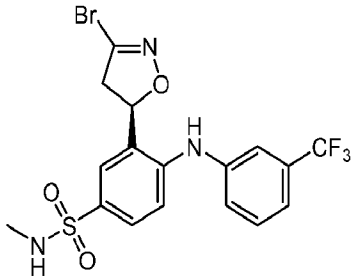
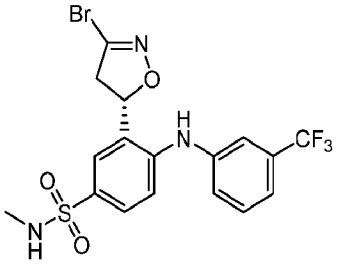
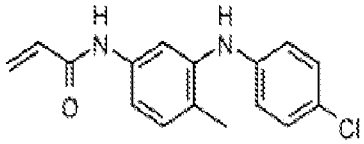
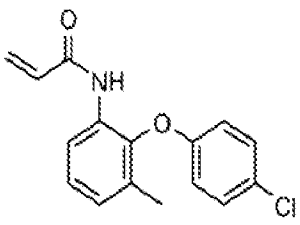
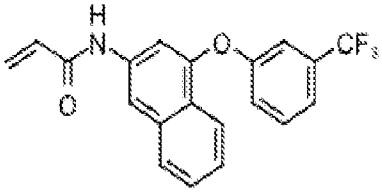
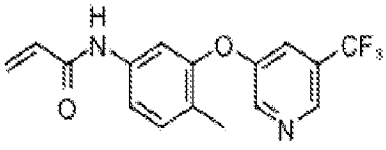
[0986] In some embodiments, R is –H. In some embodiments, R is optionally substituted -C_{1-6} aliphatic. In some embodiments, R is unsubstituted -C_{1-6} aliphatic. In some embodiments, R is $-CF_3$. In some embodiments, R is $-CH_3$, $-C(CH_3)_3$, $-CHF_2$, cyclopropyl, $-CF_2CF_3$, or .

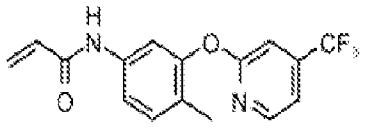
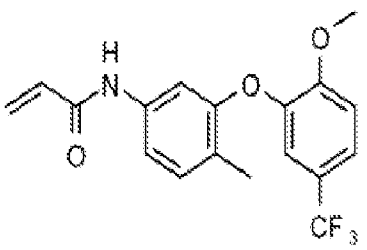
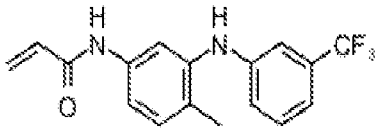
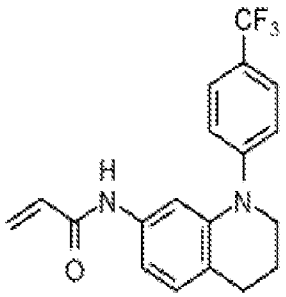
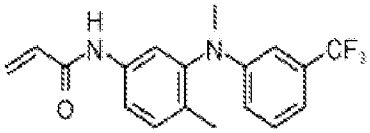
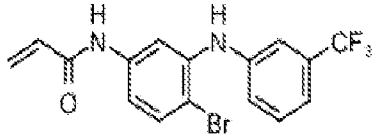
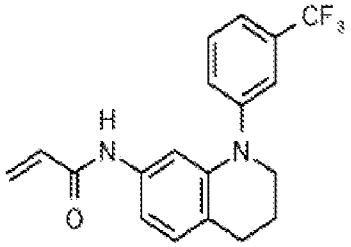
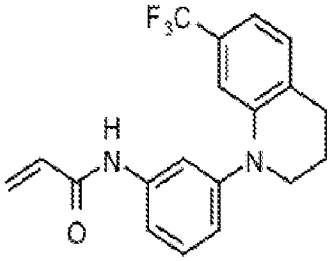
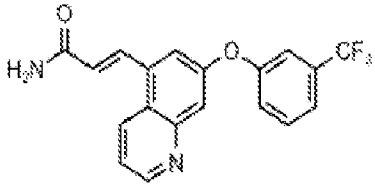
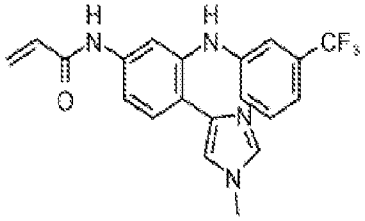
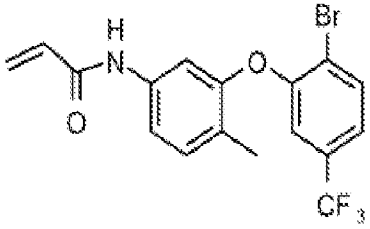
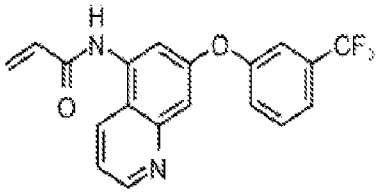
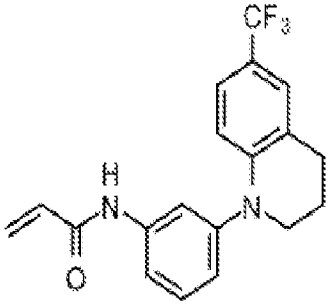
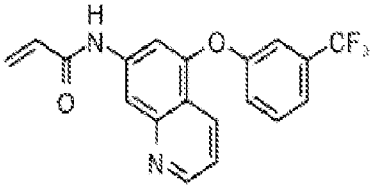
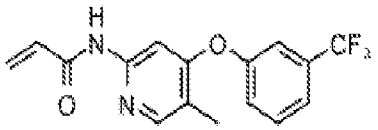
[0987] A "warhead group," as used herein, is capable of covalently binding to an amino acid residue (such as cysteine, lysine, histidine, or other residues capable of being covalently modified) present in the binding pocket of a target protein, for example, TEAD, thereby irreversibly inhibiting the protein. In some embodiments, a warhead group is as defined and described in embodiments in WO 2020/243423, the content of which is herein incorporated by reference in its entirety.

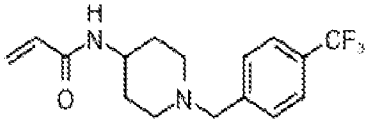
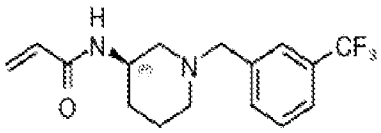
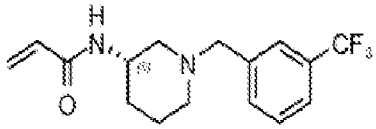
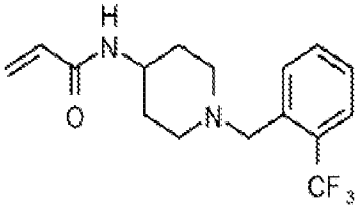
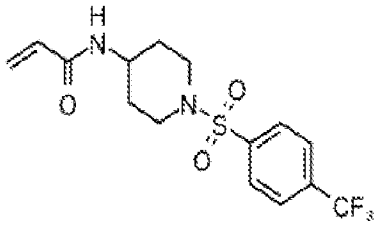
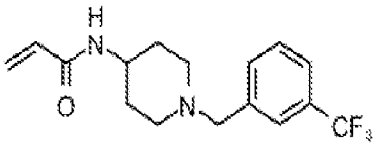
[0988] In some embodiments, a TEAD inhibitor is selected from those listed in **Table B**, or a pharmaceutically acceptable salt thereof.

Table B. Exemplary TEAD Inhibitors

T-B-1 	**T-B-2** 	**T-B-3** 
T-B-4 	**T-B-5** 	**T-B-6** 
T-B-7 	**T-B-8** 	**T-B-9** 
T-B-10 	**T-B-11** 	**T-B-12** 

T-B-13 	**T-B-14** 	**T-B-15** 
T-B-16 	**T-B-17** 	**T-B-18** 
T-B-19 	**T-B-20** 	**T-B-21** 
T-B-22 	**T-B-23** 	**T-B-24** 
T-B-25 	**T-B-26** 	**T-B-27** 
T-B-28 	**T-B-29** 	**T-B-30** 

T-B-31 	**T-B-32** 	**T-B-33** 
T-B-34 	**T-B-35** 	**T-B-36** 
T-B-37 	**T-B-38** 	**T-B-39** 
T-B-40 	**T-B-41** 	**T-B-42** 
T-B-43 	**T-B-44** 	**T-B-45** 

T-B-46 	**T-B-47** 	**T-B-48** 
T-B-49 	**T-B-50** 	**T-B-51** 

Additional Second Anti-Cancer Agents

[0989] In some embodiments, the second anti-cancer agent is a Poly ADP ribose polymerase (PARP) inhibitor. In some embodiments, a PARP inhibitor is selected from olaparib (LYNPARZA®, AstraZeneca); rucaparib (RUBRACA®, Clovis Oncology); niraparib (ZEJULA®, Tesaro); talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin); veliparib (ABT-888, AbbVie); and BGB-290 (BeiGene, Inc.).

[0990] In some embodiments, the second anti-cancer agent is a histone deacetylase (HDAC) inhibitor. In some embodiments, an HDAC inhibitor is selected from vorinostat (ZOLINZA®, Merck); romidepsin (ISTODAX®, Celgene); panobinostat (FARYDAK®, Novartis); belinostat (BELEODAQ®, Spectrum Pharmaceuticals); entinostat (SNDX-275, Syndax Pharmaceuticals) (NCT00866333); and chidamide (EPIDAZA®, HBI-8000, Chipscreen Biosciences, China).

[0991] In some embodiments, the second anti-cancer agent is a CDK inhibitor, such as a CDK4/CDK6 inhibitor. In some embodiments, a CDK 4/6 inhibitor is selected from palbociclib (IBRANCE®, Pfizer); ribociclib (KISQALI®, Novartis); abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics).

[0992] In some embodiments, the second anti-cancer agent is a phosphatidylinositol 3 kinase (PI3K) inhibitor. In some embodiments, a PI3K inhibitor is selected from idelalisib (ZYDELIG®, Gilead), alpelisib (BYL719, Novartis), taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity Pharmaceuticals); PQR309 (Piqur Therapeutics, Switzerland); and TGR1202 (formerly RP5230, TG Therapeutics).

[0993] In some embodiments, the second anti-cancer agent is a platinum-based therapeutic, also referred to as platins. Platins cause cross-linking of DNA, such that they inhibit DNA repair and/or DNA synthesis, mostly in rapidly reproducing cells, such as cancer cells. In some embodiments, a platinum-based therapeutic is selected from cisplatin (PLATINOL®, Bristol-Myers Squibb); carboplatin (PARAPLATIN®, Bristol-Myers Squibb; also, Teva; Pfizer); oxaliplatin (ELOXITIN® Sanofi-Aventis); nedaplatin (AQUPLA®, Shionogi), picoplatin (Poniard Pharmaceuticals); and satraplatin (JM-216, Agennix).

[0994] In some embodiments, the second anti-cancer agent is a taxane compound, which causes disruption of microtubules, which are essential for cell division. In some embodiments, a taxane compound is selected from paclitaxel (TAXOL®, Bristol-Myers Squibb), docetaxel (TAXOTERE®, Sanofi-Aventis; DOCEFREZ®, Sun Pharmaceutical), albumin-bound paclitaxel (ABRAXANE®; Abraxis/Celgene), cabazitaxel (JEVTANA®, Sanofi-Aventis), and SID530 (SK Chemicals, Co.) (NCT00931008).

[0995] In some embodiments, the second anti-cancer agent is a nucleoside inhibitor, or a therapeutic agent that interferes with normal DNA synthesis, protein synthesis, cell replication, or will otherwise inhibit rapidly proliferating cells.

[0996] In some embodiments, a nucleoside inhibitor is selected from trabectedin (guanidine alkylating agent, YONDELIS®, Janssen Oncology), mechlorethamine (alkylating agent, VALCHLOR®, Aktelion Pharmaceuticals); vincristine (ONCOVIN®, Eli Lilly; VINCASAR®, Teva Pharmaceuticals; MARQIBO®, Talon Therapeutics); temozolomide (prodrug to alkylating agent 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) TEMODAR®, Merck); cytarabine injection (ara-C, antimetabolic cytidine analog, Pfizer); lomustine (alkylating agent, CEENU®, Bristol-Myers Squibb; GLEOSTINE®, NextSource Biotechnology); azacitidine (pyrimidine nucleoside analog of cytidine, VIDAZA®, Celgene); omacetaxine mepesuccinate (cephalotaxine ester) (protein synthesis inhibitor, SYNRIBO®; Teva Pharmaceuticals); asparaginase *Erwinia chrysanthemi* (enzyme for depletion of asparagine, ELSPAR®, Lundbeck; ERWINAZE®, EUSA Pharma); eribulin mesylate (microtubule inhibitor, tubulin-based antimitotic, HALAVEN®, Eisai); cabazitaxel (microtubule inhibitor, tubulin-based antimitotic, JEVTANA®, Sanofi-Aventis); capacetrine (thymidylate synthase inhibitor, XELODA®, Genentech); bendamustine (bifunctional mechlorethamine derivative, believed to form interstrand DNA cross-links, TREANDA®, Cephalon/Teva); ixabepilone (semi-synthetic analog

of epothilone B, microtubule inhibitor, tubulin-based antimitotic, IXEMPRA®, Bristol-Myers Squibb); nelarabine (prodrug of deoxyguanosine analog, nucleoside metabolic inhibitor, ARRANON®, Novartis); clorafabine (prodrug of ribonucleotide reductase inhibitor, competitive inhibitor of deoxycytidine, CLOLAR®, Sanofi-Aventis); and trifluridine and tipiracil (thymidine-based nucleoside analog and thymidine phosphorylase inhibitor, LONSURF®, Taiho Oncology).

[0997] In some embodiments, the second anti-cancer agent is a kinase inhibitor or VEGF-R antagonist. Approved VEGF inhibitors and kinase inhibitors useful in the present invention include: bevacizumab (AVASTIN®, Genentech/Roche) an anti-VEGF monoclonal antibody; ramucirumab (CYRAMZA®, Eli Lilly), an anti-VEGFR-2 antibody and ziv-aflibercept, also known as VEGF Trap (ZALTRAP®; Regeneron/Sanofi). VEGFR inhibitors, such as regorafenib (STIVARGA®, Bayer); vandetanib (CAPRELSA®, AstraZeneca); axitinib (INLYTA®, Pfizer); and lenvatinib (LENVIMA®, Eisai); Raf inhibitors, such as sorafenib (NEXAVAR®, Bayer AG and Onyx); dabrafenib (TAFINLAR®, Novartis); and vemurafenib (ZELBORAF®, Genentech/Roche); MEK inhibitors, such as cobimetanib (COTELLIC®, Exelexis/Genentech/Roche); trametinib (MEKINIST®, Novartis); Bcr-Abl tyrosine kinase inhibitors, such as imatinib (GLEEVEC®, Novartis); nilotinib (TASIGNA®, Novartis); dasatinib (SPRYCEL®, BristolMyersSquibb); bosutinib (BOSULIF®, Pfizer); and ponatinib (INCLUSIG®, Ariad Pharmaceuticals); Her2 and EGFR inhibitors, such as gefitinib (IRESSA®, AstraZeneca); erlotinib (TARCEEVA®, Genentech/Roche/Astellas); lapatinib (TYKERB®, Novartis); afatinib (GILOTRIF®, Boehringer Ingelheim); osimertinib (targeting activated EGFR, TAGRISSO®, AstraZeneca); and brigatinib (ALUNBRIG®, Ariad Pharmaceuticals); c-Met and VEGFR2 inhibitors, such as cabozanitib (COMETRIQ®, Exelexis); and multikinase inhibitors, such as sunitinib (SUTENT®, Pfizer); pazopanib (VOTRIENT®, Novartis); ALK inhibitors, such as crizotinib (XALKORI®, Pfizer); ceritinib (ZYKADIA®, Novartis); and alectinib (ALECENZa®, Genentech/Roche); Bruton's tyrosine kinase inhibitors, such as ibrutinib (IMBRUVICA®, Pharmacyclics/Janssen); and Flt3 receptor inhibitors, such as midostaurin (RYDAPT®, Novartis).

[0998] Other kinase inhibitors and VEGF-R antagonists that are in development and may be used in the present invention include tivozanib (Aveo Pharmaecuticals); vatalanib (Bayer/Novartis); lucitanib (Clovis Oncology); dovitinib (TKI258, Novartis); Chiauanib

(Chipscreen Biosciences); CEP-11981 (Cephalon); linifanib (Abbott Laboratories); neratinib (HKI-272, Puma Biotechnology); radotinib (SUPECT®, IY5511, Il-Yang Pharmaceuticals, S. Korea); ruxolitinib (JAKAFI®, Incyte Corporation); PTC299 (PTC Therapeutics); CP-547,632 (Pfizer); foretinib (Exelexis, GlaxoSmithKline); quizartinib (Daiichi Sankyo) and motesanib (Amgen/Takeda).

[0999] In some embodiments, the second anti-cancer agent is an mTOR inhibitor, which inhibits cell proliferation, angiogenesis and glucose uptake. In some embodiments, an mTOR inhibitor is everolimus (AFINITOR®, Novartis); temsirolimus (TORISEL®, Pfizer); and sirolimus (RAPAMUNE®, Pfizer).

[1000] In some embodiments, the second anti-cancer agent is a proteasome inhibitor. Approved proteasome inhibitors useful in the present invention include bortezomib (VELCADE®, Takeda); carfilzomib (KYPROLIS®, Amgen); and ixazomib (NINLARO®, Takeda).

[1001] In some embodiments, the second anti-cancer agent is a growth factor antagonist, such as an antagonist of platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) or its receptor (EGFR). Approved PDGF antagonists which may be used in the present invention include olaratumab (LARTRUVO®; Eli Lilly). Approved EGFR antagonists which may be used in the present invention include cetuximab (ERBITUX®, Eli Lilly); necitumumab (PORTRAZZA®, Eli Lilly), panitumumab (VECTIBIX®, Amgen); and osimertinib (targeting activated EGFR, TAGRISSO®, AstraZeneca).

[1002] In some embodiments, the second anti-cancer agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from exemestane (AROMASIN®, Pfizer); anastazole (ARIMIDEX®, AstraZeneca) and letrozole (FEMARA®, Novartis).

[1003] In some embodiments, the second anti-cancer agent is an antagonist of the hedgehog pathway. Approved hedgehog pathway inhibitors which may be used in the present invention include sonidegib (ODOMZO®, Sun Pharmaceuticals); and vismodegib (ERIVEDGE®, Genentech), both for treatment of basal cell carcinoma.

[1004] In some embodiments, the second anti-cancer agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present invention include pemetrexed (ALIMTA®, Eli Lilly).

[1005] In some embodiments, the second anti-cancer agent is a CC chemokine receptor 4 (CCR4) inhibitor. CCR4 inhibitors being studied that may be useful in the present invention include mogamulizumab (POTELIGEO®, Kyowa Hakko Kirin, Japan).

[1006] In some embodiments, the second anti-cancer agent is an isocitrate dehydrogenase (IDH) inhibitor. IDH inhibitors being studied which may be used in the present invention include AG120 (Celgene; NCT02677922); AG221 (Celgene, NCT02677922; NCT02577406); BAY1436032 (Bayer, NCT02746081); IDH305 (Novartis, NCT02987010).

[1007] In some embodiments, the second anti-cancer agent is an arginase inhibitor. Arginase inhibitors being studied which may be used in the present invention include AEB1102 (pegylated recombinant arginase, Aeglea Biotherapeutics), which is being studied in Phase 1 clinical trials for acute myeloid leukemia and myelodysplastic syndrome (NCT02732184) and solid tumors (NCT02561234); and CB-1158 (Calithera Biosciences).

[1008] In some embodiments, the second anti-cancer agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present invention include CB-839 (Calithera Biosciences).

[1009] In some embodiments, the second anti-cancer agent is an antibody that binds to tumor antigens, that is, proteins expressed on the cell surface of tumor cells. Approved antibodies that bind to tumor antigens which may be used in the present invention include rituximab (RITUXAN®, Genentech/BiogenIdec); ofatumumab (anti-CD20, ARZERRA®, GlaxoSmithKline); obinutuzumab (anti-CD20, GAZYVA®, Genentech), ibritumomab (anti-CD20 and Yttrium-90, ZEVALIN®, Spectrum Pharmaceuticals); daratumumab (anti-CD38, DARZALEX®, Janssen Biotech), dinutuximab (anti-glycolipid GD2, UNITUXIN®, United Therapeutics); trastuzumab (anti-HER2, HERCEPTIN®, Genentech); ado-trastuzumab emtansine (anti-HER2, fused to emtansine, KADCYLA®, Genentech); and pertuzumab (anti-HER2, PERJETA®, Genentech); and brentuximab vedotin (anti-CD30-drug conjugate, ADCETRIS®, Seattle Genetics).

[1010] In some embodiments, the second anti-cancer agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present invention include irinotecan (ONIVYDE®, Merrimack Pharmaceuticals); topotecan (HYCAMTIN®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present invention include pixantrone (PIXUVRI®, CTI Biopharma).

[1011] In some embodiments, the second anti-cancer agent is an inhibitor of anti-apoptotic proteins, such as BCL-2. Approved anti-apoptotics which may be used in the present invention include venetoclax (VENCLEXTA®, AbbVie/Genentech); and blinatumomab (BLINCYTO®, Amgen). Other therapeutic agents targeting apoptotic proteins which have undergone clinical testing and may be used in the present invention include navitoclax (ABT-263, Abbott), a BCL-2 inhibitor (NCT02079740).

[1012] In some embodiments, the second anti-cancer agent is an androgen receptor inhibitor. Approved androgen receptor inhibitors useful in the present invention include enzalutamide (XTANDI®, Astellas/Medivation); approved inhibitors of androgen synthesis include abiraterone (ZYTIGA®, Centocor/Ortho); approved antagonist of gonadotropin-releasing hormone (GnRH) receptor (degaralix, FIRMAGON®, Ferring Pharmaceuticals).

[1013] In some embodiments, the second anti-cancer agent is a selective estrogen receptor modulator (SERM), which interferes with the synthesis or activity of estrogens. Approved SERMs useful in the present invention include raloxifene (EVISTA®, Eli Lilly).

[1014] In some embodiments, the second anti-cancer agent is an inhibitor of bone resorption. An approved therapeutic which inhibits bone resorption is Denosumab (XGEVA®, Amgen), an antibody that binds to RANKL, prevents binding to its receptor RANK, found on the surface of osteoclasts, their precursors, and osteoclast-like giant cells, which mediates bone pathology in solid tumors with osseous metastases. Other approved therapeutics that inhibit bone resorption include bisphosphonates, such as zoledronic acid (ZOMETA®, Novartis).

[1015] In some embodiments, the second anti-cancer agent is an inhibitor of interaction between the two primary p53 suppressor proteins, MDMX and MDM2. Inhibitors of p53 suppression proteins being studied which may be used in the present invention include ALRN-6924 (Aileron), a stapled peptide that equipotently binds to and disrupts the interaction of MDMX and MDM2 with p53. ALRN-6924 is currently being evaluated in clinical trials for the treatment of AML, advanced myelodysplastic syndrome (MDS) and peripheral T-cell lymphoma (PTCL) (NCT02909972; NCT02264613).

[1016] In some embodiments, the second anti-cancer agent is an inhibitor of transforming growth factor-beta (TGF-beta or TGFß). Inhibitors of TGF-beta proteins being studied which may be used in the present invention include NIS793 (Novartis), an anti-TGF-beta antibody being tested in the clinic for treatment of various cancers, including breast, lung, hepatocellular,

colorectal, pancreatic, prostate and renal cancer (NCT 02947165). In some embodiments, the inhibitor of TGF-beta proteins is fresolimumab (GC1008; Sanofi-Genzyme), which is being studied for melanoma (NCT00923169); renal cell carcinoma (NCT00356460); and non-small cell lung cancer (NCT02581787). Additionally, in some embodiments, the additional therapeutic agent is a TGF-beta trap, such as described in Connolly et al. (2012) Int'l J. Biological Sciences 8:964-978. One therapeutic compound currently in clinical trials for treatment of solid tumors is M7824 (Merck KgaA - formerly MSB0011459X), which is a bispecific, anti-PD-L1/TGF-β trap compound (NCT02699515); and (NCT02517398). M7824 is comprised of a fully human IgG1 antibody against PD-L1 fused to the extracellular domain of human TGF-beta receptor II, which functions as a TGF-β"trap."

[1017] In some embodiments, the second anti-cancer agent is selected from glembatumumab vedotin-monomethyl auristatin E (MMAE) (Celldex), an anti-glycoprotein NMB (gpNMB) antibody (CR011) linked to the cytotoxic MMAE. gpNMB is a protein overexpressed by multiple tumor types associated with cancer cells' ability to metastasize.

[1018] In some embodiments, the second anti-cancer agents is an antiproliferative compound. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, TEMODAL CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (TEMODAL®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as

ARRY142886 from Array BioPharma, AZd$_6$244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[1019] The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name AROMASIN™. Formestane is marketed under the trade name LENTARON™. Fadrozole is marketed under the trade name AFEMA™. Anastrozole is marketed under the trade name ARIMIDEX™. Letrozole is marketed under the trade names FEMARA™ or FEMAr™. Aminoglutethimide is marketed under the trade name ORIMETEN™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[1020] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name NOLVADEX™. Raloxifene hydrochloride is marketed under the trade name EVISTA™. Fulvestrant can be administered under the trade name FASLODEX™. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, such as breast tumors.

[1021] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX™). The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin, and goserelin acetate. Goserelin can be administered under the trade name ZOLADEX™.

[1022] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, *e.g.*, in the form as it is marketed, *e.g.*, under the trademark CAMPTOSAR™. Topotecan is marketed under the trade name HYCAMPTIN™.

[1023] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as CAELYX™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide is marketed under the trade name ETOPOPHOS™. Teniposide is marketed under the trade name VM 26-Bristol Doxorubicin is marketed under the trade name ACRIBLASTIN™ or ADRIAMYCIN™. Epirubicin is marketed under the trade name FARMORUBICIN™. Idarubicin is marketed. under the trade name ZAVEDOS™. Mitoxantrone is marketed under the trade name NOVANTRON™.

[1024] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name TAXOL™. Docetaxel is marketed under the trade name TAXOTERE™. Vinblastine sulfate is marketed under the trade name VINBLASTIN R.P™. Vincristine sulfate is marketed under the trade name FARMISTIN™.

[1025] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide is marketed under the trade name CYCLOSTIN™. Ifosfamide is marketed under the trade name HOLOXAN™.

[1026] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[1027] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name XELODA™. Gemcitabine is marketed under the trade name GEMZAR™.

[1028] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, *e.g.*, in the form as it is

marketed, *e.g.*, under the trademark CARBOPLAT™. Oxaliplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ELOXATIN™.

[1029] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-111; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the AxI receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (*e.g.*, BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine

derivatives, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; llmofosine; RO 318220 and RO 320432; GO 6976; lsis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC™) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases ($EGFR_1$ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (HERCEPTIN™), cetuximab (ERBITUX™), Iressa, Tarceva, OSI-774, Cl-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothened receptor (SMO) pathways, including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[1030] The term "PI3K inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3Kα, PI3Kγ, PI3Kδ, PI3Kβ, PI3K-C2α, PI3K-C2β, PI3K-C2γ, Vps34, p110-α, p110-β, p110-γ, p110-δ, p85-α, p85-β, p55-γ, p150, p101, and p87. Examples of PI3K inhibitors useful in this invention include but are not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib. In some embodiments, the PI3K inhibitor is alpelisib (PIQRAY, Novartis Pharmaceuticals Corporation).

[1031] The term "Bcl-2 inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta's pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; see WO2008118802), navitoclax (and analogs thereof, see US7390799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, see WO2004106328), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[1032] The term "BTK inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against Bruton's Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[1033] The term "SYK inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib.

[1034] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2008039218 and WO2011090760, the entirety of which are incorporated herein by reference.

[1035] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2003063794, WO2005007623, and WO2006078846, the entirety of which are incorporated herein by reference.

[1036] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2004019973, WO2004089925, WO2007016176, US8138347, WO2002088112, WO2007084786, WO2007129161, WO2006122806, WO2005113554, and WO2007044729 the entirety of which are incorporated herein by reference.

[1037] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2009114512, WO2008109943, WO2007053452, WO2000142246, and WO2007070514, the entirety of which are incorporated herein by reference.

[1038] Further anti-angiogenic compounds include compounds having another mechanism for their activity, *e.g.*, unrelated to protein or lipid kinase inhibition *e.g.*, thalidomide (THALOMID™) and TNP-470.

[1039] Examples of proteasome inhibitors useful for use in combination with compounds of the invention include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[1040] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are *e.g.* inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[1041] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α- γ- or δ- tocopherol or α- γ- or δ-tocotrienol.

[1042] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX™), rofecoxib (VIOXX™), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[1043] The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridonic acid is marketed under the trade name DIDRONEL™. Clodronic acid is marketed under the trade name BONEFOS™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name AREDIA™. Alendronic acid is marketed under the trade name FOSAMAX™. Ibandronic acid is marketed under the trade name

BONDRANAT™. Risedronic acid is marketed under the trade name ACTONEL™. Zoledronic acid is marketed under the trade name ZOMETA™. The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (RAPAMUNE®), everolimus (CERTICAN™), CCI-779 and ABT578.

[1044] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[1045] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R115777 (ZARNESTRA™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[1046] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[1047] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (VELCADE™) and MLN 341.

[1048] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, *e.g.*, hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211 , MMI270B or AAJ996.

[1049] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R);

interferon, 1-β-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[1050] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[1051] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[1052] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (HERCEPTIN™), Trastuzumab-DM1, erbitux, bevacizumab (AVASTIN™), rituximab (RITUXAN®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[1053] For the treatment of acute myeloid leukemia (AML), compounds of the current invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current invention can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[1054] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA,

FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including, but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1 , pp. 248-275 (1993).

[1055] Also included are EDG binders and ribonucleotide reductase inhibitors. The term "EDG binders" as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1 ,3-dione derivatives.

[1056] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; ANGIOSTATIN™; ENDOSTATIN™; anthranilic acid amides; ZD4190; Zd_6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMAb and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, Angiozyme (RPI 4610) and Bevacizumab (AVASTIN™).

[1057] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as VISUDYNE™ and porfimer sodium.

[1058] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, *e.g.*, anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[1059] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[1060] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[1061] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, *e.g.*, Patents International (*e.g.*, IMS World Publications).

Exemplary Immuno-Oncology Agents

[1062] In some embodiments, the second anti-cancer agent is an immuno-oncology agent. As used herein, the term "an immuno-oncology agent" refers to an agent which is effective to enhance, stimulate, and/or up-regulate immune responses in a subject. In some embodiments, the administration of an immuno-oncology agent with a compound of the invention has a synergic effect in treating a cancer.

[1063] An immuno-oncology agent can be, for example, a small molecule drug, an antibody, or a biologic or small molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In some embodiments, an antibody is a monoclonal antibody. In some embodiments, a monoclonal antibody is humanized or human.

[1064] In some embodiments, an immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses.

[1065] Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory

receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LTβR, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α/TNFβ, TNFR2, TNFα, LTβR, Lymphotoxin α1β2, FAS, FASL, RELT, DR6, TROY, NGFR.

[1066] In some embodiments, an immuno-oncology agent is a cytokine that inhibits T cell activation (*e.g.*, IL-6, IL-10, TGF-β, VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

[1067] In some embodiments, a combination of a compound of the invention and an immuno-oncology agent can stimulate T cell responses. In some embodiments, an immuno-oncology agent is: (i) an antagonist of a protein that inhibits T cell activation (*e.g.*, immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4; or (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

[1068] In some embodiments, an immuno-oncology agent is an antagonist of inhibitory receptors on NK cells or an agonist of activating receptors on NK cells. In some embodiments, an immuno-oncology agent is an antagonist of KIR, such as lirilumab.

[1069] In some embodiments, an immuno-oncology agent is an agent that inhibits or depletes macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

[1070] In some embodiments, an immuno-oncology agent is selected from agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (*e.g.*, block inhibitory receptor engagement (*e.g.*, PD-L1/PD-1

interactions), deplete or inhibit Tregs (*e.g.*, using an anti-CD25 monoclonal antibody (*e.g.*, daclizumab) or by *ex vivo* anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell energy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

[1071] In some embodiments, an immuno-oncology agent is a CTLA-4 antagonist. In some embodiments, a CTLA-4 antagonist is an antagonistic CTLA-4 antibody. In some embodiments, an antagonistic CTLA-4 antibody is YERVOY (ipilimumab) or tremelimumab.

[1072] In some embodiments, an immuno-oncology agent is a PD-1 antagonist. In some embodiments, a PD-1 antagonist is administered by infusion. In some embodiments, an immuno-oncology agent is an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity. In some embodiments, a PD-1 antagonist is an antagonistic PD-1 antibody. In some embodiments, an antagonistic PD-1 antibody is OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). In some embodiments, an immuno-oncology agent may be pidilizumab (CT-011). In some embodiments, an immuno-oncology agent is a recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224.

[1073] In some embodiments, an immuno-oncology agent is a PD-L1 antagonist. In some embodiments, a PD-L1 antagonist is an antagonistic PD-L1 antibody. In some embodiments, a PD-L1 antibody is MPDL3280A (RG7446; WO2010/077634), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), and MSB0010718C (WO2013/79174).

[1074] In some embodiments, an immuno-oncology agent is a LAG-3 antagonist. In some embodiments, a LAG-3 antagonist is an antagonistic LAG-3 antibody. In some embodiments, a LAG3 antibody is BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO009/44273).

[1075] In some embodiments, an immuno-oncology agent is a CD137 (4-1BB) agonist. In some embodiments, a CD137 (4-1BB) agonist is an agonistic CD137 antibody. In some embodiments, a CD137 antibody is urelumab or PF-05082566 (WO12/32433).

[1076] In some embodiments, an immuno-oncology agent is a GITR agonist. In some embodiments, a GITR agonist is an agonistic GITR antibody. In some embodiments, a GITR

antibody is BMS-986153, BMS-986156, TRX-518 (WO006/105021, WO009/009116), or MK-4166 (WO11/028683).

[1077] In some embodiments, an immuno-oncology agent is an indoleamine (2,3)-dioxygenase (IDO) antagonist. In some embodiments, an IDO antagonist is selected from epacadostat (INCB024360, Incyte); indoximod (NLG-8189, NewLink Genetics Corporation); capmanitib (INC280, Novartis); GDC-0919 (Genentech/Roche); PF-06840003 (Pfizer); BMS:F001287 (Bristol-Myers Squibb); Phy906/KD108 (Phytoceutica); an enzyme that breaks down kynurenine (Kynase, Ikena Oncology, formerly known as Kyn Therapeutics); and NLG-919 (WO09/73620, WO009/1156652, WO11/56652, WO12/142237).

[1078] In some embodiments, an immuno-oncology agent is an OX40 agonist. In some embodiments, an OX40 agonist is an agonistic OX40 antibody. In some embodiments, an OX40 antibody is MEDI-6383 or MEDI-6469.

[1079] In some embodiments, an immuno-oncology agent is an OX40L antagonist. In some embodiments, an OX40L antagonist is an antagonistic OX40 antibody. In some embodiments, an OX40L antagonist is RG-7888 (WO06/029879).

[1080] In some embodiments, an immuno-oncology agent is a CD40 agonist. In some embodiments, a CD40 agonist is an agonistic CD40 antibody. In some embodiments, an immuno-oncology agent is a CD40 antagonist. In some embodiments, a CD40 antagonist is an antagonistic CD40 antibody. In some embodiments, a CD40 antibody is lucatumumab or dacetuzumab.

[1081] In some embodiments, an immuno-oncology agent is a CD27 agonist. In some embodiments, a CD27 agonist is an agonistic CD27 antibody. In some embodiments, a CD27 antibody is varlilumab.

[1082] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[1083] In some embodiments, an immuno-oncology agent is abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, atezolimab, avelumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, or tremelimumab.

[1084] In some embodiments, an immuno-oncology agent is an immunostimulatory agent. For example, antibodies blocking the PD-1 and PD-L1 inhibitory axis can unleash activated tumor-reactive T cells and have been shown in clinical trials to induce durable anti-tumor responses in increasing numbers of tumor histologies, including some tumor types that conventionally have not been considered immunotherapy sensitive. See, *e.g.*, Okazaki, T. *et al.* (2013) Nat. Immunol. 14, 1212–1218; Zou *et al.* (2016) Sci. Transl. Med. 8. The anti-PD-1 antibody nivolumab (OPDIVO®, Bristol-Myers Squibb, also known as ONO-4538, MDX1106 and BMS-936558), has shown potential to improve the overall survival in patients with RCC who had experienced disease progression during or after prior anti-angiogenic therapy.

[1085] In some embodiments, the immunomodulatory therapeutic specifically induces apoptosis of tumor cells. Approved immunomodulatory therapeutics which may be used in the present invention include pomalidomide (POMALYST®, Celgene); lenalidomide (REVLIMID®, Celgene); ingenol mebutate (PICATO®, LEO Pharma).

[1086] In some embodiments, an immuno-oncology agent is a cancer vaccine. In some embodiments, the cancer vaccine is selected from sipuleucel-T (PROVENGE®, Dendreon/Valeant Pharmaceuticals), which has been approved for treatment of asymptomatic, or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer; and talimogene laherparepvec (IMLYGIC®, BioVex/Amgen, previously known as T-VEC), a genetically modified oncolytic viral therapy approved for treatment of unresectable cutaneous, subcutaneous and nodal lesions in melanoma. In some embodiments, an immuno-oncology agent is selected from an oncolytic viral therapy such as pexastimogene devacirepvec (PexaVec/JX-594, SillaJen/formerly Jennerex Biotherapeutics), a thymidine kinase- (TK-) deficient vaccinia virus engineered to express GM-CSF, for hepatocellular carcinoma (NCT02562755) and melanoma (NCT00429312); pelareorep (REOLYSIN®, Oncolytics Biotech), a variant of respiratory enteric orphan virus (reovirus) which does not replicate in cells that are not RAS-activated, in numerous cancers, including colorectal cancer (NCT01622543); prostate cancer (NCT01619813); head and neck squamous cell cancer (NCT01166542); pancreatic adenocarcinoma (NCT00998322); and non-small cell lung cancer (NSCLC) (NCT 00861627); enadenotucirev (NG-348, PsiOxus, formerly known as ColoAd1), an adenovirus engineered to express a full length CD80 and an antibody fragment specific for the T-cell receptor CD3 protein, in ovarian cancer (NCT02028117); metastatic or advanced epithelial

tumors such as in colorectal cancer, bladder cancer, head and neck squamous cell carcinoma and salivary gland cancer (NCT02636036); ONCOS-102 (Targovax/formerly Oncos), an adenovirus engineered to express GM-CSF, in melanoma (NCT03003676); and peritoneal disease, colorectal cancer or ovarian cancer (NCT02963831); GL-ONC1 (GLV-1h68/GLV-1h153, Genelux GmbH), vaccinia viruses engineered to express beta-galactosidase (beta-gal)/beta-glucoronidase or beta-gal/human sodium iodide symporter (hNIS), respectively, were studied in peritoneal carcinomatosis (NCT01443260); fallopian tube cancer, ovarian cancer (NCT 02759588); or CG0070 (Cold Genesys), an adenovirus engineered to express GM-CSF, in bladder cancer (NCT02365818).

[1087] In some embodiments, an immuno-oncology agent is selected from JX-929 (SillaJen/formerly Jennerex Biotherapeutics), a TK- and vaccinia growth factor-deficient vaccinia virus engineered to express cytosine deaminase, which is able to convert the prodrug 5-fluorocytosine to the cytotoxic drug 5-fluorouracil; TG01 and TG02 (Targovax/formerly Oncos), peptide-based immunotherapy agents targeted for difficult-to-treat RAS mutations; and TILT-123 (TILT Biotherapeutics), an engineered adenovirus designated: Ad5/3-E2F-delta24-hTNFα-IRES-hIL20; and VSV-GP (ViraTherapeutics) a vesicular stomatitis virus (VSV) engineered to express the glycoprotein (GP) of lymphocytic choriomeningitis virus (LCMV), which can be further engineered to express antigens designed to raise an antigen-specific $CD8^+$ T cell response.

[1088] In some embodiments, an immuno-oncology agent is a T-cell engineered to express a chimeric antigen receptor, or CAR. The T-cells engineered to express such chimeric antigen receptor are referred to as a CAR-T cells.

[1089] CARs have been constructed that consist of binding domains, which may be derived from natural ligands, single chain variable fragments (scFv) derived from monoclonal antibodies specific for cell-surface antigens, fused to endodomains that are the functional end of the T-cell receptor (TCR), such as the CD3-zeta signaling domain from TCRs, which is capable of generating an activation signal in T lymphocytes. Upon antigen binding, such CARs link to endogenous signaling pathways in the effector cell and generate activating signals similar to those initiated by the TCR complex.

[1090] For example, in some embodiments the CAR-T cell is one of those described in U.S. Patent 8,906,682 (June *et al.*; hereby incorporated by reference in its entirety), which discloses

CAR-T cells engineered to comprise an extracellular domain having an antigen binding domain (such as a domain that binds to CD19), fused to an intracellular signaling domain of the T cell antigen receptor complex zeta chain (such as CD3 zeta). When expressed in the T cell, the CAR is able to redirect antigen recognition based on the antigen binding specificity. In the case of CD19, the antigen is expressed on malignant B cells. Over 200 clinical trials are currently in progress employing CAR-T in a wide range of indications. [https://clinicaltrials.gov/ct2/results?term=chimeric+antigen+receptors&pg=1].

[1091] In some embodiments, an immunostimulatory agent is an activator of retinoic acid receptor-related orphan receptor γ (RORγt). RORγt is a transcription factor with key roles in the differentiation and maintenance of Type 17 effector subsets of CD4+ (Th17) and CD8+ (Tc17) T cells, as well as the differentiation of IL-17 expressing innate immune cell subpopulations such as NK cells. In some embodiments, an activator of RORγt is LYC-55716 (Lycera), which is currently being evaluated in clinical trials for the treatment of solid tumors (NCT02929862).

[1092] In some embodiments, an immunostimulatory agent is an agonist or activator of a toll-like receptor (TLR). Suitable activators of TLRs include an agonist or activator of TLR9 such as SD-101 (Dynavax). SD-101 is an immunostimulatory CpG which is being studied for B-cell, follicular and other lymphomas (NCT02254772). Agonists or activators of TLR8 which may be used in the present invention include motolimod (VTX-2337, VentiRx Pharmaceuticals) which is being studied for squamous cell cancer of the head and neck (NCT02124850) and ovarian cancer (NCT02431559).

[1093] Other immuno-oncology agents that can be used in the present invention include urelumab (BMS-663513, Bristol-Myers Squibb), an anti-CD137 monoclonal antibody; varlilumab (CDX-1127, Celldex Therapeutics), an anti-CD27 monoclonal antibody; BMS-986178 (Bristol-Myers Squibb), an anti-OX40 monoclonal antibody; lirilumab (IPH2102/BMS-986015, Innate Pharma, Bristol-Myers Squibb), an anti-KIR monoclonal antibody; monalizumab (IPH2201, Innate Pharma, AstraZeneca) an anti-NKG2A monoclonal antibody; andecaliximab (GS-5745, Gilead Sciences), an anti-MMP9 antibody; MK-4166 (Merck & Co.), an anti-GITR monoclonal antibody.

[1094] In some embodiments, an immunostimulatory agent is selected from elotuzumab, mifamurtide, an agonist or activator of a toll-like receptor, and an activator of RORγt.

[1095] In some embodiments, an immunostimulatory therapeutic is recombinant human interleukin 15 (rhIL-15). rhIL-15 has been tested in the clinic as a therapy for melanoma and renal cell carcinoma (NCT01021059 and NCT01369888) and leukemias (NCT02689453). In some embodiments, an immunostimulatory agent is recombinant human interleukin 12 (rhIL-12). In some embodiments, an IL-15 based immunotherapeutic is heterodimeric IL-15 (hetIL-15, Novartis/Admune), a fusion complex composed of a synthetic form of endogenous IL-15 complexed to the soluble IL-15 binding protein IL-15 receptor alpha chain (IL15:sIL-15RA), which has been tested in Phase 1 clinical trials for melanoma, renal cell carcinoma, non-small cell lung cancer and head and neck squamous cell carcinoma (NCT02452268). In some embodiments, a recombinant human interleukin 12 (rhIL-12) is NM-IL-12 (Neumedicines, Inc.), NCT02544724, or NCT02542124.

[1096] In some embodiments, an immuno-oncology agent is selected from those described in Jerry L. Adams *et al.*, "Big opportunities for small molecules in immuno-oncology," Cancer Therapy **2015**, Vol. 14, pages 603-622, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is selected from the examples described in Table 1 of Jerry L. Adams *et al.* In some embodiments, an immuno-oncology agent is a small molecule targeting an immuno-oncology target selected from those listed in Table 2 of Jerry L. Adams *et al.* In some embodiments, an immuno-oncology agent is a small molecule agent selected from those listed in Table 2 of Jerry L. Adams *et al.*

[1097] In some embodiments, an immuno-oncology agent is selected from the small molecule immuno-oncology agents described in Peter L. Toogood, "Small molecule immuno-oncology therapeutic agents," Bioorganic & Medicinal Chemistry Letters **2018**, Vol. 28, pages 319-329, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is an agent targeting the pathways as described in Peter L. Toogood.

[1098] In some embodiments, an immuno-oncology agent is selected from those described in Sandra L. Ross et al., "Bispecific T cell engager (BITE®) antibody constructs can mediate bystander tumor cell killing", PLoS ONE 12(8): e0183390, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is a bispecific T cell engager (BITE®) antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct is a CD19/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct is an EGFR/CD3

bispecific antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells, which release cytokines inducing upregulation of intercellular adhesion molecule 1 (ICAM-1) and FAS on bystander cells. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells which result in induced bystander cell lysis. In some embodiments, the bystander cells are in solid tumors. In some embodiments, the bystander cells being lysed are in proximity to the BITE®-activated T cells. In some embodiments, the bystander cells comprises tumor-associated antigen (TAA) negative cancer cells. In some embodiment, the bystander cells comprise EGFR-negative cancer cells. In some embodiments, an immuno-oncology agent is an antibody which blocks the PD-L1/PD1 axis and/or CTLA4. In some embodiments, an immuno-oncology agent is an *ex vivo* expanded tumor-infiltrating T cell. In some embodiments, an immuno-oncology agent is a bispecific antibody construct or chimeric antigen receptors (CARs) that directly connect T cells with tumor-associated surface antigens (TAAs).

Exemplary Immune Checkpoint Inhibitors

[1099] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[1100] The terms "immune checkpoint inhibitor" and "checkpoint inhibitor" as used herein relate to agents useful in preventing cancer cells from avoiding the immune system of the patient. One of the major mechanisms of anti-tumor immunity subversion is known as "T-cell exhaustion," which results from chronic exposure to antigens that has led to up-regulation of inhibitory receptors. These inhibitory receptors serve as immune checkpoints in order to prevent uncontrolled immune reactions.

[1101] PD-1 and co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4, B and T Lymphocyte Attenuator (BTLA; CD272), T cell Immunoglobulin and Mucin domain-3 (Tim-3), Lymphocyte Activation Gene-3 (Lag-3; CD223), and others are often referred to as a checkpoint regulators. They act as molecular "gatekeepers" that allow extracellular information to dictate whether cell cycle progression and other intracellular signaling processes should proceed.

[1102] In some embodiments, an immune checkpoint inhibitor is an antibody to PD-1. PD-1 binds to the programmed cell death 1 receptor (PD-1) to prevent the receptor from binding to the

inhibitory ligand PDL-1, thus overriding the ability of tumors to suppress the host anti-tumor immune response.

[1103] In some embodiments, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In some embodiments, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a fusion protein or a combination thereof. In some embodiments, the checkpoint inhibitor inhibits a checkpoint protein selected from CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In some embodiments, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In some embodiments, the checkpoint inhibitor is an immunostimulatory agent, a T cell growth factor, an interleukin, an antibody, a vaccine or a combination thereof. In some embodiments, the interleukin is IL-7 or IL-15. In some embodiments, the interleukin is glycosylated IL-7. In an additional aspect, the vaccine is a dendritic cell (DC) vaccine.

[1104] Checkpoint inhibitors include any agent that blocks or inhibits in a statistically significant manner, the inhibitory pathways of the immune system. Such inhibitors can include small molecule inhibitors or can include antibodies, or antigen binding fragments thereof, that bind to and block or inhibit immune checkpoint receptors or antibodies that bind to and block or inhibit immune checkpoint receptor ligands. Illustrative checkpoint molecules that can be targeted for blocking or inhibition include, but are not limited to, CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, GAL9, LAG3, TIM3, VISTA, KIR, 2B4 (belongs to the CD2 family of molecules and is expressed on all NK, γδ, and memory $CD8^+$ (αβ) T cells), CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, and various B-7 family ligands. B7 family ligands include, but are not limited to, B7- 1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7. Checkpoint inhibitors include antibodies, or antigen binding fragments thereof, other binding proteins, biologic therapeutics, or small molecules, that bind to and block or inhibit the activity of one or more of CTLA-4, PDL1, PDL2, PD1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160 and CGEN-15049. Illustrative immune checkpoint inhibitors include, but are not limited to, Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-L1 monoclonal Antibody (Anti-B7-Hl; MEDI4736), MK-

3475 (PD-1 blocker), Nivolumab (anti-PD1 antibody), CT-011 (anti-PD1 antibody), BY55 monoclonal antibody, AMP224 (anti-PDL1 antibody), BMS- 936559 (anti-PDL1 antibody), MPLDL3280A (anti-PDL1 antibody), MSB0010718C (anti-PDL1 antibody), and ipilimumab (anti-CTLA-4 checkpoint inhibitor). Checkpoint protein ligands include, but are not limited to PD-L1, PD-L2, B7-H3, B7-H4, CD28, CD86 and TIM-3.

[1105] In certain embodiments, the immune checkpoint inhibitor is selected from a PD-1 antagonist, a PD-L1 antagonist, and a CTLA-4 antagonist. In some embodiments, the checkpoint inhibitor is selected from the group consisting of nivolumab (OPDIVO®), ipilimumab (YERVOY®), and pembrolizumab (KEYTRUDA®). In some embodiments, the checkpoint inhibitor is selected from nivolumab (anti-PD-1 antibody, OPDIVO®, Bristol-Myers Squibb); pembrolizumab (anti-PD-1 antibody, KEYTRUDA®, Merck); ipilimumab (anti-CTLA-4 antibody, YERVOY®, Bristol-Myers Squibb); durvalumab (anti-PD-L1 antibody, IMFINZI®, AstraZeneca); and atezolizumab (anti-PD-L1 antibody, TECENTRIQ®, Genentech).

[1106] In some embodiments, the checkpoint inhibitor is selected from the group consisting of lambrolizumab (MK-3475), nivolumab (BMS-936558), pidilizumab (CT-011), AMP-224, MDX-1105, MEDI4736, MPDL3280A, BMS-936559, ipilimumab, lirlumab, IPH2101, pembrolizumab (KEYTRUDA®), and tremelimumab.

[1107] In some embodiments, an immune checkpoint inhibitor is REGN2810 (Regeneron), an anti-PD-1 antibody tested in patients with basal cell carcinoma (NCT03132636); NSCLC (NCT03088540); cutaneous squamous cell carcinoma (NCT02760498); lymphoma (NCT02651662); and melanoma (NCT03002376); pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (BAVENCIO®, Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; or PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors. Tremelimumab (CP-675,206; Astrazeneca) is a fully human monoclonal antibody against CTLA-4 that has been in studied in clinical trials for a number of indications, including: mesothelioma, colorectal cancer, kidney cancer, breast cancer, lung cancer and non-small cell lung cancer, pancreatic ductal

adenocarcinoma, pancreatic cancer, germ cell cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, prostate cancer, endometrial cancer, metastatic cancer in the liver, liver cancer, large B-cell lymphoma, ovarian cancer, cervical cancer, metastatic anaplastic thyroid cancer, urothelial cancer, fallopian tube cancer, multiple myeloma, bladder cancer, soft tissue sarcoma, and melanoma. AGEN-1884 (Agenus) is an anti-CTLA4 antibody that is being studied in Phase 1 clinical trials for advanced solid tumors (NCT02694822).

[1108] In some embodiments, a checkpoint inhibitor is an inhibitor of T-cell immunoglobulin mucin containing protein-3 (TIM-3). TIM-3 inhibitors that may be used in the present invention include TSR-022, LY3321367 and MBG453. TSR-022 (Tesaro) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT02817633). LY3321367 (Eli Lilly) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT03099109). MBG453 (Novartis) is an anti-TIM-3 antibody which is being studied in advanced malignancies (NCT02608268).

[1109] In some embodiments, a checkpoint inhibitor is an inhibitor of T cell immunoreceptor with Ig and ITIM domains, or TIGIT, an immune receptor on certain T cells and NK cells. TIGIT inhibitors that may be used in the present invention include BMS-986207 (Bristol-Myers Squibb), an anti-TIGIT monoclonal antibody (NCT02913313); OMP-313M32 (Oncomed); and anti-TIGIT monoclonal antibody (NCT03119428).

[1110] In some embodiments, a checkpoint inhibitor is an inhibitor of Lymphocyte Activation Gene-3 (LAG-3). LAG-3 inhibitors that may be used in the present invention include BMS-986016 and REGN3767 and IMP321. BMS-986016 (Bristol-Myers Squibb), an anti-LAG-3 antibody, is being studied in glioblastoma and gliosarcoma (NCT02658981). REGN3767 (Regeneron), is also an anti-LAG-3 antibody, and is being studied in malignancies (NCT03005782). IMP321 (Immutep S.A.) is an LAG-3-Ig fusion protein, being studied in melanoma (NCT02676869); adenocarcinoma (NCT02614833); and metastatic breast cancer (NCT00349934).

[1111] Checkpoint inhibitors that can be used in the present invention include OX40 agonists. OX40 agonists that are being studied in clinical trials include PF-04518600/PF-8600 (Pfizer), an agonistic anti-OX40 antibody, in metastatic kidney cancer (NCT03092856) and advanced cancers and neoplasms (NCT02554812; NCT05082566); GSK3174998 (Merck), an agonistic anti-OX40 antibody, in Phase 1 cancer trials (NCT02528357); MEDI0562 (Medimmune/AstraZeneca), an agonistic anti-OX40 antibody, in advanced solid tumors

(NCT02318394 and NCT02705482); MEDI6469, an agonistic anti-OX40 antibody (Medimmune/AstraZeneca), in patients with colorectal cancer (NCT02559024), breast cancer (NCT01862900), head and neck cancer (NCT02274155) and metastatic prostate cancer (NCT01303705); and BMS-986178 (Bristol-Myers Squibb) an agonistic anti-OX40 antibody, in advanced cancers (NCT02737475).

[1112] Checkpoint inhibitors that can be used in the present invention include CD137 (also called 4-1BB) agonists. CD137 agonists that are being studied in clinical trials include utomilumab (PF-05082566, Pfizer) an agonistic anti-CD137 antibody, in diffuse large B-cell lymphoma (NCT02951156) and in advanced cancers and neoplasms (NCT02554812 and NCT05082566); urelumab (BMS-663513, Bristol-Myers Squibb), an agonistic anti-CD137 antibody, in melanoma and skin cancer (NCT02652455) and glioblastoma and gliosarcoma (NCT02658981); and CTX-471 (Compass Therapeutics), an agonistic anti-CD137 antibody in metastatic or locally advanced malignancies (NCT03881488).

[1113] Checkpoint inhibitors that can be used in the present invention include CD27 agonists. CD27 agonists that are being studied in clinical trials include varlilumab (CDX-1127, Celldex Therapeutics) an agonistic anti-CD27 antibody, in squamous cell head and neck cancer, ovarian carcinoma, colorectal cancer, renal cell cancer, and glioblastoma (NCT02335918); lymphomas (NCT01460134); and glioma and astrocytoma (NCT02924038).

[1114] Checkpoint inhibitors that can be used in the present invention include glucocorticoid-induced tumor necrosis factor receptor (GITR) agonists. GITR agonists that are being studied in clinical trials include TRX518 (Leap Therapeutics), an agonistic anti-GITR antibody, in malignant melanoma and other malignant solid tumors (NCT01239134 and NCT02628574); GWN323 (Novartis), an agonistic anti-GITR antibody, in solid tumors and lymphoma (NCT02740270); INCAGN01876 (Incyte/Agenus), an agonistic anti-GITR antibody, in advanced cancers (NCT02697591 and NCT03126110); MK-4166 (Merck), an agonistic anti-GITR antibody, in solid tumors (NCT02132754) and MEDI1873 (Medimmune/AstraZeneca), an agonistic hexameric GITR-ligand molecule with a human IgG1 Fc domain, in advanced solid tumors (NCT02583165).

[1115] Checkpoint inhibitors that can be used in the present invention include inducible T-cell co-stimulator (ICOS, also known as CD278) agonists. ICOS agonists that are being studied in clinical trials include MEDI-570 (Medimmune), an agonistic anti-ICOS antibody, in

lymphomas (NCT02520791); GSK3359609 (Merck), an agonistic anti-ICOS antibody, in Phase 1 (NCT02723955); JTX-2011 (Jounce Therapeutics), an agonistic anti-ICOS antibody, in Phase 1 (NCT02904226).

[1116] Checkpoint inhibitors that can be used in the present invention include killer IgG-like receptor (KIR) inhibitors. KIR inhibitors that are being studied in clinical trials include lirilumab (IPH2102/BMS-986015, Innate Pharma/Bristol-Myers Squibb), an anti-KIR antibody, in leukemias (NCT01687387, NCT02399917, NCT02481297, NCT02599649), multiple myeloma (NCT02252263), and lymphoma (NCT01592370); IPH2101 (1-7F9, Innate Pharma) in myeloma (NCT01222286 and NCT01217203); and IPH4102 (Innate Pharma), an anti-KIR antibody that binds to three domains of the long cytoplasmic tail (KIR3DL2), in lymphoma (NCT02593045).

[1117] Checkpoint inhibitors that can be used in the present invention include CD47 inhibitors of interaction between CD47 and signal regulatory protein alpha (SIRPa). CD47/SIRPa inhibitors that are being studied in clinical trials include ALX-148 (Alexo Therapeutics), an antagonistic variant of (SIRPa) that binds to CD47 and prevents CD47/SIRPa-mediated signaling, in phase 1 (NCT03013218); TTI-621 (SIRPa-Fc, Trillium Therapeutics), a soluble recombinant fusion protein created by linking the N-terminal CD47-binding domain of SIRPa with the Fc domain of human IgG1, acts by binding human CD47, and preventing it from delivering its "do not eat" signal to macrophages, is in clinical trials in Phase 1 (NCT02890368 and NCT02663518); CC-90002 (Celgene), an anti-CD47 antibody, in leukemias (NCT02641002); and Hu5F9-G4 (Forty Seven, Inc.), in colorectal neoplasms and solid tumors (NCT02953782), acute myeloid leukemia (NCT02678338) and lymphoma (NCT02953509).

[1118] Checkpoint inhibitors that can be used in the present invention include CD73 inhibitors. CD73 inhibitors that are being studied in clinical trials include MEDI9447 (Medimmune), an anti-CD73 antibody, in solid tumors (NCT02503774); and BMS-986179 (Bristol-Myers Squibb), an anti-CD73 antibody, in solid tumors (NCT02754141).

[1119] Checkpoint inhibitors that can be used in the present invention include agonists of stimulator of interferon genes protein (STING, also known as transmembrane protein 173, or TMEM173). Agonists of STING that are being studied in clinical trials include MK-1454 (Merck), an agonistic synthetic cyclic dinucleotide, in lymphoma (NCT03010176); and ADU-S100 (MIW815, Aduro Biotech/Novartis), an agonistic synthetic cyclic dinucleotide, in Phase 1 (NCT02675439 and NCT03172936).

[1120] Checkpoint inhibitors that can be used in the present invention include CSF1R inhibitors. CSF1R inhibitors that are being studied in clinical trials include pexidartinib (PLX3397, Plexxikon), a CSF1R small molecule inhibitor, in colorectal cancer, pancreatic cancer, metastatic and advanced cancers (NCT02777710) and melanoma, non-small cell lung cancer, squamous cell head and neck cancer, gastrointestinal stromal tumor (GIST) and ovarian cancer (NCT02452424); and IMC-CS4 (LY3022855, Lilly), an anti-CSF-1R antibody, in pancreatic cancer (NCT03153410), melanoma (NCT03101254), and solid tumors (NCT02718911); and BLZ945 (4-[2((1R,2R)-2-hydroxycyclohexylamino)-benzothiazol-6-yloxyl]-pyridine-2-carboxylic acid methylamide, Novartis), an orally available inhibitor of CSF1R, in advanced solid tumors (NCT02829723).

[1121] Checkpoint inhibitors that can be used in the present invention include NKG2A receptor inhibitors. NKG2A receptor inhibitors that are being studied in clinical trials include monalizumab (IPH2201, Innate Pharma), an anti-NKG2A antibody, in head and neck neoplasms (NCT02643550) and chronic lymphocytic leukemia (NCT02557516).

[1122] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

Additional Combination Therapy Considerations

[1123] In certain embodiments, the method further comprises administering to the subject a third anti-cancer agent. In certain embodiments, the method further comprises administering to the subject a fourth anti-cancer agent. In certain embodiments, the method further comprises administering to the subject a fifth anti-cancer agent.

[1124] In certain embodiments, the third anti-cancer agent is one of the second anti-cancer agents described above. In certain embodiments, the fourth anti-cancer agent is one of the second anti-cancer agents described above. In certain embodiments, the fifth anti-cancer agent is one of the second anti-cancer agents described above.

[1125] The doses and dosage regimen of the active ingredients used in the combination therapy may be determined by an attending clinician. In certain embodiments, the substituted 4-piperidinyl-quinazoline or related compound described herein (e.g., a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) are administered in doses commonly

employed when such agents are used as monotherapy for treating the disorder. In other embodiments, the substituted 4-piperidinyl-quinazoline or related compound described herein (e.g., a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating the disorder. In certain embodiments, the substituted 4-piperidinyl-quinazoline or related compound described herein (e.g., a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) are present in the same composition, which is suitable for oral administration.

[1126] In certain embodiments, the substituted 4-piperidinyl-quinazoline or related compound described herein (e.g., a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) may act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

[1127] The doses and dosage regimen of the active ingredients used in the combination therapy may be determined by an attending clinician. In certain embodiments, the substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein (e.g., a compound of Formula I, or other compounds in Section I-A) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) are administered in doses commonly employed when such agents are used as monotherapy for treating the disorder. In other embodiments, the substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein (e.g., a compound of Formula I, or other compounds in Section I-A) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating the disorder. In certain embodiments, the substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein (e.g., a compound of Formula I, or other compounds in Section I-A) and the additional therapeutic agent(s) (e.g. the

second, third, or fourth, or fifth anti-cancer agent, described above) are present in the same composition, which is suitable for oral administration.

[1128] In certain embodiments, the substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein (e.g., a compound of Formula I, or other compounds in Section I-A) and the additional therapeutic agent(s) (e.g. the second, third, or fourth, or fifth anti-cancer agent, described above) may act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

[1129] Another aspect of this invention is a kit comprising a therapeutically effective amount of the substituted 4-piperidinyl-quinazoline or related compound described herein (e.g., a compound of Formula I or II, or other compounds in Section I), a pharmaceutically acceptable carrier, vehicle or diluent, and optionally at least one additional therapeutic agent listed above.

[1130] Another aspect of this invention is a kit comprising a therapeutically effective amount of the substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein (e.g., a compound of Formula I, or other compounds in Section I-A), a pharmaceutically acceptable carrier, vehicle or diluent, and optionally at least one additional therapeutic agent listed above.

IV. Pharmaceutical Compositions and Dosing Considerations

[1131] As indicated above, the invention provides pharmaceutical compositions, which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8)

nasally. In certain embodiments, the invention provides a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula I or II in Section I) and a pharmaceutically acceptable carrier. In certain embodiments, the invention provides a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula I, I-A, I-1, or I-A1 in Sectoin I-A) and a pharmaceutically acceptable carrier.

[1132] The phrase "therapeutically effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment. In certain embodiments, a therapeutically effective amount is an amount sufficient for inhibition of ERK5. In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a proliferative disease, such as cancer.

[1133] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[1134] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[1135] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[1136] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any

methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[1137] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, *e.g.*, bile acids, and polymeric carriers, *e.g.*, polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[1138] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[1139] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[1140] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose,

mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[1141] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[1142] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, *e.g.*, freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that

they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[1143] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[1144] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[1145] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[1146] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[1147] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[1148] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[1149] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[1150] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[1151] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[1152] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[1153] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[1154] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[1155] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[1156] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[1157] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[1158] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for

example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[1159] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[1160] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[1161] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[1162] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[1163] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[1164] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective

to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[1165] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[1166] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[1167] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

[1168] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

[1169] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a substituted 4-piperidinyl-quinazoline or related compound described herein in a therapeutically effective amount for the treatment of a medical disorder described herein.

[1170] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a substituted 4-piperidinyl-pyrimidine-2-amine or related compound described herein in a therapeutically effective amount for the treatment of a medical disorder described herein.

EXAMPLES

[1171] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. Starting materials described herein can be obtained from commercial sources or may be readily prepared from commercially available materials using transformations known to those of skill in the art.

[1172] Abbreviations used in the Examples are described below. Any abbreviations not described are intended to convey their generally accepted meaning.

Abbreviations

Ac	acetyl ($C(O)CH_3$)
aq	aqueous
Ar	Aromatic ring
BEH	ethylene bridged hybrid
Bz	benzyl (CH_2-phenyl)
Boc	*tert*-butyloxycarbonyl protecting group
CSH	charged surface hybrid
d	doublet
DCM	dichloromethane
dioxane	1,4-dioxane
DIPEA	*N,N*-Diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Eq	Molar equivalents
(ES^+)	electrospray ionisation, positive mode
(ES^-)	electrospray ionisation, negative mode

ESI	electrospray ionisation
Et	ethyl
g	grams
Hal	halogen
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HPLC	high performance liquid chromatography
h	hour(s)
H_2	Hydrogen gas
IC_{50}	50% inhibitory concentration
iPr	*iso*-propyl
LCMS	liquid chromatography-mass spectrometry
LHMDS	lithium hexamethyldisilazide
$(M+H)^+$	protonated molecular ion
$(M-H)^-$	unprotonated molecular ion
M	molar concentration
mL	millilitre
mm	millimiter
mmol	millimole
Me	methyl
$Mn(dpm)_3$	Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III)
MHz	megahertz
min	minute(s)
MSD	mass selective detector
m/z	mass-to-charge ratio
N_2	nitrogen gas
nm	nanometre
NMR	nuclear magnetic resonance (spectroscopy)
O_2	oxygen gas
P4HB	poly-4-hydroxybutyrate
Pd/C	Palladium on Carbon

Pd-170	XPhos Pd(crotyl)Cl
Pd-171	RuPhos Pd(crotyl)Cl
PDA	photodiode array
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PMB	4-methoxybenzyl
prep HPLC	preparative high performance liquid chromatography
Ph	phenyl
pos/neg	positive/negative
q	quartet
RT	room temperature
Rt	retention time
RP	reverse phase
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	singlet
sat	saturated
SCX	solid supported cation exchange (resin)
t	triplet
tBu	*tert*-butyl
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography
UV	ultraviolet
v/v	volume/volume
VWD	variable wave detector
wt	weight
μm	micrometre
μL	microlitre
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
°C	degrees Celsius

[1173] Unless otherwise stated, compounds containing one or more stereocenters are a mixture of stereoisomers. All starting materials and solvents were obtained either from

commercial sources or prepared according to the literature. Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate. Hydrogenations were performed on a Thales H-cube flow reactor under the conditions stated.

[1174] Column chromatography was performed on pre-packed silica (230-400 mesh, 40-63 μm) cartridges using the amount indicated. SCX was purchased from Supelco and treated with 1M hydrochloric acid prior to use. Unless stated otherwise, the reaction mixture to be purified was first diluted with MeOH and made acidic with a few drops of AcOH. This solution was loaded directly onto the SCX and washed with MeOH. The desired material was then eluted by washing with 0.7 M NH_3 in MeOH.

[1175] Preparative reverse-phase HPLC was performed according to one of the following methods:

- Acidic Prep: Waters X-Select CSH column C18, 5 μm (19 x 50 mm), flow rate 28 mL min^{-1} eluting with a H_2O-MeCN gradient containing 0.1 % v/v formic acid over 6.5 min with diode array detection.
- Basic Prep: Waters X-Bridge Prep column C18, 5 μm (19 x 50 mm), flow rate 28 mL min^{-1} eluting with a 10 mM NH_4HCO_3-MeCN gradient over 6.5 min with diode array detection.

[1176] Analytical reverse-phase HPLC mass spectrometry was performed according to one of the following methods:

- HPLC Acidic: Acidic LCMS 4 minute (5-95%). Analytical LCMS was carried out using a Waters X-Select CSH C18, 2.5 μm, 4.6x30 mm column eluting with a gradient of 0.1 % formic acid in MeCN in 0.1 % Formic acid in water. The gradient from 5-95 % 0.1 % Formic acid in MeCN occurs between 0.00-3.00 minutes at 2.5 mL/min with a flush from 3.01-3.5 minutes at 4.5 mL/min. A column re-equilibration to 5% MeCN is from 3.60-4.00 minutes at 2.5 mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity VWD at 254 nm. Mass spectra were measured using an Agilent 6120 MSD running with positive/negative switching.
- HPLC Basic: Basic LCMS 4 minute (5-95%). Analytical LCMS was carried out using a Waters X-Select BEH C18, 2.5 μm, 4.6 x 30 mm column eluting with a gradient of MeCN in aqueous 0.1 % ammonium hydroxide. The gradient from 5-95% MeCN occurs between

0.00-3.00 minutes at 2.5mL/min with a flush from 3.01-3.5 minutes at 4.5 mL/min. A column re-equilibration to 5% MeCN is from 3.60-4.00 minutes at 2.5mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity VWD at 254nm. Mass spectra were measured using an Agilent 6120 MSD running with positive/negative switching.

- HPLC2 Basic: Basic LCMS 4 minute (5-95%). Analytical LCMS was carried out using a Waters X-Select BEH C18, 2.5 µm, 4.6 x 30 mm column eluting with a gradient of MeCN in aqueous 10mM ammonium bicarbonate. The gradient from 5-95% MeCN occurs between 0.00-3.00 minutes at 2.5mL/min with a flush from 3.01-3.5 minutes at 4.5 mL/min. A column re-equilibration to 5% MeCN is from 3.60-4.00 minutes at 2.5mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity VWD at 254nm. Mass spectra were measured using an Agilent 6120 MSD running with positive/negative switching.

[1177] Analytical reverse-phase UPLC mass spectrometry was performed according to one of the following methods:

- UPLC Acidic: Acidic UPLC 3 minute (5-95%). Analytical UPLC/MS was carried out using a Waters Acquity CSH C18, 1.7 µm, 2.1x30 mm column eluting with a gradient of 0.1% Formic acid in MeCN in 0.1% Formic acid in water. The gradient is structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurs between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN is from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity PDA and mass spectra were recorded using an Acquity QDa detector with ESI pos/neg switching.

- UPLC Basic: Basic UPLC 3 minute (5-95%). Analytical UPLC/MS was carried out using a Waters Acquity BEH C18, 1.7 µm, 2.1x30 mm column eluting with a gradient of MeCN in aqueous 0.1 % ammonium hydroxide. The gradient is structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurs between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN is from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity

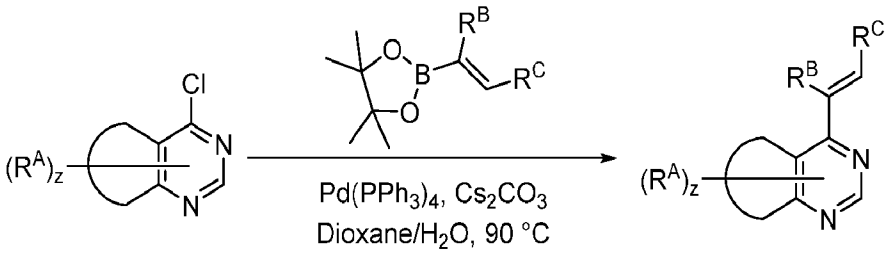
PDA and mass spectra were recorded using an Acquity QDa detector with ESI pos/neg switching.

- UPLC2 Basic: Basic UPLC 3 minute (5-95%). Analytical UPLC/MS was carried out using a Waters Acquity BEH C18, 1.7 µm, 2.1x30 mm column eluting with a gradient of MeCN in aqueous 10 mM Ammonium Bicarbonate. The gradient is structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurs between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN is from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity PDA and mass spectra were recorded using an Acquity QDa detector with ESI pos/neg switching.

[1178] Column temperature was 40 °C in all runs. Injection volume was 3 µL and the flow rate was 0.77 mL/min. PDA scan from 210-400 nm on all runs.

[1179] ^{1}H NMR spectra were acquired on a Bruker Avance III spectrometer at 400 MHz or a Bruker Avance III HD spectrometer at 500 MHz using residual undeuterated solvent as reference and, unless specified otherwise, were run in DMSO-d6.

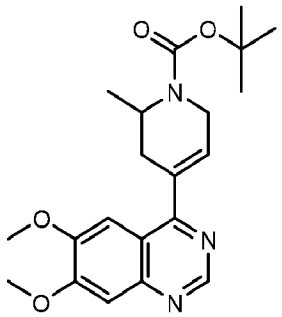
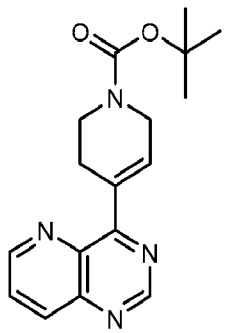
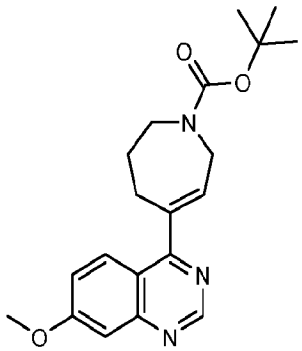
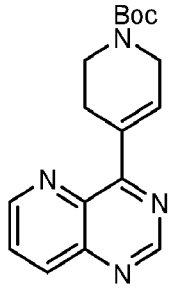
EXAMPLE 1 -- Synthesis of 4-(Tetrahydropyridinyl)-quinazolines and Related Compounds via Suzuki Coupling



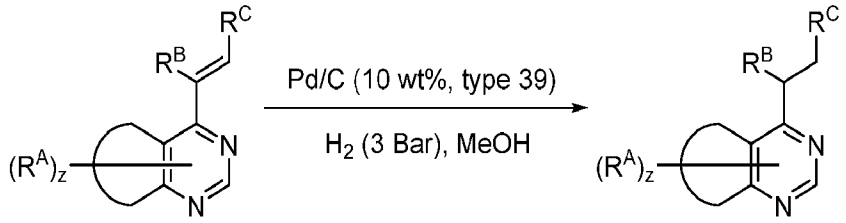
[1180] Bicyclic chloride (1 Eq), pinacol boronate (1.04 Eq,) and cesium carbonate (1 Eq) were dissolved in a 6:1 mixture of dioxane (10-30 Volumes), before the mixture was degassed with a flow of N_2 for 15 mins. $Pd(PPh_3)_4$ (0.05 Eq) was added, and the mixture was degassed with a flow of N_2 for 5 mins. The reaction mixture was then heated to 70-100 °C for 2-18 h. The reaction was cooled to RT, and then diluted with EtOAc (10-30 Volumes). The solution was filtered through Celite and rinsed with additional EtOAc. The filtrate was then concentrated *in vacuo*, and the residue was purified by chromatography on silica gel (0-100% EtOAc/*iso*-hexane) to afford the desired products.

[1181] Compounds prepared according to the procedure of Example 1 and corresponding characterization data are listed in Table 8 below.

TABLE 8.

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-1		UPLC2 Basic, 386.3, (1.38)	Not Determined
Int-2		UPLC2 Basic, 313.2, (2.00)	9.31 (s, 1H), 9.11 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.43 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.00 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.49 (br.s, 1H), 4.20 (br.s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 2.84 - 2.76 (m, 2H), 1.45 (s, 9H).
Int-3		UPLC Basic, 356.3, (1.40)	Not Determined
Int-16		HPLC Basic, 313.2, (2.00)	9.31 (s, 1H), 9.11 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.43 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.00 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.49 (br.s, 1H), 4.20 (br.s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 2.84 - 2.76 (m, 2H), 1.45 (s, 9H).

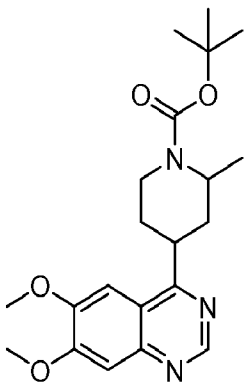
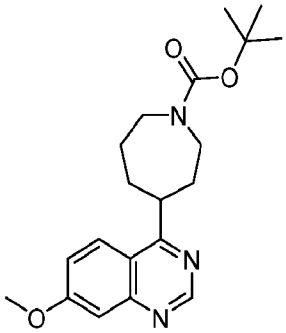
EXAMPLE 2 -- Synthesis of 4-(Piperidinyl)-quinazolines and Related Compounds via Hydrogenation



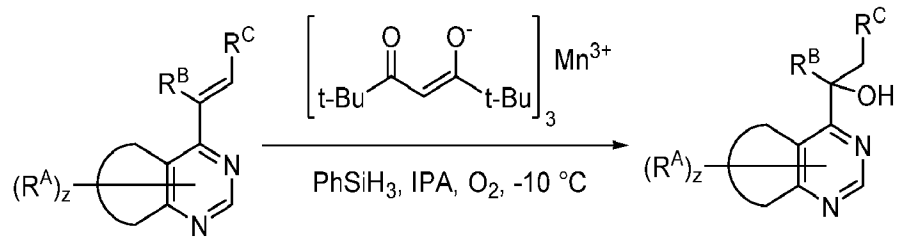
[1182] To a glass-lined steel pressure vessel was added a solution of alkene (1 Eq) in methanol (10-20 volumes) to which was added Pd/C (10 wt%, type-39, 0.11 Eq). The vessel was purged with N_2 and then purged with H_2. The reaction mixture was subjected to H_2 (3 bar) at RT for 22 h. The mixture was filtered through a glass fiber filter pad, and washed with ethanol (20-30 volume). The filtrate was then concentrated *in vacuo*, and the residue was purified by chromatography on silica gel (0-100% EtOAc/*iso*-hexane), to afford the desired product.

[1183] Compounds prepared according to the procedure of Example 2 (from alkenes **Int-1** and **Int-3**, for example) and corresponding characterization data are listed in Table 9 below.

TABLE 9.

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-4		UPLC Basic, 388.4, (1.42)	9.00 (s, 0.6H), 8.99 (s, 0.4H), 7.48 (s, 0.4H), 7.47 (s, 0.6H), 7.34 (s, 0.4H), 7.34 (s, 0.6H), 4.09 (q, J = 5.3 Hz, 0.8H), 4.00 – 3.96 (m, 7.4H), 3.92 – 3.83 (m, 0.6H), 3.77-3.69 (m, 0.6H), 3.42-3.34 (m, 0.6H), 2.10-1.69 (m, 4H), 1.44 (s, 6H), 1.43 (s, 3H), 1.35 (d, J = 6.9 Hz, 1H), 1.13 (d, J = 6.4 Hz, 2H).
Int-5		UPLC Basic, 258.1, (1.45)	Not Determined

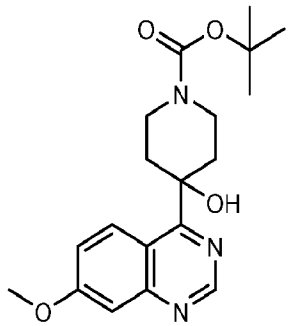
EXAMPLE 3 -- Synthesis of 4-(Hydroxypiperidinyl)-quinazolines and Related Compounds via Mukaiyama Hydration

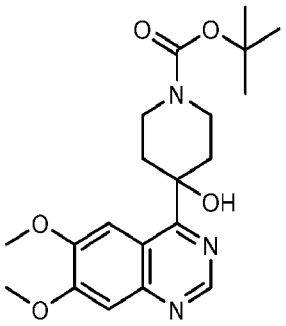
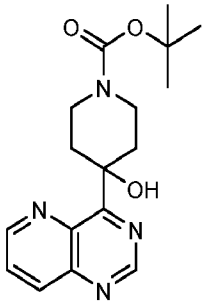


[1184] Alkene (1 Eq) was dissolved in 2-propanol (10-30 Volumes) before the addition of $Mn(dpm)_3$ (0.3 Eq). The reaction was cooled to -10 °C before degassing the solution with 3 vacuum/O_2 cycles. Phenylsilane (2 Eq) was then added to the solution at -10 °C. The reaction was stirred for 1 hr at -10 °C before being quenched with *sat.* sodium thiosulfate aqueous solution (30 mL). The reaction was warmed to RT over 20 mins before extracting with DCM (3 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (40 g cartridge, dry-loaded, 0-20% (0.7M Ammonia/MeOH)/EtOAc)) to afford the desired tertiary alcohol product.

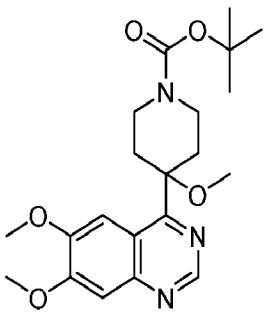
[1185] Compounds prepared according to the procedure of Example 3 (from alkene **Int-16**, for example) and corresponding characterization data are listed in Table 10 below.

TABLE 10.

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^1H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-6		UPLC2 Basic, 360.2, (1.33)	9.09 (s, 1H), 9.02 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 2.7 Hz, 1H), 7.31 (dd, *J* = 9.5, 2.7 Hz, 1H), 5.96 (s, 1H), 3.96 (s, 3H), 3.85 (d, *J* = 12.7 Hz, 2H), 3.28 (s, 2H), 2.19 – 2.02 (m, 2H), 2.01 – 1.87 (m, 2H), 1.42 (s, 9H).

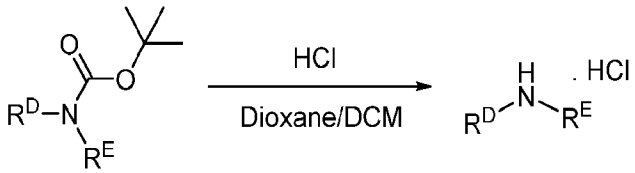
Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^1H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-7		UPLC Acidic, 390.3, (0.87)	Not Determined
Int-8		UPLC2 Basic, 353.2 $[M+Na]^+$, (1.96)	9.39 (s, 1H), 9.12 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.55 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.08 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.59 (s, 1H), 4.00 – 3.87 (m, 2H), 3.70 – 3.55 (m, 2H), 1.85 (d, *J* = 13.2 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.44 (s, 9H).

EXAMPLE 4 -- Synthesis of tert-Butyl 4-(6,7-dimethoxyquinazolin-4-yl)-4-methoxypiperidine-1-carboxylate (Int-9)



[1186] To a stirred solution of *tert*-butyl 4-(6,7-dimethoxyquinazolin-4-yl)-4-hydroxypiperidine-1-carboxylate **Int-7** (350 mg, 1 Eq, 0.90 mmol) in THF (5 mL) under N_2 at 0 °C was added NaH (54 mg, 60% Wt, 1.5 Eq, 1.35 mmol) and left at this temp for 30 mins. To this was added methyl iodide (383 mg, 0.169 mL, 3.0 Eq, 2.70 mmol) and left to warm to RT over 18 h. The reaction mixture was quenched by addition of NH_4Cl (sat, aq, 50 mL). The product was extracted into EtOAc (50 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered and solvent removed to afford **Int-9** (421 mg, 0.91 mmol, 100 %) as a viscous oil. Rt 2.25 min (UPLC, Acidic); m/z 404.3 $(M+H)^+$ (ES^+).

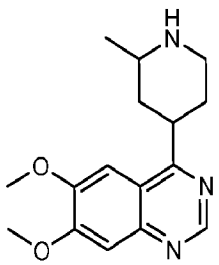
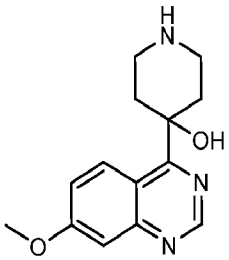
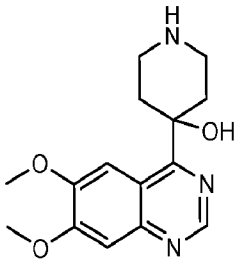
EXAMPLE 5 -- Acid Deprotection of Boc-Protected 4-(Piperidinyl)-quinazolines and Related Compounds

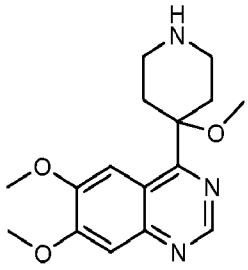
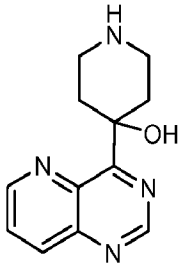
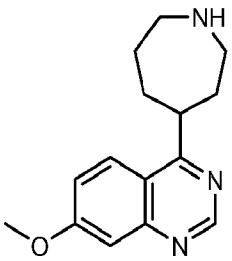


[1187] To a solution of Boc-protected amine (1.00 Eq) in DCM (5-20 Volumes) was added HCl 4M in dioxanes (4 molar, 2-20 Eq) and stirred at RT for 18 h. The reaction mixture was evaporated *in vacuo*. The residue was optionally sonicated in isohexanes (10-50 Volumes). The solid was isolated by filtration and dried under suction to afford the deprotected secondary amine as the HCl salt.

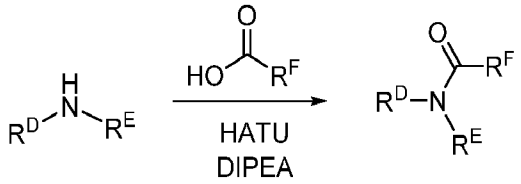
[1188] Compounds prepared according to the procedure of Example 5 (from alkenes **Int-4** through **Int-9**, for example) and corresponding characterization data are listed in Table 11 below.

TABLE 11.

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-10		UPLC2 Basic, 288.1, (0.878/0.917)	9.05 (s, 1H), 7.59 (s, 0.7H), 7.51 (s, 0.3H), 7.38 (s, 1H), 4.23 – 4.17 (m, 0.3H), 4.08 – 4.02 (m, 0.7H), 4.02 – 3.96 (m, 6H), 3.49 – 3.40 (m, 1H), 3.35 – 3.28 (m, 1H), 3.21 (q, *J* = 12.5 Hz, 1H), 2.28 – 1.84 (m, 4H), 1.38 (d, *J* = 6.7 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 2H), 2H not observed.
Int-11		UPLC Basic, 260.1, (0.764)	9.15 (s, 1H), 9.00 (br s, 1H), 8.97 (d, *J* = 9.5 Hz, 1H), 8.87 (br s, 1H), 7.40 (d, *J* = 2.7 Hz, 1H), 7.35 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.97 (s, 3H), 3.36 – 3.20 (m, 4H), 2.49 – 2.38 (m, 2H), 2.15 (d, *J* = 14.2 Hz, 2H), 2.08 (s, 1H).
Int-12		UPLC Basic, 290.1, (0.714)	9.05 (d, *J* = 1.4 Hz, 1H), 8.81 (s, 1H), 8.67 (s, 1H), 8.35 (s, 1H), 7.39 (s, 1H), 6.34 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.34 – 3.26 (m, 4H), 2.47 – 2.38 (m, 2H), 2.19 (d, *J* = 14.2 Hz, 2H)

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-13		UPLC Basic, 304.2, (1.343)	9.09 (s, 1H), 9.06 – 8.77 (m, 2H), 8.10 (s, 1H), 7.42 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.29 – 3.12 (m, 4H), 3.02 (s, 3H), 2.47 – 2.30 (m, 4H)
Int-14		UPLC Basic, 231.2, (1.001)	Not Determined
Int-15		UPLC Basic, 258.3, (1.093)	9.10 (s, 1H), 9.00 (s, 1H), 8.84 (s, 1H), 8.32 (d, J = 9.0 Hz, 1H), 7.41 – 7.34 (m, 2H), 4.09 – 4.02 (m, 1H), 3.97 (s, 3H), 3.44 – 3.20 (m, 3H), 3.20 – 3.06 (m, 1H), 2.31 – 2.19 (m, 1H), 2.17 – 2.10 (m, 1H), 2.07 – 1.93 (m, 3H), 1.93 – 1.83 (m, 1H). 1 x H not observed, obscured by NMR solvent.

EXAMPLE 6 – Amide Coupling in Deepwell Plates



[1189] To a well of a 96-deepwell plate were added amine (10-50 mg, 1 Eq) and carboxylic acid (1.2 Eq) reagents, which were dissolved in DMF (10-30 volumes). DIPEA (3-5 Eq) was added, followed by a solution of HATU (1.2 Eq) in DMF (20 volumes). The well plate was shaken at RT for 20 h. The samples were submitted for analysis by LCMS using the UPLC Basic method. The samples were filtered and submitted for purification by mass-directed preparative HPLC using the Basic prep method described above. The compounds were dried in a Genevac HT-12, dissolved in MeCN and submitted for analysis by LCMS using methods described. The

compounds were dried in a Genevac HT-4X and then were further dried in a desiccator at 40 °C for 3 h. The compounds were analysed by ^{1}H NMR in DMSO-d6.

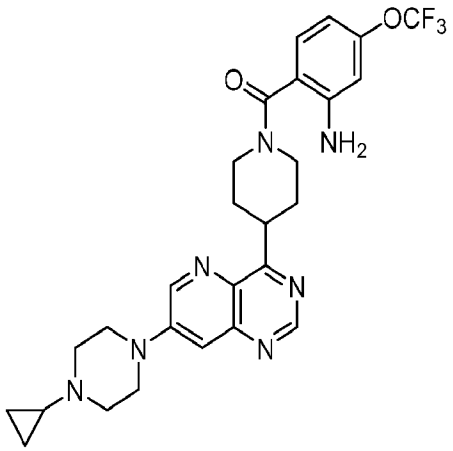
[1190] Compounds prepared according to the procedure of Example 6 (from amine **Int-10** through **Int-15**, for example) and corresponding characterization data are listed in Table 12 below. Chemical structures are depicted in Tables 1 and 2 for the compounds listed in Table 12 below.

TABLE 12.

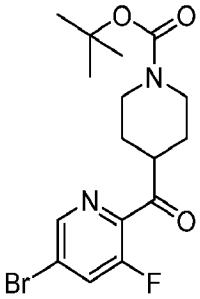
Compound No.	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
I-1	UPLC Basic, 491.3, (1.27)	9.05 – 8.96 (m, 1H), 7.56 – 7.48 (m, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.91 – 6.80 (m, 1H), 6.69 – 6.51 (m, 1H), 5.67 – 5.51 (m, 2H), 5.05 – 4.06 (m, 2H), 4.02 – 3.95 (m, 6H), 3.72 – 3.48 (m, 1H), 2.08 (s, 3H), 2.03 – 1.63 (m, 3H), 1.49 – 1.41 (m, 1H), 1.18 – 1.12 (m, 1H).
I-2	UPLC Basic, 463.3, (1.21)	9.11 (s, 1H), 9.03 (d, *J* = 9.5 Hz, 1H), 7.37 (d, *J* = 2.7 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.19 – 7.12 (m, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.58 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.08 (s, 1H),5.63 – 5.50 (m, 2H), 4.41 – 4.28 (m, 1H), 3.96 (s, 3H), 3.69 – 3.47 (m, 2H), 2.27 – 2.15 (m, 2H), 2.12 – 1.86 (m, 2H), 1 x CH not observed
I-3	UPLC Basic, 478.3, (1.26)	9.01 (s, 1H), 8.42 (s, 1H), 7.62 – 7.53 (m, 2H), 7.49 – 7.39 (m, 2H), 7.36 (s, 1H), 6.08 (s, 1H), 4.51 – 4.26 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.68 – 3.36 (m, 3H), 2.31 – 2.09 (m, 3H), 2.06 – 1.92 (m, 1H).
I-4	UPLC Basic, 424.3, (1.05)	9.01 (s, 1H), 8.43 (s, 1H), 7.42 – 7.37 (m, 2H), 7.36 (s, 1H), 7.03 – 6.91 (m, 2H), 6.05 (s, 1H), 4.60 – 4.09 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H), 3.76 – 3.33 (m, 3H), 2.28 – 2.14 (m, 2H), 2.14 – 1.86 (m, 2H).
I-5	UPLC Basic, 462.3, (1.23)	9.01 (s, 1H), 8.41 (s, 1H), 7.85 – 7.77 (m, 2H), 7.69 – 7.62 (m, 2H), 7.36 (s, 1H), 6.09 (s, 1H), 4.48 – 4.32 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.67 – 3.51 (m, 1H), 3.51 – 3.35 (m, 2H), 2.31 – 2.09 (m, 3H), 2.05 – 1.93 (m, 1H).
I-6	UPLC Basic, 493.3, (1.22)	9.01 (s, 1H), 8.42 (s, 1H), 7.36 (s, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.66 (dd, *J* = 2.4, 1.2 Hz, 1H), 6.49 (ddd, *J* = 8.3, 2.4, 1.1 Hz, 1H), 6.04 (s, 1H), 5.59 (s, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 3.63 – 3.39 (m, 2H), 2.31 – 2.15 (m, 2H), 2.15 – 2.00 (m, 2H), 2H not observed due to overlap with other peaks.
I-7	UPLC Basic, 492.3, (1.41)	9.06 (s, 1H), 8.16 (s, 1H), 7.63 – 7.55 (m, 2H), 7.48 – 7.41 (m, 2H), 7.39 (s, 1H), 4.39 – 4.35 (m, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.60 – 3.40 (m, 2H), 3.05 – 3.01 (m, 3H), 2.46 – 1.96 (m, 5H).

Compound No.	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
I-8	UPLC Basic, 476.3, (1.38)	9.06 (s, 1H), 8.16 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 1H), 4.43 – 4.35 (m, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.47 – 3.42 (m, 2H), 3.03 (s, 3H), 2.46 – 1.98 (m, 5H).
I-9	UPLC Basic, 507.3, (1.37)	9.05 (s, 1H), 8.17 (s, 1H), 7.39 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.65 (dd, *J* = 2.4, 1.2 Hz, 1H), 6.54 – 6.44 (m, 1H), 5.59 (s, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.48 – 3.32 (m, 2H), 3.02 (s, 3H), 2.36 – 2.28 (m, 3H), 2.22 – 2.11 (m, 2H), 1 x CH not observed
I-10	UPLC Basic, 493.3, (1.15)	8.99 (s, 1H), 8.44 (s, 1H), 7.35 (s, 1H), 7.16 – 7.10 (m, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.0 Hz, 1H), 5.81 (s, 1H), 5.25 (s, 2H), 3.99 (s, 3H), 3.96 – 3.92 (m, 1H), 3.93 (s, 3H), 3.51 (t, *J* = 11.9 Hz, 2H), 2.34 – 2.24 (m, 2H), 2.06 (d, *J* = 13.6 Hz, 2H), 1.95 – 1.91 (m, 1H).
I-11	UPLC 3 min Basic, 434.2, (1.22)	9.40 (s, 1H), 9.14 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.56 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.6, 4.2 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 5.61 (s, 2H), 3.61 – 3.37 (m, 2H), 2.53 – 2.44 (obsc. m, 2H), 2.05 – 1.87 (m, 2H). 2 x CH not observed.
I-12	UPLC 3 min Basic, 461.3, (1.38)	9.07 (s, 1H), 8.29 (s, 1H), 7.34 (s, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 6.69 – 6.65 (m, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.56 (s, 2H), 4.11 – 3.70 (m, 5H), 3.69 – 3.38 (m, 3H), 2.03 – 1.64 (m, 2H), 4 x CH not observed due to signal broadening
II-1	UPLC Basic, 491.3, (1.37)	9.06 (d, *J* = 2.9 Hz, 1H), 9.03 (s, 1H), 7.73 (dq, *J* = 3.7, 1.2 Hz, 1H), 7.53 (dq, *J* = 3.7, 1.2 Hz, 1H), 7.38 (d, *J* = 2.9 Hz, 1H), 4.47 – 4.19 (m, 2H), 3.56 – 3.49 (m, 4H), 2.48 (m, 4H, overlapping with DMSO), 2.24 (s, 3H), 2.02 – 1.75 (m, 4H), 3 x CH not observed
II-2	UPLC Basic, 459.3, (1.12)	9.06 (d, *J* = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 732 (s, 1H), 7.22 – 7.15 (m, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.57 (t, *J* = 8.8 Hz, 2H), 4.33 – 4.29 (m, 1H), 3.55 – 3.48 (m, 4H), 3.26 – 3.17 (m, 2H), 2.47 (m, 4H, overlapping with DMSO), 2.24 (s, 3H), 1.87 – 1.83 (m, 4H), 4 x CH not observed
II-3	UPLC Basic, 475.4, (1.11)	9.05 (d, *J* = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, *J* = 2.9 Hz, 1H), 6.91 (d, *J* = 1.0 Hz, 3H), 4.29 – 4.25 (m, 4H), 3.55 – 3.48 (m, 4H), 2.47 (m, 4H, overlapping with DMSO), 2.24 (s, 3H), 1.87 – 1.79 (m, 4H), 5 x CH not observed

EXAMPLE 7 -- Synthesis of (2-Amino-4-(trifluoromethoxy)phenyl)(4-(7-(4-cyclopropylpiperazin-1-yl)pyrido[3,2-*d*]pyrimidin-4-yl)piperidin-1-yl)methanone (VI-7)

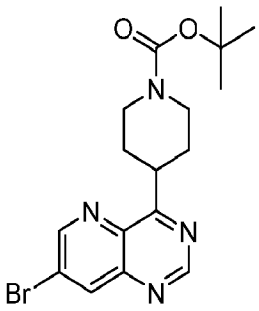


Part I – Synthesis of tert-butyl 4-(5-bromo-3-fluoropicolinoyl)piperidine-1-carboxylate



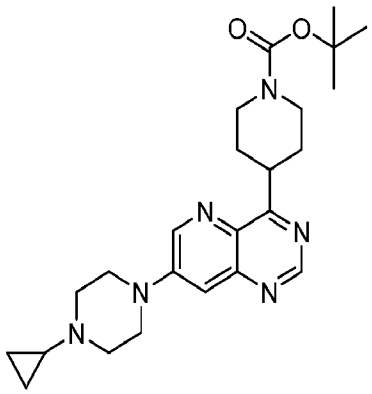
[1191] 2,5-Dibromo-3-fluoropyridine (0.9887 g, 1.0 Eq, 3.879 mmol) was dissolved in toluene (15 mL), the reaction vessel cooled to -78 °C and cycled thrice with nitrogen/vacuum. n-butyllithium (1.55 mL, 2.5 molar, 1.0 Eq, 3.88 mmol) was added and the solution stirred for 23 min. A solution of tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (1.1270 g, 1.067 Eq, 4.1381 mmol) in toluene (5 mL) was added and the solution stirred for 4h. The reaction was quenched with water (15 mL) and the solution allowed to warm to rt. Ethyl acetate (10 mL) was added and the phases separated. The aqueous phase was back-extracted with ethyl acetate (10 mL) and the combined organic phases dried over magnesium sulfate, filtered and concentrated onto silica gel. The crude product was purified by chromatography on silica gel (40 g cartridge, 0-50% EtOAc/isohexane) to afford tert-butyl 4-(5-bromo-3-fluoropicolinoyl)piperidine-1-carboxylate (0.9089 g, 2.27 mmol, 58.6 %, 96.9% Purity) as a clear colorless crystalline solid. ^{1}H NMR (500 MHz, DMSO-d 6) δ 8.75 (dd, J = 1.8, 0.9 Hz, 1H), 8.41 (dd, J = 10.5, 1.8 Hz, 1H), 3.96 (broad d, J = 13.1 Hz, 2H), 3.77 (tt, J = 11.4, 3.6 Hz, 1H), 2.86 (broad s, 2H), 1.80 (d, J = 13.1 Hz, 2H), 1.40 (s, 9H), 1.44 – 1.34 (m, 2H).

Part II – Synthesis of tert-butyl 4-(7-bromopyrido[3,2-d]pyrimidin-4-yl)piperidine-1-carboxylate



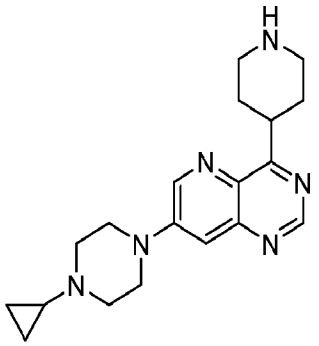
[1192] To a solution of tert-butyl 4-(5-bromo-3-fluoropicolinoyl)piperidine-1-carboxylate (0.8751 g, 96.9% Wt, 1 Eq, 2.190 mmol) in DMF (15 mL) was added potassium carbonate (956.9 mg, 3.162 Eq, 6.924 mmol) followed by formimidamide acetate (458.4 mg, 2.030 Eq, 4.446 mmol). The solution was heated to 90 °C and stirred for 3.5 h. The reaction mixture was allowed to warm to rt. Water (50 mL) was added and the solution filtered. The resulting viscous oil and solid was re-dissolved in ethyl acetate (50 mL) and the organic phase separated from the aqueous phase. The aqueous phase was back-extracted with ethyl acetate (25 mL) and the combined organic fractions washed with brine (25 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated onto silica gel. The crude product was purified by chromatography on silica gel (40 g cartridge, 0-30% EtOAc/isohexane) to afford tert-butyl 4-(7-bromopyrido[3,2-d]pyrimidin-4-yl)piperidine-1-carboxylate (407.8 mg, 1.02 mmol, 46.7 %, 98.7% Purity) as a clear yellow glass. 1H NMR (500 MHz, DMSO-d 6) δ 9.34 (s, 1H), 9.22 (d, J = 2.2 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H), 4.28 (tt, J = 11.7, 3.7 Hz, 1H), 4.12 (broad d, J = 12.0 Hz, 2H), 2.97 (broad s, 2H), 1.88 (d, J = 12.7 Hz, 2H), 1.76 (qd, J = 12.7, 4.2 Hz, 2H), 1.43 (s, 9H).

Part III – Synthesis of tert-butyl 4-(7-(4-cyclopropylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4-yl)piperidine-1-carboxylate



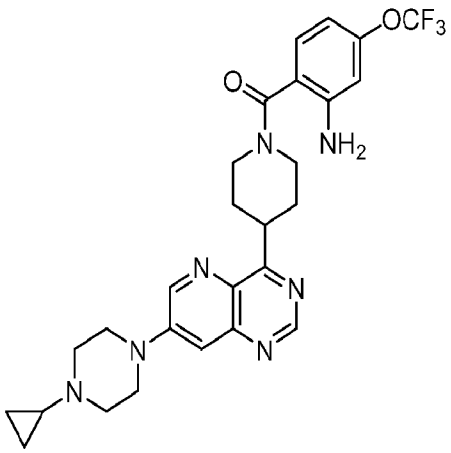
[1193] To a vial was added 2,2'-bis(diphenylphosphaneyl)-1,1'-binaphthalene (49.7 mg, 0.106 Eq, 79.8 μmol), diacetoxypalladium (8.45 mg, 0.05 Eq, 37.6 μmol), and cesium carbonate (515 mg, 2.1 Eq, 1.58 mmol). The vial was cycled three times between vacuum and nitrogen. A solution of tert-butyl 4-(7-bromopyrido[3,2-d]pyrimidin-4-yl)piperidine-1-carboxylate (300 mg, 98.7% Wt, 1 Eq, 753 μmol) in dry toluene (8 mL) was added, followed by 1-cyclopropyl-piperazine (171 mg, 1.8 Eq, 1.36 mmol). The vial was cycled three times between vacuum and nitrogen and the reaction mixture heated to 100 °C under stirring for 18 hours. The reaction mixture was cooled on ice and filtered through celite. The filter cake was washed with ethyl acetate (20 mL) and the filtrate concentrated onto silica gel. The reaction mixture was diluted with water (25 mL) and transferred into a separating funnel. The layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were collected, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-10% MeOH/DCM) to afford tert-butyl 4-(7-(4-cyclopropylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4-yl)piperidine-1-carboxylate (290 mg, 0.61 mmol, 81 %, 92% Purity) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (d, J = 2.9 Hz, 1H), 9.02 (s, 1H), 7.36 (d, J = 2.9 Hz, 1H), 4.25 – 4.05 (m, 4H), 3.48 (t, J = 5.1 Hz, 3H), 3.17 (d, J = 5.2 Hz, 2H), 2.71 (t, J = 5.1 Hz, 3H), 1.84 – 1.65 (m, 6H), 1.42 (s, 9H), 0.46 (d, J = 6.3 Hz, 2H), 0.37 (s, 2H).

Part IV – Synthesis of 7-(4-cyclopropylpiperazin-1-yl)-4-(piperidin-4-yl)pyrido[3,2-d]pyrimidine, HCl salt



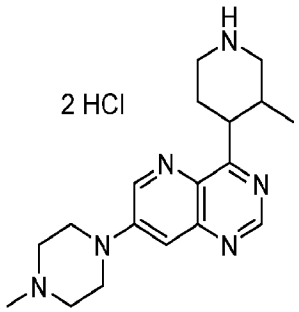
[1194] Hydrochloric acid (0.66 mL, 4 molar, 5.84 Eq, 2.63 mmol) then water (2 mL) were added slowly to a stirred solution of tert-butyl 4-(7-(4-cyclopropylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4-yl)piperidine-1-carboxylate (210 mg, 94% Wt, 1 Eq, 450 µmol) in 1,4-dioxane (10 mL) at rt. The reaction mixture was stirred at rt for 1.5 h. Additional HCl (326 mg, 0.219 mL, 4 molar, 1.95 Eq, 876 µmol) was added and the solution heated to 45 °C under stirring for 3 h. The solution was allowed to cool to rt and stirred for 18 h. The solution was concentrated in vacuo to yield 7-(4-cyclopropylpiperazin-1-yl)-4-(piperidin-4-yl)pyrido[3,2-d]pyrimidine, HCl salt (165 mg, 0.40 mmol, 88 %, 90% Purity) as a white solid. The solid was dried in a vacuum oven for 2 h, and used directly for the next step without further purification. The product was analysed by LCMS (Agilent, ACQUITY UPLC XSelect CSH C18 Column, 130Å, 1.7 µm, 2.1 mm x 30 mm, Acidic (0.1% Formic acid), 3 min method, 5-95% MeCN/water): m/z 339.0 (M+H)+ (ES+); at 0.13 min, 90% purity at (254 nm).

Part V – Synthesis of (2-Amino-4-(trifluoromethoxy)phenyl)(4-(7-(4-cyclopropylpiperazin-1-yl)pyrido[3,2-*d*]pyrimidin-4-yl)piperidin-1-yl)methanone (VI-7)

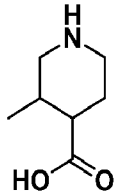


[1195] To a solution of 7-(4-cyclopropylpiperazin-1-yl)-4-(piperidin-4-yl)pyrido[3,2-d]pyrimidine, HCl salt (240 mg, 96% Wt, 1.0 Eq, 560 µmol) in DMF (5 mL) was added DIPEA (309 mg, 0.417 mL, 4.27 Eq, 2.39 mmol), followed by 2-amino-4-(trifluoromethoxy)benzoic acid (149 mg, 1.2 Eq, 672 µmol) and HATU (215 mg, 1.01 Eq, 566 µmol). The solution was stirred at rt for 18 hours. The reaction mixture was diluted with water (25 mL) and transferred into a separating funnel. The layer was extracted with EtOAc (2 x 25 mL). The combined organic layers was collected, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 0-100% MeCN/10 mM Ammonium Bicarbonate) to afford (2-amino-4-(trifluoromethoxy)phenyl)(4-(7-(4-cyclopropylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4-yl)piperidin-1-yl)methanone (190 mg, 0.33 mmol, 60 %, 95% Purity) as a pale yellow gum. LCMS *m/z*: 542 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.99 (d, J = 2.8 Hz, 1H), 7.34 (d, J = 2.8 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.70 (s, 1H), 6.50 (dd, J = 8.4, 2.5 Hz, 1H), 5.39 (s, 2H), 4.36 – 4.24 (m, 1H), 4.18 (d, J= 13.2 Hz, 2H), 3.50 (t, J = 5.1 Hz, 4H), 3.20 – 3.12 (m, 2H), 2.75 (t, J = 5.1 Hz, 4H), 1.97 – 1.87 (m, 4H), 1.78 – 1.69 (m, 1H), 0.48 (tt, J = 6.0, 3.6 Hz, 2H), 0.43 – 0.36 (m, 2H).

EXAMPLE 8 -- Synthesis of 7-(4-Methylpiperazin-1-yl)-4-(3-methylpiperidin-4-yl)pyrido[3,2-*d*]pyrimidine Dihydrochloride Salt



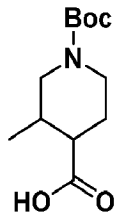
Part I – Synthesis of 3-Methylpiperidine-4-carboxylic acid



[1196] To a solution of 3-methylpyridine-4-carboxylic acid (9.00 g, 65.62 mmol, 1.00 equiv) and HCl (g) in MeOH (54 mL) in methanol (150 mL) was added Adam's catalyst (1.80 g, 7.93 mmol, 0.12 equiv) in a pressure tank. The mixture was hydrogenated at room temperature under

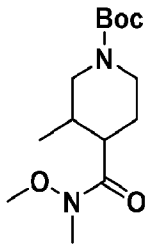
50 psi of hydrogen pressure for 48 h. The mixture was filtered through a Celite pad and concentrated under reduced pressure to afford 3-methylpiperidine-4-carboxylic acid (12.5 g) as a light yellow oil.

Part II – Synthesis of 1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid



[1197] A mixture of 3-methylpiperidine-4-carboxylic acid (12.50 g, 87.30 mmol, 1.00 equiv) and caustic soda (10.48 g, 261.89 mmol, 3.00 equiv) in water (440 mL) was added di-tert-butyl dicarbonate (28.58 g, 130.95 mmol, 1.50 equiv), and the mixture was stirred at 25 degrees C for 14 h. The reaction was adjusted to pH=3~4 by satd. citric acid solution, and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (17.5 g, 82.39%) as an off-white solid.

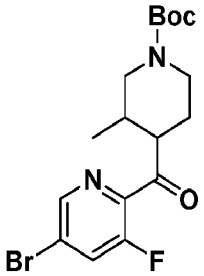
Part III – Synthesis of tert-butyl 4-[methoxy(methyl)carbamoyl]-3-methylpiperidine-1-carboxylate



[1198] To a solution of 1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (10.50 g, 43.15 mmol, 1.00 equiv) in DCM (200 mL) was added CDI (10.50 g, 64.73 mmol, 1.50 equiv) for three batches, and the mixture was stirred at 25 degrees C for 1.5 h. Then N,O-dimethylhydroxylamine (5.27 g, 86.31 mmol, 2.00 equiv) was added in a portion, and the mixture was stirred at 25 degrees C for 2 h. The resulting mixture was diluted with water (200 mL), and extracted with DCM (3 x 150 mL). The combined organic layers were washed with brine (3 x 510 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated

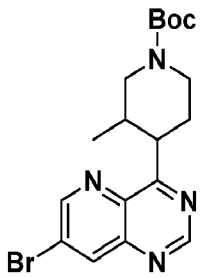
under reduced pressure. This resulted in tert-butyl 4-[methoxy(methyl)carbamoyl]-3-methylpiperidine-1-carboxylate (12 g, 97.10%) as a colorless oil.

Part IV – Synthesis of tert-butyl 4-(5-bromo-3-fluoropyridine-2-carbonyl)-3-methylpiperidine-1-carboxylate



[1199] Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2,5-dibromo-3-fluoropyridine (3.20 g, 12.55 mmol, 1.00 equiv), toluene (40 mL). This was followed by the addition of n-BuLi (1.24 mL, 19.38 mmol, 1.05 equiv) dropwise with stirring at -78 degrees C in 30 min. To this was added a solution of tert-butyl 4-[methoxy(methyl)carbamoyl]-3-methylpiperidine-1-carboxylate (3.78 g, 13.18 mmol, 1.05 equiv) in THF (40 mL) dropwise with stirring at -78 °C. The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 70 mL of water/ice. The resulting solution was extracted with 2 x 70 mL of ethyl acetate. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl 4-(5-bromo-3-fluoropyridine-2-carbonyl)-3-methylpiperidine-1-carboxylate (2.3 g, 45.65%) as a light yellow solid.

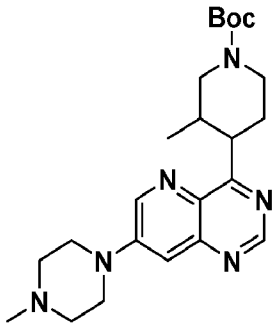
Part V – Synthesis of tert-butyl 4-[7-bromopyrido[3,2-d]pyrimidin-4- yl]-3-methylpiperidine-1-carboxylate



[1200] Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl 4-(5-bromo-3-fluoropyridine-2-carbonyl)-3-

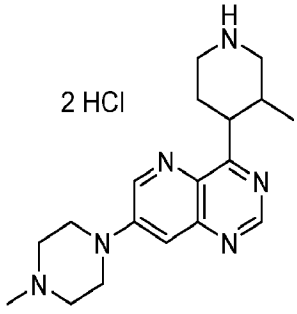
methylpiperidine-1-carboxylate (4.30 g, 10.72 mmol, 1.00 equiv), formamidine acetate (2.23 g, 21.43 mmol, 2.00 equiv), K_2CO_3 (7.40 g, 53.58 mmol, 5.00 equiv), and DMF (100 mL). The resulting solution was stirred for 72 h at 20 °C. The reaction mixture was poured into water (100 mL), and stirred for 1h, filtered to give the filtered cake. This resulted in tert-butyl 4-[7-bromopyrido[3,2-d]pyrimidin-4- yl]-3-methylpiperidine-1-carboxylate (3.7 g, 84.77%) as a yellow solid.

Part VI – Synthesis of tert-butyl 3-methyl-4-[7- (4-methylpiperazin- 1-yl)pyrido[3,2-d]pyrimidin-4-yl]piperidine-1-carboxylate



[1201] To a solution of tert-butyl 4-[7-bromopyrido[3,2-d]pyrimidin-4-yl]-3-methylpiperidine-1-carboxylate (1.10 g, 2.70 mmol, 1.00 equiv) and 1-methylpiperazine (0.35 g, 3.51 mmol, 1.30 equiv) in dioxane (20 mL) were added Cs_2CO_3 (1.76 g, 5.40 mmol, 2.00 equiv) and RuPhos Palladacycle Gen.3 (0.23 g, 0.27 mmol, 0.10 equiv). After stirring overnight at 90 degrees C under nitrogen atmosphere, the resulting mixture was filtered, and the filter cake was washed with CH_2Cl_2 (3 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (12:1) to afford tert-butyl 3-methyl-4-[7-(4-methylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4-yl]piperidine-1-carboxylate (700 mg, 60.76%) as a yellow solid.

Part VII – Synthesis of 1-Methyl-4-[4-(3-methylpiperidin-4-yl)pyrido[3,2-d]pyrimidin-7-yl]piperazine dihydrochloride



[1202] A mixture of tert-butyl 3-methyl-4-[7-(4-methylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4-yl]piperidine -1-carboxylate (600 mg, 1.41 mmol, 1.00 equiv) in DCM (10 mL) was added HCl (gas) in 1,4-dioxane (6 mL), and the mixture was stirred at 25 degrees C for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL). The precipitated solids were collected by filtration. This resulted in 1-methyl-4-[4-(3-methylpiperidin-4-yl)pyrido[3,2-d]pyrimidin-7-yl]piperazine dihydrochloride (400 mg, 71.21%) as a yellow solid. LCMS (ES, *m/z*): 327.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.66 (s, 1H), 9.50 (d, J = 9.6 Hz, 1H), 9.26 (t, J = 9.2 Hz, 1H), 9.18 (s, 1H), 9.11 (d, J = 2.8 Hz, 1H), 7.58 (d, J = 2.8 Hz, 1H), 4.37 (d, J = 13.6 Hz, 2H), 4.13 (td, J = 11.4, 3.6 Hz, 1H), 3.54 (s, 2H), 3.51 (s, 2H), 3.35 (td, J = 13.6, 12.7, 4.4 Hz, 2H), 3.27 – 3.14 (m, 2H), 3.07 (q, J = 12.4 Hz, 1H), 2.91 – 2.76 (m, 4H), 2.59 – 2.52 (m, 1H), 2.09 (qd, J = 13.6, 4.0 Hz, 1H), 1.87 (dd, J = 14.0, 3.2 Hz, 1H), 0.62 (d, J = 6.4 Hz, 3H).

EXAMPLE 9 – Synthesis of Additional 4-Piperidinyl-quinazolines and Related Compounds

[1203] The compounds listed in Table 13 below were prepared using experimental procedures described in the Examples and Detailed Description. Table 13 also lists each compound's ^1H NMR characterization data and mass-to-charge ratio observed by LC/MS. Chemical structures are presented in Tables 1-A, 2-A, 6, and 7, above.

TABLE 13.

Compound No.	Mass Spec. m/z	^1H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
I-13	438	9.05 (s, 1H), 8.17 (s, 1H), 7.43-7.36 (m, 3H), 7.01-6.94 (m, 2H), 4.40-4.18 (m, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.75-3.55 (m, 1H), 3.53-3.34 (m, 2H), 3.03 (s, 3H), 2.39-2.21 (m, 2H), 2.20-2.10 (m, 2H).
I-14	384	9.08 (s, 1H), 8.28 (d, J = 9.3 Hz, 1H), 7.83-7.77 (m, 2H), 7.80-7.73 (m, 1H), 7.73-7.66 (m, 2H), 7.33 (d, J = 2.6 Hz, 1H), 7.26 (dd, J = 9.3, 2.6 Hz, 1H), 3.94 (s, 3H), 3.83-3.75 (m, 2H), 3.71-3.60 (m, 1H), 2.57-2.50 (m, 2H), 1.98-1.87 (m, 4H).
I-15	503	8.99 (s, 1H), 8.92 (d, J = 2.9 Hz, 1H), 8.49 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 8.6, 1.9 Hz, 1H), 7.78-7.68 (m, 2H), 7.34 (d, J = 2.8 Hz, 1H), 3.95-3.84 (m, 3H), 3.47 (t, J = 5.1 Hz, 4H), 2.60-2.52 (m, 2H), 2.46 (t, J = 5.0 Hz, 4H), 2.22 (s, 3H), 1.97-1.89 (m, 4H).
I-16	483	9.01 (s, 1H), 8.97 (d, J = 2.9 Hz, 1H), 7.75-7.69 (m, 2H), 7.35 (d, J = 2.9 Hz, 1H), 7.21-7.16 (m, 2H), 3.88 (s, 4H), 3.81-3.74 (m, 2H), 3.49 (t, J = 5.1 Hz, 4H), 2.47 (t, J = 5.1 Hz, 4H), 2.45-2.35 (m, 2H), 2.23 (s, 3H), 1.97-1.86 (m, 4H).

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
I-17	453	9.01 (s, 1H), 8.97 (d, J = 2.9 Hz, 1H), 7.82-7.73 (m, 3H), 7.68 (dd, J = 8.3, 7.0 Hz, 2H), 7.35 (d, J = 2.9 Hz, 1H), 3.91 (p, J = 7.8, 7.1 Hz, 1H), 3.82 (d, J = 11.8 Hz, 2H), 3.49 (t, J = 5.1 Hz, 4H), 2.47 (t, J = 5.1 Hz, 5H), 2.23 (s, 3H), 1.97-1.88 (m, 4H). Missing 1 proton.
I-18	521	9.00 (s, 1H), 8.97 (d, J = 2.9 Hz, 1H), 8.14 (dd, J = 16.7, 7.9 Hz, 2H), 8.02 (s, 1H), 7.95 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 2.9 Hz, 1H), 4.02-3.92 (m, 1H), 3.92-3.83 (m, 2H), 3.49 (t, J = 5.1 Hz, 4H), 2.58 (td, J = 11.5, 4.0 Hz, 2H), 2.47 (t, J = 5.1 Hz, 4H), 1.97-1.82 (m, 4H).
I-19	531	9.00 (s, 1H), 8.96 (d, J = 2.9 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 2.9 Hz, 1H), 3.97 (p, J = 8.9, 8.4 Hz, 1H), 3.84 (d, J = 11.7 Hz, 2H), 3.49 (t, J = 5.2 Hz, 4H), 2.66-2.55 (m, 2H), 2.47 (t, J = 5.2 Hz, 4H), 2.23 (s, 3H), 1.91 (td, J = 10.7, 9.5, 3.6 Hz, 4H).
I-20	478	Not determined.
I-21	530	9.08-9.03 (m, 2H), 7.37 (d, J = 2.9 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.69-6.65 (m, 1H), 6.53-6.47 (m, 1H), 5.60 (s, 2H), 4.11-4.01 (m, 1H), 3.55-3.49 (m, 4H), 3.12 (s, 1H), 2.80 (s, 1H), 2.50-2.46 (m, 3H), 2.24 (s, 3H), 1.79-1.75 (m, 2H), 0.58-0.55 (m, 3H), 4H not observed due to peak broadening; Mix of diastereoisomers – ratio not determined.
I-22	515	9.07 (s, 1H), 9.05 (d, J = 2.9 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.48-7.43 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 4.11-4.07 (m, 1H), 3.53 (t, J = 5.1 Hz, 4H), 2.24 (s, 3H), 0.67-0.63 (m, 1H), 0.50-0.47 (m, 1H), 12H not observed.
I-23	499	9.07 (s, 1H), 9.05 (d, J = 2.4 Hz, 1H), 7.84 (s, 2H), 7.66 (s, 2H), 7.38 (s, 1H), 4.70-4.56 (m, 1H), 4.14-4.05 (m, 1H), 3.63-3.55 (m, 1H), 3.53 (s, 4H), 3.29 (s, 2H), 2.24 (s, 4H), 0.66 (s, 1H), 0.48 (s, 1H). Missing 7 protons.
I-24	461	9.06 (s, 1H), 9.05 (d, J = 2.9 Hz, 1H), 7.43-7.39 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 7.04-6.97 (m, 2H), 4.91-4.32 (m, 1H), 4.14-4.03 (m, 1H), 3.95-3.64 (m, 4H), 3.59-3.49 (m, 4H), 3.27-2.71 (m, 2H), 2.28-2.13 (m, 4H), 1.92-1.58 (m, 2H), 0.83-0.29 (m, 3H), 4 H not observed.
I-25	538	Not determined.
I-26	491	Not determined.
I-27	491	Not determined.
II-4	447	12.86 (s, 1H), 9.09-8.99 (m, 2H), 7.37 (d, J = 2.9 Hz, 1H), 6.21 (s, 1H), 4.86-4.79 (m, 1H), 4.68-4.60 (m, 1H), 4.40-4.19 (m, 1H), 3.52 (t, J = 5.1 Hz, 4H), 2.95-2.91 (m, 1H), 2.48 (m, 5H- overlapping with DMSO), 2.24 (s, 3H), 2.02-1.69 (m, 5H), 0.94 (d, J = 7.9 Hz, 2H), 0.71 (d, J = 5.4 Hz, 2H), 1x CH not observed
II-5	469	9.08-9.02 (m, 2H), 9.02-8.98 (m, 2H), 7.38 (d, J = 2.8 Hz, 1H), 7.18 (t, J = 54.0 Hz, 1H), 4.72-4.64 (m, 1H), 4.41-4.31 (m, 1H), 3.84-3.76 (m, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.42-3.34 (m, 1H), 3.17-3.06 (m, 1H), 2.47 (m, 4H, overlapping with DMSO), 2.24 (s, 3H), 2.04-1.86 (m, 3H), 1.84-1.76 (m, 1H).

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-6	448	9.08-9.01 (m, 2H), 8.00-7.95 (m, 1H), 7.59-7.54 (m, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.38-4.31 (m, 1H), 4.62-4.11 (m, 2H), 3.55-3.49 (m, 4H), 3.45-3.33 (m, 1H), 3.28-3.01 (m, 1H), 2.50-2.46 (m, 1H), 2.24 (s, 3H), 1.97-1.85 (m, 4H). 3 methylene protons unobserved
II-7	465	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.56 (d, J = 1.4 Hz, 1H), 7.38 (d, J = 2.9 Hz, 1H), 6.97-6.93 (m, 1H), 4.68-4.41 (m, 1H), 4.35-4.27 (m, 1H), 4.22-3.86 (m, 1H), 3.55-3.49 (m, 4H), 3.21-3.12 (m, 1H), 3.11-2.88 (m, 2H), 2.50-2.46 (m, 1H), 2.24 (s, 3H), 1.92-1.79 (m, 4H), 1.28 (d, J = 6.9 Hz, 6H). 3 methylene protons unobserved.
II-8	457	13.23 (s, 1H), 9.06 (d, J = 2.8 Hz, 1H), 9.05-9.04 (m, 1H), 8.18-8.14 (m, 1H), 7.88 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.42 (dd, J = 8.6, 1.5 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.78-4.42 (m, 1H), 4.38-4.28 (m, 1H), 3.99-3.76 (m, 1H), 3.59-3.42 (m, 4H), 3.27-3.02 (m, 2H), 2.48 (d, J = 4.4 Hz, 2H), 2.24 (s, 3H), 1.95-1.80 (m, 4H). 2 methylene protons not observed.
II-9	488	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 6.89 (dd, J = 8.2, 2.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.32-4.25 (m, 1H), 4.45-4.11 (m, 2H), 4.25-4.21 (m, 2H), 3.55-3.49 (m, 4H), 3.32-3.26 (m, 3H), 3.18-3.06 (m, 2H), 2.87 (s, 3H), 2.49-2.46 (m, 1H), 2.24 (s, 3H), 1.88-1.76 (m, 4H). 2 methylene protons not observed.
II-10	459	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 8.72 (s, 2H), 7.38 (d, J = 2.9 Hz, 1H), 4.69-4.61 (m, 1H), 4.31 (s, 1H), 3.81-3.68 (m, 1H), 3.55-3.49 (m, 4H), 3.41-3.38 (m, 1H), 3.06-3.02 (m, 1H), 2.30-2.21 (m, 4H), 1.97-1.82 (m, 4H), 1.13-1.02 (m, 4H). 4 methylene protons not observed.
II-11	462	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 7.25 (t, J = 2.1 Hz, 1H), 6.95 (t, J = 2.7 Hz, 1H), 6.23 (dd, J = 2.9, 1.8 Hz, 1H), 4.53-4.47 (m, 2H), 4.35-4.25 (m, 1H), 3.55-3.49 (m, 4H), 3.18-2.99 (m, 2H), 2.50-2.46 (m, 1H), 2.24 (s, 3H), 1.90-1.77 (m, 4H), 1.49 (s, 9H). 3 methylene protons not observed.
II-12	463	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.22 (d, J = 3.7 Hz, 1H), 6.81 (dd, J = 3.7, 0.7 Hz, 1H), 4.46-4.39 (m, 2H), 4.33 (s, 1H), 3.55-3.49 (m, 4H), 3.28-3.15 (m, 2H), 2.51-2.46 (m, 2H), 2.24 (s, 3H), 2.17 (tt, J = 8.4, 5.0 Hz, 1H), 1.94-1.80 (m, 4H), 1.09-0.99 (m, 2H), 0.76-0.69 (m, 2H). 2 methylene protons not observed.
II-13	475	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.85 (s, 2H), 7.38 (d, J = 2.9 Hz, 1H), 4.68-4.64 (m, 1H), 4.37-4.23 (m, 1H), 3.76-3.72 (m, 1H), 3.55-3.49 (m, 4H), 3.47-3.36 (m, 1H), 3.07-3.04 (m, 1H), 2.50-2.46 (m, 2H), 2.24 (s, 3H), 1.97-1.84 (m, 4H), 1.38 (s, 9H). 2 methylene protons not observed.
II-14	437	9.01 (s, 1H), 9.00 (d, J = 2.9 Hz, 1H), 7.35 (d, J = 2.9 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 6.84-6.79 (m, 1H), 4.47-4.39 (m, 2H), 4.38-4.29 (m, 1H), 3.57-3.51 (m, 4H), 3.29-3.20 (m, 2H), 2.56-2.51 (m, 4H), 2.49-2.48 (m, 3H), 2.28 (s, 3H), 1.98-1.87 (m, 4H).

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-15	480	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.97 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.67-4.18 (m, 2H), 4.38-4.30 (m, 1H), 3.55-3.50 (m, 4H), 3.46-3.04 (m, 2H), 2.50-2.46 (m, 1H), 2.24 (s, 3H), 1.97-1.84 (m, 4H), 1.40 (s, 9H). 3 methylene protons not observed.
II-16	482	9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 1.9 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 8.6, 1.9 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.77-4.62 (m, 1H), 4.42-4.24 (m, 1H), 3.88-3.71 (m, 1H), 3.55-3.49 (m, 4H), 3.15-2.98 (m, 1H), 2.67 (s, 3H), 2.49-2.46 (m, 3H), 2.24 (s, 3H), 1.97-1.86 (m, 3H), 1.86-1.73 (m, 1H). 2 methylene protons not observed.
II-17	471	12.36 (s, 1H), 9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 7.53-7.43 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 7.21-7.17 (m, 1H), 4.85-4.44 (m, 1H), 4.35-4.27 (m, 1H), 4.19-3.71 (m, 1H), 3.55-3.49 (m, 4H), 3.27-3.01 (m, 2H), 2.48 (d, J = 4.6 Hz, 3H), 2.24 (s, 3H), 1.86 (s, 4H). 4 methylene protons not observed.
II-18	468	9.08-9.04 (m, 2H), 8.99-8.94 (m, 1H), 8.51-8.46 (m, 1H), 8.12-8.06 (m, 2H), 7.79 (dd, J = 8.6, 1.9 Hz, 1H), 7.60 (dd, J = 8.3, 4.1 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.81-4.61 (m, 1H), 4.45-4.26 (m, 1H), 3.87-3.72 (m, 1H), 3.55-3.49 (m, 4H), 3.45-3.34 (m, 1H), 3.14-3.03 (m, 2H), 2.49-2.46 (m, 2H), 2.24 (s, 3H), 1.97-1.86 (m, 3H), 1.86-1.75 (m, 1H). 1 proton not observed.
II-19	483	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.84 (s, 1H), 7.99 (s, 1H), 7.94-7.89 (m, 2H), 7.56-7.48 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 7.37-7.33 (m, 1H), 4.80-4.41 (m, 1H), 4.39-4.12 (m, 2H), 3.61-3.36 (m, 5H), 3.17-2.88 (m, 1H), 2.48-2.46 (m, 2H), 2.24 (s, 3H), 1.96-1.82 (m, 4H). 2 methylene protons not observed.
II-20	469	9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 9.02 (dd, J = 1.8 Hz, 2H), 8.20 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.90 (dd, J = 8.5, 1.8 Hz, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.73-4.70 (m, 1H), 4.36-4.33 (m, 1H), 3.55-3.49 (m, 4H), 3.19-3.05 (m, 1H), 2.49-2.46 (m, 3H), 2.24 (s, 3H), 1.97-1.86 (m, 3H), 1.84-1.75 (m, 1H). 3 methylene protons not observed.
II-21	438	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.93 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.61-4.09 (m, 3H), 3.55-3.49 (m, 4H), 3.45-2.95 (m, 2H), 2.68 (s, 3H), 2.49-2.46 (m, 1H), 2.24 (s, 3H), 1.99-1.79 (m, 4H). 3 methylene protons not observed.
II-22	435	9.06 (d, J = 2.9 Hz, 1H), 9.02 (s, 1H), 8.11 (s, 1H), 7.70-7.66 (m, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.61-4.36 (m, 2H), 4.36-4.23 (m, 1H), 4.15 (q, J = 7.3 Hz, 2H), 3.55-3.49 (m, 4H), 3.29-2.80 (m, 2H), 2.48-2.42 (m, 1H), 2.25 (s, 3H), 1.93-1.76 (m, 4H), 1.38 (t, J = 7.3 Hz, 3H). 3 methylene protons not observed.
II-23	456	11.27 (s, 1H), 9.08-9.03 (m, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.47-7.44 (m, 1H), 7.38 (d, J = 2.8 Hz, 1H), 7.06 (dd, J = 8.1, 1.4 Hz, 1H), 6.50-6.44 (m, 1H), 4.90-3.83 (m, 3H), 3.56-3.47 (m, 4H), 3.26-3.00 (m, 2H), 2.24 (s, 3H), 1.99-1.73 (m, 4H), 4H overlapped with solvent peaks.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-24	421	9.06 (d, J = 2.9 Hz, 1H), 9.02 (s, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 2.8 Hz, 1H), 6.54 (d, J = 2.2 Hz, 1H), 4.84-4.74 (m, 1H), 4.71-4.60 (m, 1H), 4.41-4.28 (m, 1H), 3.88 (s, 3H), 3.58-3.46 (m, 4H), 3.05-2.86 (m, 1H), 2.24 (s, 3H), 1.98-1.72 (m, 4H), 5H overlapped with solvent peaks.
II-25	470	9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 7.66-7.62 (m, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 3.1 Hz, 1H), 7.37 (d, J = 2.9 Hz, 1H), 7.23 (dd, J = 8.4, 1.6 Hz, 1H), 6.53-6.49 (m, 1H), 4.84-3.98 (m, 3H), 3.81 (s, 3H), 3.57-3.49 (m, 4H), 3.28-2.97 (m, 2H), 2.24 (s, 3H), 2.02-1.68 (m, 4H), 4H overlapped with solvent peaks.
II-26	453	9.06 (d, J = 2.9 Hz, 1H), 9.02 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 5.76 (s, 2H), 4.41-4.23 (m, 3H), 3.58-3.46 (m, 4H), 3.27-3.18 (m, 2H), 2.30 (s, 3H), 2.24 (s, 3H), 1.96-1.80 (m, 4H), 4H not observed; overlapped with solvent peaks.
II-27	423	12.25 (s, 1H), 9.06 (d, J = 2.9 Hz, 1H), 9.02 (s, 1H), 7.37 (d, J = 2.8 Hz, 1H), 6.13 (s, 2H), 4.68-4.55 (m, 1H), 4.41-4.24 (m, 2H), 3.58-3.47 (m, 4H), 3.28-3.20 (m, 1H), 3.01-2.88 (m, 1H), 2.24 (s, 3H), 1.99-1.70 (m, 4H), 4H overlapped with solvent peaks.
II-28	468	9.08-9.03 (m, 2H), 8.06-7.95 (m, 4H), 7.61-7.56 (m, 2H), 7.54 (dd, J = 8.3, 1.7 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.85-4.57 (m, 1H), 4.40-4.28 (m, 1H), 3.97-3.70 (m, 1H), 3.57-3.46 (m, 4H), 3.20-2.96 (m, 1H), 2.24 (s, 3H), 2.06-1.68 (m, 4H), 5H overlapped with solvent peaks.
II-29	438	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.92 (s, 1H), 7.37 (d, J = 2.8 Hz, 1H), 4.76-4.50 (m, 1H), 4.44-4.18 (m, 2H), 3.62-3.44 (m, 4H), 3.10-2.89 (m, 1H), 2.69 (s, 3H), 2.24 (s, 3H), 2.03-1.72 (m, 4H), 5H overlapped with solvent peaks.
II-30	472	9.07-9.02 (m, 2H), 7.39-7.36 (m, 1H), 7.31-7.26 (m, 1H), 7.17-7.01 (m, 2H), 4.56 (d, J = 35.8 Hz, 2H), 4.32 (s, 1H), 3.96-3.67 (m, 2H), 3.64-3.58 (m, 1H), 3.55-3.48 (m, 4H), 3.12-2.78 (m, 8H), 2.77-2.54 (m, 2H), 2.27-2.22 (m, 3H), 1.98-1.71 (m, 4H).
II-31	436	12.35 (s, 1H), 9.09-8.99 (m, 2H), 7.37 (d, J = 2.8 Hz, 1H), 5.62-5.15 (m, 1H), 4.94-4.49 (m, 1H), 4.47-4.20 (m, 3H), 3.59-3.46 (m, 4H), 3.10-2.71 (m, 2H), 2.24 (s, 3H), 2.09 (s, 3H), 1.94-1.72 (m, 4H), 4H overlapped with solvent peaks.
II-32	492	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 8.56 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.72-4.57 (m, 1H), 4.43-4.29 (m, 1H), 4.12-3.99 (m, 1H), 3.59-3.46 (m, 4H), 3.46-3.35 (m, 1H), 3.16-3.01 (m, 1H), 2.24 (s, 3H), 2.05-1.78 (m, 4H), 4H overlapped with solvent peaks.
II-33	462	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 5.80 (d, J = 1.0 Hz, 1H), 4.49-4.20 (m, 3H), 3.81 (q, J = 7.2 Hz, 2H), 3.57-3.48 (m, 4H), 3.12-2.91 (m, 2H), 2.29-2.22 (m, 6H), 2.17 (s, 3H), 1.88-1.74 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H), 4H overlapped with solvent peaks.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-34	484	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.80 (d, J = 2.7 Hz, 1H), 8.70-8.65 (m, 2H), 7.93-7.87 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 4.74-4.55 (m, 2H), 4.44-4.32 (m, 1H), 3.58-3.48 (m, 4H), 3.43-3.38 (m, 1H), 3.11-3.01 (m, 1H), 2.24 (s, 3H), 2.03-1.82 (m, 4H), 4H overlapped with solvent peaks.
II-35	471	9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 8.13 (d, J = 0.9 Hz, 1H), 7.88-7.85 (m, 1H), 7.73-7.69 (m, 1H), 7.46 (dd, J = 8.6, 1.5 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.89-4.24 (m, 2H), 4.07 (s, 3H), 4.02-3.71 (m, 1H), 3.57-3.46 (m, 4H), 3.27-2.87 (m, 2H), 2.24 (s, 3H), 2.03-1.71 (m, 4H), 4H overlapped with solvent peaks.
II-36	449	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 6.27 (s, 1H), 4.63 (s, 1H), 4.38-4.27 (m, 1H), 3.96 (d, J = 39.0 Hz, 1H), 3.78 (s, 3H), 3.52 (t, J = 5.1 Hz, 4H), 3.44-3.34 (m, 1H), 3.03 (s, 1H), 2.58-2.51 (m, 2H), 2.24 (s, 3H), 2.03-1.76 (m, 4H), 1.17 (t, J = 7.6 Hz, 3H), 4H overlapped with solvent peaks.
II-37	471	9.05 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 2.8 Hz, 1H), 7.27 (dd, J = 8.4, 1.7 Hz, 1H), 6.64 (t, J = 1.1 Hz, 1H), 4.99-4.42 (m, 1H), 4.39-4.25 (m, 1H), 4.05-3.66 (m, 1H), 3.58-3.45 (m, 4H), 3.27-2.87 (m, 2H), 2.47-2.45 (m, 3H), 2.24 (s, 3H), 2.05-1.65 (m, 4H), 4H overlapped with solvent peaks.
II-38	451	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 6.86 (dt, J = 3.7, 1.1 Hz, 1H), 4.53-4.38 (m, 2H), 4.38-4.28 (m, 1H), 3.58-3.44 (m, 4H), 3.28-3.08 (m, 2H), 2.89-2.78 (m, 2H), 2.24 (s, 3H), 1.96-1.81 (m, 4H), 1.26 (t, J = 7.5 Hz, 3H), 4H overlapped with solvent peaks.
II-39	457	12.61 (s, 1H), 9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 8.30 (s, 1H), 7.69-7.60 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 7.27 (dd, J = 8.2, 1.5 Hz, 1H), 4.91-3.72 (m, 3H), 3.58-3.45 (m, 4H), 3.25-2.87 (m, 2H), 2.24 (s, 3H), 2.04-1.68 (m, 4H), 4H overlapped with solvent peaks.
II-40	468	9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 8.97 (dd, J = 4.2, 1.7 Hz, 1H), 8.47-8.42 (m, 1H), 8.09 (d, J = 8.3 Hz, 1H), 8.03-7.99 (m, 1H), 7.65 (dd, J = 8.3, 1.6 Hz, 1H), 7.61 (dd, J = 8.3, 4.2 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.80-4.64 (m, 1H), 4.44-4.29 (m, 1H), 3.88-3.69 (m, 1H), 3.60-3.48 (m, 4H), 3.45-3.35 (m, 1H), 3.17-3.01 (m, 1H), 2.24 (s, 3H), 2.05-1.73 (m, 4H), 4H overlapped with solvent peaks.
II-41	437	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.34-7.31 (m, 1H), 7.25 (d, J = 1.4 Hz, 1H), 4.50-4.30 (m, 3H), 3.58-3.46 (m, 4H), 3.29-3.08 (m, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 1.95-1.80 (m, 4H), 3H overlapped with solvent peaks.
II-42	438	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 6.73 (s, 1H), 4.54 (d, J = 13.1 Hz, 1H), 4.35 (tt, J = 10.4, 4.4 Hz, 1H), 3.99 (s, 1H), 3.95 (s, 3H), 3.52 (t, J = 5.1 Hz, 4H), 3.48-3.38 (m, 1H), 3.14-3.04 (m, 1H), 2.24 (s, 3H), 2.01-1.78 (m, 4H). Missing 4Hs.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-43	474	9.48 (s, 1H), 9.06 (d, J = 2.9 Hz, 1H), 9.05 (s, 1H), 8.31 (d, J = 1.7 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 8.4, 1.7 Hz, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.76-4.60 (m, 1H), 4.38-4.27 (m, 1H), 3.85-3.71 (m, 1H), 3.57-3.48 (m, 4H), 3.15-2.98 (m, 1H), 2.24 (s, 3H), 2.06-1.66 (m, 5H). Missing 4 protons.
II-44	468	9.06 (d, J = 3.5 Hz, 2H), 8.52 (d, J = 8.5 Hz, 1H), 8.09-8.02 (m, 2H), 7.83 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.72-7.65 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 4.74 (d, J = 12.8 Hz, 1H), 4.41-4.32 (m, 1H), 3.87 (d, J = 13.6 Hz, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.36 (d, J = 12.8 Hz, 1H), 3.11 (td, J = 12.7, 3.2 Hz, 1H), 2.24 (s, 3H), 2.06-1.87 (m, 3H), 1.79 (d, J = 13.1 Hz, 1H). Missing 4 protons.
II-45	461	9.05 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 6.99-6.96 (m, 2H), 6.94-6.91 (m, 1H), 6.07 (s, 2H), 4.35-4.26 (m, 1H), 3.52 (t, J = 5.0 Hz, 4H), 2.24 (s, 3H), 1.94-1.76 (m, 4H). Missing 8 protons.
II-46	491	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.18 (s, 1H), 8.15 (d, J = 4.9 Hz, 1H), 7.66 (d, J = 4.9 Hz, 1H), 7.37 (d, J = 2.9 Hz, 1H), 4.71-4.60 (m, 1H), 4.37-4.25 (m, 1H), 3.84-3.72 (m, 1H), 3.55-3.49 (m, 4H), 3.31-3.20 (m, 2H), 3.04-2.86 (m, 2H), 2.24 (s, 3H), 2.02-1.71 (m, 4H). Missing 2 protons.
II-47	499	9.09-9.00 (m, 3H), 8.36 (d, J = 8.1 Hz, 1H), 8.08 (s, 1H), 7.40-7.35 (m, 1H), 7.19 (d, J = 8.1 Hz, 1H), 4.74-4.60 (m, 1H), 4.32-4.22 (m, 1H), 3.81-3.68 (m, 1H), 3.56-3.48 (m, 6H), 2.95-2.84 (m, 4H), 2.55 (s, 3H), 2.24 (s, 3H), 2.02-1.67 (m, 3H). Missing 1 proton.
II-48	468	9.35 (s, 1H), 9.06 (d, J = 2.8 Hz, 1H), 9.05 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.13-8.06 (m, 2H), 7.85 (t, J = 7.6 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.73 (d, J = 12.9 Hz, 1H), 4.40-4.30 (m, 1H), 3.89 (d, J = 13.6 Hz, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.13-3.02 (m, 1H), 2.24 (s, 3H), 2.02-1.85 (m, 3H), 1.82-1.71 (m, 1H). Missing 5 protons
II-49	487	9.24 (s, 1H), 9.09 (s, 1H), 9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.68 (d, J = 13.5 Hz, 1H), 4.42-4.32 (m, 1H), 3.82 (d, J = 13.5 Hz, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.40-3.33 (m, 1H), 3.19-3.09 (m, 1H), 2.24 (s, 3H), 2.05-1.74 (m, 4H). Missing 4 protons.
II-50	487	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.71 (d, J = 12.9 Hz, 1H), 4.43-4.33 (m, 1H), 3.72 (d, J = 13.6 Hz, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.39 (t, J = 12.9 Hz, 1H), 3.23-3.11 (m, 1H), 2.24 (s, 3H), 2.08-1.86 (m, 3H), 1.81 (d, J = 12.9 Hz, 1H). 4 missing protons.
II-51	502	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 8.28 (s, 1H), 7.38 (d, J = 2.8 Hz, 1H), 4.68-4.51 (m, 1H), 4.33-4.21 (m, 1H), 3.73-3.58 (m, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.15-2.94 (m, 1H), 2.24 (s, 3H), 2.07 (s, 2H), 2.02-1.73 (m, 4H). 4 protons missing.
II-52	460	9.51 (s, 1H), 9.02 (s, 1H), 8.99 (d, J = 2.8 Hz, 1H), 8.44 (s, 1H), 7.36 (d, J = 2.8 Hz, 1H), 4.07-3.96 (m, 1H), 3.87-3.78 (m, 2H), 3.50 (t, J = 5.3 Hz, 4H), 2.68 (td, J = 11.4, 4.3 Hz, 2H), 2.49-2.45 (m, 4H), 2.23 (s, 3H), 2.01-1.89 (m, 4H).

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-53	454	Not determined.
II-54	509	8.99 (s, 1H), 8.95 (d, J = 2.9 Hz, 1H), 8.63 (s, 1H), 8.25-8.16 (m, 2H), 7.61-7.51 (m, 2H), 7.34 (d, J = 2.8 Hz, 1H), 4.00-3.87 (m, 3H), 3.48 (t, J = 5.1 Hz, 4H), 2.72-2.58 (m, 2H), 2.46 (t, J = 5.1 Hz, 4H), 2.22 (s, 3H), 1.97-1.82 (m, 4H).
II-55	473	9.02 (s, 1H), 8.99 (d, J = 2.9 Hz, 1H), 7.49 (d, J = 3.7 Hz, 1H), 7.36 (d, J = 2.9 Hz, 1H), 7.04 (dd, J = 3.8, 1.1 Hz, 1H), 4.00-3.89 (m, 1H), 3.77 (d, J = 11.7 Hz, 2H), 3.50 (t, J = 5.1 Hz, 4H), 2.56 (d, J = 1.0 Hz, 5H), 2.48 (t, J = 5.0 Hz, 4H), 2.23 (s, 3H), 1.95 (td, J = 10.8, 9.5, 3.7 Hz, 4H).
II-56	490	11.52 (s, 1H), 9.05 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.52-7.46 (m, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.16-7.11 (m, 2H), 6.54 (dd, J = 3.2, 2.0 Hz, 1H), 4.35-4.26 (m, 1H), 3.56-3.47 (m, 4H), 3.27-3.09 (m, 2H), 2.25 (s, 3H), 2.05-1.65 (m, 4H), 6H from piperidine ring not observed.
II-57	484	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.97-7.89 (m, 2H), 7.61-7.51 (m, 3H), 7.38 (d, J = 2.9 Hz, 1H), 7.34 (s, 1H), 4.72-4.61 (m, 1H), 4.43-4.34 (m, 1H), 4.13 (d, J = 13.7 Hz, 1H), 3.53 (t, J = 5.1 Hz, 4H), 3.49-3.38 (m, 1H), 3.11 (td, J = 12.8, 3.0 Hz, 1H), 2.25 (s, 3H), 2.04-1.95 (m, 1H), 1.95-1.81 (m, 3H). Missing 4 protons.
II-58	483	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.81-7.74 (m, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.40-7.33 (m, 2H), 7.13 (q, J = 3.6 Hz, 2H), 4.61-4.52 (m, 2H), 4.42-4.32 (m, 1H), 3.53 (t, J = 5.1 Hz, 4H), 2.25 (s, 3H), 2.02-1.84 (m, 4H). Missing 6 protons.
II-59	499	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.74-7.69 (m, 2H), 7.52 (d, J = 3.8 Hz, 1H), 7.48-7.42 (m, 3H), 7.41-7.33 (m, 2H), 4.53-4.40 (m, 2H), 4.41-4.30 (m, 1H), 3.53 (t, J = 5.1 Hz, 4H), 2.25 (s, 3H), 1.98-1.84 (m, 4H). Missing 6 protons.
II-60	499	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.06 (s, 1H), 7.82 (s, 1H), 7.76 (d, J = 7.7 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 2.9 Hz, 1H), 7.36-7.28 (m, 1H), 4.59-4.41 (m, 2H), 4.41-4.27 (m, 1H), 3.52 (t, J = 5.1 Hz, 4H), 2.24 (s, 3H), 1.99-1.85 (m, 4H). Missing 6 protons.
II-61	500	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.17 (s, 1H), 8.01-7.93 (m, 2H), 7.52 (dd, J = 5.2, 2.0 Hz, 3H), 7.38 (d, J = 2.9 Hz, 1H), 4.72-4.57 (m, 1H), 4.46-4.30 (m, 2H), 3.52 (t, J = 5.1 Hz, 4H), 3.44-3.35 (m, 1H), 3.15-2.99 (m, 1H), 2.24 (s, 3H), 2.03-1.82 (m, 4H). Missing 5 protons.
II-62	483	13.61 (s, 1H), 9.07 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.80 (d, J = 7.7 Hz, 2H), 7.54-7.27 (m, 4H), 7.01 (s, 1H), 4.88-4.78 (m, 1H), 4.74-4.63 (m, 1H), 4.43-4.28 (m, 1H), 3.52 (s, 4H), 3.42-3.33 (m, 1H), 3.06-2.93 (m, 1H), 2.25 (s, 3H), 2.01-1.78 (m, 4H). Missing 4 protons. 3:1 mixture of tautomers.
II-63	484	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.02-7.91 (m, 2H), 7.57 (s, 1H), 7.56-7.51 (m, 3H), 7.38 (d, J = 2.9 Hz, 1H), 4.61 (d, J = 13.1 Hz, 1H), 4.44-4.33 (m, 1H), 4.13-4.01 (m, 1H), 3.53 (t, J = 5.1 Hz, 4H), 3.50-3.44 (m, 1H), 3.20-3.05 (m, 1H), 2.24 (s, 3H), 2.05-1.81 (m, 4H). Missing 4 protons.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
II-64	499	9.06 (d, J = 2.9 Hz, 1H), 9.02 (s, 1H), 7.88-7.81 (m, 2H), 7.47-7.39 (m, 2H), 7.37 (d, J = 2.9 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 5.58 (s, 1H), 4.91 (d, J = 13.0 Hz, 1H), 4.63 (d, J = 13.0 Hz, 1H), 4.39-4.27 (m, 1H), 3.52 (t, J = 5.1 Hz, 4H), 2.94 (t, J = 12.6 Hz, 1H), 2.24 (s, 3H), 1.98-1.77 (m, 4H), 1.14 (d, J = 6.5 Hz, 6H).
II-65	484	9.27 (s, 1H), 9.07 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 7.4 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.39 (d, J = 2.9 Hz, 1H), 4.86 (d, J = 13.6 Hz, 1H), 4.70 (d, J = 13.1 Hz, 1H), 4.45-4.32 (m, 1H), 3.60-3.51 (m, 4H), 3.47 (d, J = 12.5 Hz, 1H), 3.07 (t, J = 12.5 Hz, 1H), 2.25 (s, 3H), 2.04-1.81 (m, 4H). Missing 4 protons.
II-66	497	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.79 (s, 1H), 7.60-7.53 (m, 4H), 7.51-7.44 (m, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.38-4.29 (m, 1H), 3.53 (t, J = 5.1 Hz, 4H), 2.38 (s, 3H), 2.25 (s, 3H), 1.99-1.80 (m, 4H). Missing 8 protons.
II-67	498	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 8.01-7.96 (m, 2H), 7.61-7.53 (m, 2H), 7.47-7.41 (m, 1H), 7.38 (d, J = 2.9 Hz, 1H), 4.70 (d, J = 12.9 Hz, 1H), 4.43-4.28 (m, 2H), 3.52 (t, J = 5.1 Hz, 4H), 3.48-3.35 (m, 1H), 3.13-3.00 (m, 1H), 2.45 (s, 3H), 2.24 (s, 3H), 2.05-1.80 (m, 4H). Missing 4 protons
II-68	511	9.07 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.75 (s, 1H), 7.60-7.54 (m, 2H), 7.54-7.48 (m, 3H), 7.38 (d, J = 2.9 Hz, 1H), 4.38-4.26 (m, 1H), 3.52 (t, J = 5.1 Hz, 4H), 2.79 (q, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.96-1.78 (m, 4H), 1.00 (t, J = 7.5 Hz, 3H). Missing 8 protons.
II-69	497	9.08-9.03 (m, 2H), 7.86-7.81 (m, 2H), 7.43-7.36 (m, 3H), 7.31 (td, J = 7.2, 1.4 Hz, 1H), 6.98 (d, J = 1.3 Hz, 1H), 4.68-4.64 (m, 1H), 4.44-4.26 (m, 1H), 4.07-4.04 (m, 1H), 3.91 (s, 3H), 3.55-3.49 (m, 4H), 3.42 (s, 1H), 3.07 (s, 1H), 2.51-2.46 (m, 2H), 2.24 (s, 3H), 2.04-1.78 (m, 4H), 2H not observed
II-70	498	9.07 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.72 (s, 1H), 7.61-7.50 (m, 4H), 7.44-7.36 (m, 2H), 6.24 (s, 2H), 4.51-4.45 (m, 2H), 4.37-4.29 (m, 1H), 3.56-3.50 (m, 4H), 3.23-3.14 (m, 2H), 2.25 (s, 3H), 1.95-1.81 (m, 4H). 4 protons not observed.
VI-1	483	9.05 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.28-7.20 (m, 1H), 7.18-7.11 (m, 1H), 4.69-4.62 (m, 1H), 4.34-4.28 (m, 1H), 3.96 (s, 3H), 3.60-3.54 (m, 1H), 3.54-3.49 (m, 4H), 3.08-2.99 (m, 1H), 2.50-2.46 (m, 2H), 2.24 (s, 3H), 1.98-1.93 (m, 1H), 1.87-1.76 (m, 3H). 3 methylene protons not observed.
VI-2	483	9.05 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 4.60-4.57 (m, 1H), 4.36-4.24 (m, 1H), 3.99-3.95 (m, 3H), 3.75-3.71 (m, 1H), 3.55-3.49 (m, 4H), 3.14-2.95 (m, 1H), 2.49-2.46 (m, 2H), 2.24 (s, 3H), 1.97-1.75 (m, 4H). 3 methylene protons not observed.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
VI-3	462	11.70-11.47 (m, 1H), 9.10-9.04 (m, 1H), 9.03 (d, J = 4.1 Hz, 1H), 7.37 (t, J = 3.0 Hz, 1H), 5.97-5.87 (m, 1H), 4.67 (d, J = 13.0 Hz, 1H), 4.34-4.20 (m, 1H), 3.58 (d, J = 13.3 Hz, 1H), 3.52 (t, J = 5.1 Hz, 4H), 3.29-3.13 (m, 1H), 2.97-2.85 (m, 1H), 2.24 (s, 3H), 2.14 (s, 3H), 2.08 (s, 2H), 1.99 (s, 1H), 1.97-1.62 (m, 4H). Missing 4 protons.
VI-4	512	9.08-9.01 (m, 2H), 7.37 (d, J = 2.8 Hz, 1H), 7.16-7.03 (m, 2H), 4.67 (t, J = 12.0 Hz, 1H), 4.36-4.22 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.52 (t, J = 4.9 Hz, 4H), 3.49-3.40 (m, 1H), 3.29-3.15 (m, 1H), 3.04-2.95 (m, 1H), 2.24 (s, 3H), 2.01-1.68 (m, 4H). Missing 4 protons.
VI-5	484	9.05 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 7.09 (d, J = 9.3 Hz, 1H), 6.86 (d, J = 6.5 Hz, 1H), 5.29 (s, 2H), 4.32-4.22 (m, 1H), 3.55-3.49 (m, 4H), 3.25-3.03 (m, 2H), 2.49-2.46 (m, 3H), 2.24 (s, 3H), 1.98-1.79 (m, 4H). 3 protons not observed.
VI-6	561	9.01 (s, 1H), 8.99 (d, J = 2.9 Hz, 1H), 7.34 (d, J = 2.9 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.70 (s, 1H), 6.50 (d, J = 8.4, 2.4, 1.2 Hz, 1H), 5.40 (s, 2H), 4.37-4.24 (m, 1H), 4.18 (d, J = 13.2 Hz, 2H), 3.56-3.48 (m, 6H), 3.29 (s, 3H), 3.20-3.13 (m, 2H), 2.65 (t, J = 4.9 Hz, 4H), 2.59 (t, J = 5.8 Hz, 2H), 1.96-1.88 (m, 4H)
VI-8	587	9.06 (d, J = 2.8 Hz, 1H), 9.03 (s, 1H), 7.84-7.79 (m, 1H), 7.37 (d, J = 2.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.69-6.64 (m, 1H), 6.53-6.47 (m, 1H), 5.59 (s, 2H), 4.31-4.23 (m, 1H), 3.53-3.48 (m, 4H), 3.23-3.04 (m, 2H), 2.63-2.52 (m, 10H), 2.31-2.24 (m, 2H), 1.88-1.84 (m, 4H). 1 H not observed.
VI-9	584	9.05 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.49 (d, 1H), 5.59 (s, 2H), 4.33-4.23 (m, 1H), 3.53 (t, J = 5.1 Hz, 4H), 3.31-3.24 (m, 2H), 3.21-3.04 (m, 2H), 2.80 (t, J = 5.0 Hz, 4H), 1.93-1.80 (m, 4H). Missing 2 protons.
VI-10	599	9.07 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.68-6.65 (m, 1H), 6.52-6.47 (m, 1H), 5.59 (s, 2H), 4.33-4.22 (m, 2H), 3.52 (t, J = 5.1 Hz, 4H), 3.14 (s, 2H), 2.63-2.57 (m, 6H), 2.56-2.52 (m, 2H), 1.92-1.81 (m, 4H). One proton missing
VI-11	530	9.03 (s, 1H), 8.98 (d, J = 2.9 Hz, 1H), 7.35 (d, J = 2.9 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.71-6.68 (m, 1H), 6.53-6.48 (m, 1H), 5.39 (s, 2H), 4.36-4.27 (m, 1H), 4.18 (d, J = 13.5 Hz, 2H), 4.13 (s, 2H), 3.88-3.83 (m, 2H), 3.57-3.52 (m, 2H), 3.23-3.15 (m, 2H), 2.95 (s, 3H), 1.96-1.90 (m, 4H).
VI-12	417	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.49-7.44 (m, 3H), 7.44-7.40 (m, 2H), 7.38 (d, J = 2.9 Hz, 1H), 4.76-4.55 (m, 1H), 4.37-4.27 (m, 1H), 3.82-3.64 (m, 1H), 3.57-3.47 (m, 4H), 3.14-2.91 (m, 1H), 2.24 (s, 3H), 2.02-1.72 (m, 4H), 5H ovelapped with solvent peaks.
VI-13	485	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 2.9 Hz, 1H), 4.69-4.63 (m, 1H), 4.36-4.27 (m, 1H), 3.66-3.60 (m, 1H), 3.55-3.49 (m, 4H), 3.13-3.00 (m, 1H), 2.50-2.46 (m, 2H), 2.24 (s, 3H), 2.08 (d, J = 5.8 Hz, 1H), 1.97 (s, 1H), 1.93-1.75 (m, 3H). 2 protons obscured by solvent peak.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
VI-14	447	9.05 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.43-7.35 (m, 3H), 7.03-6.96 (m, 2H), 4.75-4.40 (m, 1H), 4.34-4.27 (m, 1H), 4.09-3.84 (m, 1H), 3.79 (s, 3H), 3.54-3.49 (m, 4H), 3.28-2.91 (m, 2H), 2.49-2.46 (m, 3H), 2.24 (s, 3H), 1.94-1.78 (m, 4H). 1 proton obscured by solvent peak.
VI-15	457	9.05 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.38 (d, J = 2.9 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 6.96 (dd, J = 7.7, 1.6 Hz, 1H), 5.62 (s, 2H), 4.84-4.39 (m, 1H), 4.27 (q, J = 7.4 Hz, 1H), 3.74-3.43 (m, 5H), 3.26-2.85 (m, 2H), 2.25 (s, 3H), 2.05-1.65 (m, 4H), 4 H not observed.
VI-16	500	9.06 (d, J = 2.9 Hz, 1H), 9.03 (s, 1H), 7.37 (d, J = 2.9 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.05-7.03 (m, 1H), 6.89-6.83 (m, 1H), 5.61 (s, 2H), 4.85-4.43 (m, 1H), 4.33-4.24 (m, 1H), 3.55-3.49 (m, 4H), 3.24-2.94 (m, 2H), 2.48-2.44 (m, 2H), 2.24 (s, 3H), 1.89-1.85 (m, 4H). 3 protons not observed.
VII-1	516	9.06 (d, J = 2.9 Hz, 1H), 9.04 (s, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.69-6.65 (m, 1H), 6.51-6.48 (m, 1H), 5.59 (s, 2H), 4.28 (p, J = 7.8 Hz, 1H), 3.65-3.45 (m, 4H), 3.25-3.01 (m, 2H), 2.62-2.52 (m, 3H), 2.30 (s, 3H), 1.93-1.78 (m, 4H), 3H overlapped with solvent peaks.
VII-2	502	9.08-9.02 (m, 2H), 8.71 (d, J = 2.7 Hz, 1H), 8.13 (s, 0H), 8.07-8.01 (m, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.39 (s, 1H), 4.69-4.63 (m, 1H), 4.39-4.31 (m, 1H), 3.80-3.74 (m, 1H), 3.53 (s, 4H), 3.11-3.02 (m, 1H), 2.28 (s, 3H), 2.00-1.85 (m, 2H), 1.82-1.76 (m, 1H), 6 x CH not observed.
VII-3	418	9.32 (s, 1H), 9.15 (dd, J = 4.1, 1.6 Hz, 1H), 8.45 (dd, J = 8.6, 1.6 Hz, 1H), 8.04 (dd, J = 8.6, 4.1 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.54-6.47 (m, 1H), 5.60 (s, 2H), 4.49-4.38 (m, 1H), 3.29-3.01 (m, 2H), 2.02-1.81 (m, 4H). Missing 2 CH.
VII-4	416	9.11 (s, 1H), 8.38 (d, J = 10.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.40-7.34 (m, 2H), 4.67-4.64 (m, 1H), 4.03-3.99 (m, 1H), 3.97 (s, 3H), 3.64-3.60 (m, 1H), 3.38-3.35 (m, 1H), 3.12-3.08 (m, 1H), 1.98-1.94 (m, 1H), 1.95-1.83 (m, 2H), 1.82-1.79 (m, 1H).
VII-5	417	9.23 (s, 1H), 8.53-8.45 (m, 1H), 8.08-7.98 (m, 2H), 7.79 (ddd, J = 8.3, 5.4, 2.7 Hz, 1H), 7.16 (dt, J = 8.2, 1.6 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.59 (dd, J = 8.3, 2.0 Hz, 1H), 5.60 (s, 2H), 4.78-4.45 (m, 1H), 4.16-4.02 (m, 1H), 3.93-3.60 (m, 1H), 3.16-2.93 (m, 1H), 2.05-1.78 (m, 4H), 1H overlap with solvent peak.
VII-6	477	9.01 (s, 1H), 7.57 (s, 1H), 7.35 (s, 1H), 7.16 (dd, J = 8.3, 1.6 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 8.3, 2.0 Hz, 1H), 5.60 (s, 2H), 4.68-4.52 (m, 1H), 4.00 (s, 3H), 4.01-3.97 (m, 1H), 3.98 (s, 3H), 3.84-3.73 (m, 1H), 3.39-3.34 (m, 1H), 3.12-2.99 (m, 1H), 1.99-1.78 (m, 4H).
VII-7	398	9.09 (s, 1H), 8.41-8.33 (m, 1H), 7.39-7.31 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 2.1 Hz, 1H), 6.58 (dd, J = 8.2, 2.1 Hz, 1H), 5.49 (s, 2H), 3.96 (s, 3H), 3.96-3.89 (m, 1H), 3.27-3.05 (m, 2H), 1.95-1.77 (m, 4H), 2H not observed.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
VII-8	435	9.24 (s, 1H), 8.01 (td, J = 8.1, 5.5 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 12.5, 7.9 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.49 (d, J = 8.7 Hz, 1H), 5.59 (s, 2H), 3.93 (t, J = 11.3 Hz, 1H), 3.22-3.03 (m, 2H), 1.98 (s, 2H), 1.88 (dd, J = 20.5, 9.4 Hz, 2H). Missing 2 protons.
VII-9	420	9.25 (s, 1H), 8.05-7.97 (m, 1H), 7.92-7.87 (m, 1H), 7.66-7.53 (m, 3H), 7.45 (d, J = 8.2 Hz, 2H), 4.65 (s, 1H), 3.99-3.95 (m, 1H), 3.71 (s, 1H), 3.02 (s, 1H), 2.18-1.73 (m, 2H), 3H not observed.
VII-10	404	9.26 (s, 1H), 8.01 (td, J = 8.1, 5.6 Hz, 1H), 7.90 (dd, J = 8.4, 1.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.64-7.57 (m, 1H), 4.70-4.64 (m, 1H), 4.03-3.91 (m, 1H), 3.68-3.62 (m, 1H), 3.08-3.02 (m, 1H), 2.10-2.06 (m, 1H), 1.93-1.82 (m, 3H), 1 H not observed.
VII-11	366	9.25 (s, 1H), 8.01 (td, J = 8.2, 5.8 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 12.6, 8.1 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.02-3.90 (m, 1H), 3.80 (s, 3H), 2.08-1.93 (m, 2H), 1.93-1.79 (m, 2H). missing 4 protons.

EXAMPLE 10 – Biological Assay for Inhibiting Isolated ERK5

[1204] Exemplary compounds were tested for ability to inhibit isolated ERK5 using the LANCE® Ultra time-resolved FRET assay. Assay procedures and results are described below.

Part I – Procedures for Time-Resolved FRET Assay

[1205] Recombinant human Erk5 catalytic domain (1-398 amino acids of accession number NP_002740.2) was purchased from Carna Biosciences (Product number 04-146, Lot 13CBS-0805 C). The protein was expressed as an N-terminal GST-fusion protein (73 kDa) in E.coli. GST-Erk5 was purified using glutathione Sepharose chromatography and activated using His-tagged MAP2K5. The activated GST-Erk5 was then purified using Ni-NTA chromatography resulting in 53% purity. The protein was stored at 515 µg/mL (7.05 µM) in storage buffer (50 mM Tris-HCl, 150 mM NaCl, 0.05% Brij35, 1 mM DTT, 10% v/v glycerol, pH 7.5), at -80°C.

[1206] The substrate for the kinase was LANCE® Ultra Europium-anti-phospho-eIF4E-binding protein 1 (Thr37/46) peptide (Perkin Elmer TRF0216-D). The sequence motif for the peptide was ST(pT)PGGTLFST(pT)PG, with (pT) denoting the two potential phospo-theronines. The peptide was stored as a 5 µM stock solution in 50 mM Tris-HCl (pH7.4), 0.9% w/v NaCl, 0.1% w/v BSA and 0.05% w/v sodium azide, at -20°C.

[1207] Test compounds were prepared as 30 mM stock solutions in DMSO, stored under dry nitrogen gas. Solutions were plated into Echo® Qualified 384-well low dead volume microplates (Labcyte LP-0200). Compounds were then dosed into white, low-volume 384-well assay plates (Greiner Bio-One Ltd 784075) using the Labcyte Echo® 650 acoustic dosing platform. Test compounds were dosed in a 12-point, 2-fold dilution series at 100 µM top concentration then backfilled to 1% v/v DMSO. The top concentration was adjusted based on expected compound potency. A tool compound (BAY-885) was included in each assay plate as a standard. High controls (1% v/v DMSO) were included in rows A and O, with low controls (10 µM BAY-885) in rows B and P. Two identical sets of assay plates were prepared and tested in two independent experiments.

[1208] At the beginning of the assay, 3 µL of 2-fold concentrated peptide buffer (100 nM ULight-eIF4E-binding protein 1 (Thr37/46) peptide, 300 µM ATP, 10 mM $MgCl_2$, 1 mM EGTA, 50 mM HEPES, 1 mM DTT, 0.01% v/v Tween 20, pH 7.5) was added to each well using an electronic multichannel pipette. The reaction was initiated by adding 3 µL of 2-fold concentrated kinase buffer (15 nM Erk5, 10 mM $MgCl_2$, 1 mM EGTA, 50 mM HEPES, 1 mM DTT, 0.01% v/v Tween 20, pH 7.5), using an electronic multichannel pipette and mixing the assay volume three times. The final reaction composition was 7.5 nM Erk5, 50 nM ULight-eIF4E-binding protein 1 (Thr37/46) peptide, 150 µM ATP, 10 mM $MgCl_2$, 1 mM EGTA, 50 mM HEPES, 1 mM DTT, 0.01% v/v Tween 20, pH 7.5. As the protein purity was 53%, the true concentration of Erk5 was approximately 3.75 nM.

[1209] The reaction was allowed to progress for 1 hour at 22°C sealed and protected from light. To terminate the reaction and detect substrate phosphorylation, 6 µL of 2-fold concentrated detection buffer (12mM EDTA and 4 nM Eu-anti-phosphoeIF4E-binding protein 1 (Thr37/46) antibody in LANCE® Detection Buffer (Perkin Elmer CR97-100)) was added to each well using an electronic multichannel pipette. The assay volume was mixed three times.

[1210] The terminated reaction was allowed to incubate for 1 hour at 22°C sealed and protected from light. The level of resonance energy transfer was detected using an Envision Xcite plate reader (Perkin Elmer), with excitation at 350 nm and emission at 620 nm and 665 nm. The ratio of signal at 665 nm and 620 nm was taken as the level of phosphorylated substrate. The data was normalised to % inhibition by setting 0% as the signal from the high control and

100% as that from the low control. Values were plotted, and IC_{50} values were calculated using Dotmatics Studies (Dotmatics Knowledge Solutions).

Part II – Results

[1211] Experimental results are provided in Tables 14 and 14-A, below. The symbol "++++" indicates an IC_{50} less than or equal to 0.05 μM. The symbol "+++" indicates an IC_{50} in the range of 0.5 μM to greater than 0.05 μM. The symbol "++" indicates an IC_{50} in the range of 5 μM to greater than 0.5 μM. The symbol "+" indicates an IC_{50} in the range of 30 μM to greater than 5 μM.

TABLE 14.

Compound No.	IC_{50}
I-1	+++
I-2	++
I-3	++
I-4	++
I-5	++
I-6	+++
I-7	+
I-8	+
I-9	++
I-10	++
I-11	++
I-12	++
II-1	++
II-2	++
II-3	++

TABLE 14-A.

Compound No.	IC_{50}
I-13	+

Compound No.	IC_{50}
I-14	+
I-15	+
I-16	+
I-17	+
I-18	+
I-19	+
I-20	+
I-21	++++
I-22	++++
I-23	+++
I-24	+++
I-25	+++
I-26	+++
I-27	++
II-4	+
II-5	+
II-6	+
II-7	++
II-8	+
II-9	+
II-10	++
II-11	+
II-12	++
II-13	+
II-14	++
II-15	+
II-16	+
II-17	++
II-18	+
II-19	+++

Compound No.	IC_{50}
II-20	++
II-21	+
II-22	+
II-23	+++
II-24	+
II-25	++
II-26	+
II-27	+
II-28	++
II-29	+
II-30	+
II-31	+
II-32	+
II-33	+
II-34	+
II-35	+
II-36	+
II-37	+++
II-38	++
II-39	+
II-40	++
II-41	++
II-42	+
II-43	++
II-44	++
II-45	++
II-46	+
II-47	+
II-48	++
II-49	+

Compound No.	IC_{50}
II-50	+
II-51	+
II-52	+
II-53	+
II-54	+
II-55	+
II-56	++
II-57	+++
II-58	+
II-59	+++
II-60	++
II-61	+
II-62	+
II-63	+++
II-64	+
II-65	++
II-66	+
II-67	+
II-68	+
II-69	+
II-70	+
VI-1	++
VI-2	+++
VI-3	+
VI-4	+
VI-5	++++
VI-6	++++
VI-7	++++
VI-8	++++
VI-9	++++

Compound No.	IC_{50}
VI-10	++++
VI-11	++++
VI-12	++
VI-13	+++
VI-14	+++
VI-15	++
VI-16	++++
VII-1	++++
VII-2	++
VII-3	+++
VII-4	++
VII-5	++
VII-6	+++
VII-7	+++
VII-8	++
VII-9	++
VII-10	++
VII-11	+

EXAMPLE 11 – Biological Assay for Inhibiting ERK5 in Cells

[1212] Exemplary compounds were tested for ability to inhibit ERK5 activity in SN12C cells using a MEF2-responsive transcription element and two luciferase reporter genes. Assay procedures and results are described below.

Part I – Procedures for Luciferase Reporter Gene Assay

[1213] The polyclonal SN12C-MEF2-luc cell line was generated by stably transducing SN12C cells with a MEF2-responsive transcription element upstream of a firefly luciferase gene and a cytomegalovirus (CMV) promoter element upstream of a renilla luciferase gene. Generation of this cell line was carried out at Sygnature Discovery. This cell line was grown in RPMI 1640 media (Gibco #11530406) without phenol red supplemented with 10 % FBS, 1 % L-

glutamine, 1 % penicillin/streptomycin, 250 µg/mL Hygromycin B gold and 1.25 µg/mL puromycin. Cells were grown at 37 °C in a humidified environment with 5 % CO_2.

[1214] On day 1 cells were seeded in 384-well black-walled plates (Greiner 781091) at a density of 10,000 cells per well in 20 µL of culture media. On day 2, using an ECHO 650, test compounds were added in serial dilutions and trametinib was added to all wells at a final concentration of 125 nM. Plates were then incubated for 24 hours at 37 °C. On day 3, 20 µL of Dual-glo luciferase reagent (Promega, E2940) was added to each well, and the plates were incubated at room temperature for 10 minutes. Luminescence signal was then read on an EnVision Xcite multimode plate reader (Perkin-Elmer). Renilla luciferase substrate (Dual-glo stop & Glo Promega E2940) was added to all wells (20 µL per well), and the plates were incubated at room temperature for 10 minutes. Luminescence signal was then read on an EnVision Xcite multimode plate reader (Perkin-Elmer).

[1215] The firefly signal was then normalised to the renilla signal, and IC_{50} values were calculated using Dotmatics Studies (Dotmatics Knowledge Solutions) or GraphPad Prism. Values for cells treated only with DMSO were defined as the minimum control. Values for cells treated only with trametinib (125 nM) were defined as the maximum control.

Part II – Results

[1216] Experimental results are provided in Tables 15 and 15-A, below. The symbol "***" indicates an IC_{50} less than or equal to 0.05 µM. The symbol "**" indicates an IC_{50} in the range of 0.5 µM to greater than 0.05 µM. The symbol "*" indicates an IC_{50} greater than 0.5 µM.

TABLE 15.

Compound No.	IC_{50}
I-1	**
I-2	*
I-3	*
I-6	**
I-9	*
II-1	*

TABLE 15-A.

Compound No.	IC_{50}
I-21	***
I-27	*
II-23	**
VI-5	**
VI-8	***
VI-9	***
VI-10	***
VII-1	***
VII-4	*
VII-7	**

EXAMPLE 12 – Biological Assay for Inhibiting 3D Cancer Cell Cultures with Combination Therapy

[1217] An exemplary compound from the prior published literature having ERK5 inhibitory activity was tested for ability to inhibit 3D cancer cell cultures of pancreatic cancer and lung cancer as part of a combination therapy with a MEK1/2 inhibitor. Assay procedures and results are described below.

Part I – Procedures for 3D Cancer Cell Culture Assay

[1218] Assays were conducted using KRAS mutant (NCI-H2122 and A549) and KRAS wild-type (NCI-H520) human lung cancer cell lines according to the procedures described in Haagensen, E. J., et al. *Eur. J. Cancer* (2016) Vol. 56, pp. 69-76. Briefly, cells were seeded in soft agar in 96-well, low-attachment tissue-culture plates. After 24 hours, cells were treated with a concentration range of an ERK5 inhibitor alone, a MEK1/2 inhibitor alone, or a combination of the ERK5 inhibitor and MEK1/2 inhibitor. At the time of treatment, assay plates that did not receive treatment were collected and cell viability was measured using alamarBlue reagent to establish baseline cell viability. Treated plates were incubated for 7 days, and alamarBlue readout was then collected.

[1219] Inhibition (%) was used as a measure of cell viability and was calculated using the equation I = 1 - T/U, where T is treated and U is untreated control. Single-agent response curve fitting, and the analysis of combination effects, were performed using CHALICE™ software from Horizon. The calculated synergy scores were based on the Loewe Additivity model and characterize the strength of synergistic interaction. A score greater than 1.5 represents synergistic activity between treatment agents.

Part II – Results

[1220] Experimental results are depicted in Figure 1, demonstrating *in vitro* synergy of ERK5 and MEK inhibition in KRAS-mutant cancer cells, but not wild-type cancer cells, in this 3D culture system.

EXAMPLE 13 – Biological Assay for Inhibiting Mouse Xenograft Tumor Growth

[1221] An exemplary compound from the prior published literature having ERK5 inhibitory activity was tested, alone or in combination with trametinib, for ability to inhibit tumor growth in patient-derived mouse xenograft models of pancreatic cancer and lung cancer. Assay procedures and results are described below.

Part I – Procedures for Patient-Derived Mouse Xenograft (PDX) Tumor Growth Assay

[1222] Balb/c mice (6-8 weeks old) were inoculated subcutaneously in the right flank with a primary human tumor xenograft model tumor fragment (2-3 mm^3 in diameter) for tumor development. In one study, mice were inoculated with a human lung adenocarcinoma tumor model (MSCLC, ADC model LU6424) that harbors a BRAF mutation (LU6424); in a second study, mice were inoculated with a human pancreatic tumor model (adenosquamous carcinoma model PA6258) with a KRAS G12D mutation (PA6258). When mean tumor volume reached approximately 150 -200 mm^3, animals were randomly allocated to four treatment groups of 3 mice each. Mice were treated with one of the following:

1. Vehicle control,
2. Exemplary ERK5 inhibitor alone (60 mg/kg, dosed daily by intraperitoneal injection),
3. Trametinib alone (0.3 mg/kg, dosed daily orally), or
4. Combination of ERK5 inhibitor and trametinib (60 mg/kg, dosed daily by intraperitoneal injection, and 0.3 mg/kg, dosed daily orally, respectively).

[1223] Tumors were measured twice per week using calipers. The exemplary ERK5 inhibitor used in this experiment is a potent and selective tool compound from the prior published literature having an IC_{50} *in vitro* of approximately 35 nM in each of the assays described in Examples 10 and 11, and with high selectivity for ERK5, but with a short half-life and short PD effect.

Part II – Results

[1224] Experimental results are depicted in Figures 2 and 3, demonstrating that the exemplary ERK5 inhibitor from the prior published literature reduces tumor growth in patient-derived mouse xenograft (PDX) models of pancreatic cancer (Figure 2) and lung cancer (Figure 3), and that tumor growth is further synergistically reduced when the ERK5 inhibitor is combined with trametinib (a MEK1/2 inhibitor).

EXAMPLE 14 – Biological Assay for Inhibiting Cancer Cells with Combination Therapy

[1225] Exemplary compounds are tested to determine their ability to inhibit cancer cell growth in combination with selected standard-of-care agents in cancer cell lines by CellTiter Glo Luminescent Cell Viability Assay. Assay procedures are described below.

Part I – Procedures for Combination Therapy Assay for Inhibiting Cancer Cells

[1226] Combinations to be examined with selected cell lines are listed in Table 16. Plates are prepared in matrix fashion, with one axis having a blank row and 8 serial dilutions (3-fold) of a second anti-cancer agent, and the other axis having a blank row and 6 serial dilutions (3-fold) of an exemplary ERK5 inhibitor compound. Final DMSO concentration in the cell cultures is 0.2%. Top concentration for most second anti-cancer agents is 3 μM. Top concentration for trametinib and cobimetinib is 1 μM. Top concentration for a TEAD inhibitor, MRTX1133, and a MEK-RAF inhibitor is 10 μM. Top concentration for an exemplary ERK5 inhibitor is 3 μM or 10 μM.

TABLE 16.

Combination Treatment	Cell Line	Indication
ERK5 inhibitor + trametinib; ERK5 inhibitor + cobimetinib; ERK5 inhibitor + selumetinib; or ERK5 inhibitor + binimetinib	H2122	NSCLC
	A549	NSCLC
	H520	Lung squamous
	Capan 2	Pancreatic Cancer
	H441	LAD
ERK5 inhibitor + sotorasib (AMG510); or ERK5 inhibitor + adagrasib (MRTX849)	H2122	NSCLC
	MiaPaca2	PDAC
	NCI-H38	NSCLC
ERK5 inhibitor + alpelisib	MDA-MB-361	Breast cancer
	HT-29	CRC
	HCT116	CRC
	SK-OV03	Ovarian cancer
ERK5 inhibitor + vemurafenib; or ERK5 inhibitor + dabrafenib	Colo 205	CRC
	HT-29	CRC
ERK5 inhibitor + osimertinib; or ERK5 inhibitor + erlotinib	H1975	NSCLC
	HCC4006	NSCLC
	PC-9	NSCLC
ERK5 inhibitor + ceritinib; or ERK5 inhibitor + crizotinib	NCI H2228	NSCLC
ERK5 inhibitor + palbociclib	HCC38	Breast cancer
	MDA-MB-231	Breast cancer
ERK5 inhibitor + taletrectinib (DS-6051b)	HCC38	Breast cancer
	U-118MG	Brain cancer

Combination Treatment	Cell Line	Indication
ERK5 inhibitor + MRTX1133	Panc 04.03	Pancreatic cancer
	H441	LAD
ERK5 inhibitor + sorafenib	CAKI2	Kidney cancer
ERK5 inhibitor + TEAD Inhibitor	H2122	NSCLC
	A549	NSCLC
ERK5 inhibitor + MEK-RAF inhibitor	H2122	NSCLC
	A549	NSCLC

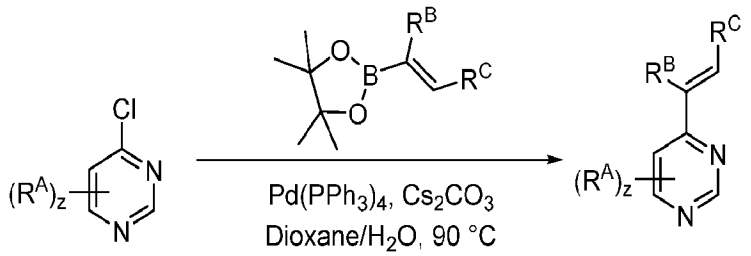
[1227] Cells are seeded according to the following procedure.

1. Prepare complete medium: Add FBS and appropriate additives according to the information sheet provided by the vendor. Mix gently.
2. Remove and discard culture medium using a vacuum pump. Briefly rinse the cell layer with 0.25% (w/v) Trypsin-0.038% (w/v) EDTA solution to remove all traces of serum that contains trypsin inhibitor.
3. Add 3.0 ml of Trypsin-EDTA solution to flask and observe cells under an inverted microscope until cell layer is dispersed.
4. Add 9.0 ml of complete growth medium and aspirate cells by gently pipetting.
5. Transfer the cell suspension to a centrifuge tube, and centrifuge at 1000 rpm for 4 minutes.
6. Discard the supernatant using a vacuum pump.
7. Add appropriate volume of complete medium. Suspend the cell pellet by gently pipetting.
8. Count the cell numbers with Vi-cell XR and adjust cells to appropriate density.
9. Add 200µL of cell suspension to 96-well opaque-walled clear bottom plates according to the planned plate layout, and place the plates in the CO_2 incubator overnight.
10. Incubate the plate for 10 days at 5% CO_2, 37°C.

[1228] Determination of cell viability following incubation using the CellTiter Glo Luminescent Cell Viability Assay is performed according to the following procedure.

1. Thaw the CellTiter-Glo buffer and equilibrate the lyophilized CellTiter-Glo substrate to room temperature prior to use.
2. Transfer the appropriate volume of CellTiter-Glo buffer into the bottle containing CellTiter-Glo substrate to reconstitute the lyophilized enzyme/substrate mixture. This forms the CellTiter-Glo reagent.
3. Mix by gently vortexing, swirling or by inverting the contents to obtain a homogeneous solution. The CellTiter-Glo substrate should go into solution easily in less than one minute.
4. Observe the cell morphology under an inverted microscope after corresponding treatment.
5. Equilibrate the plate and its contents to room temperature for approximately 30 minutes.
6. Add 100µL of CellTiter-Glo reagent to the assay plate.
7. Mix contents for 10 minutes on an orbital shaker to induce cell lysis.
8. Allow the plate to incubate at room temperature for 10 minutes to stabilize luminescent signal.
9. Paste the clear bottom with white back seal and record luminescence with Enspire plate reader, measurement time 0.1ms.

EXAMPLE 1-A -- Synthesis of 4-(Tetrahydropyridinyl)-pyrimidines and Related Compounds via Suzuki Coupling

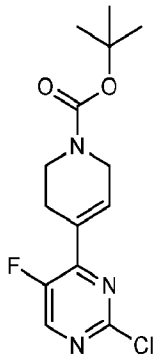
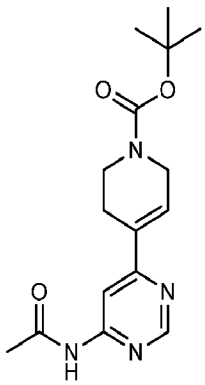
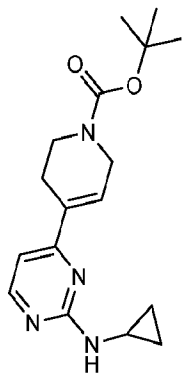


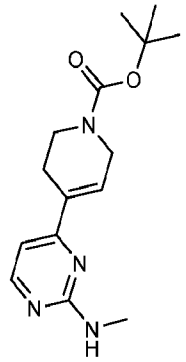
[1229] Pyrimidinyl chloride (1 Eq), pinacol boronate (1.04 Eq,) and cesium carbonate (1 Eq) were dissolved in a 6:1 mixture of dioxane (10-30 Volumes), before the mixture was degassed with a flow of N_2 for 15 mins. $Pd(PPh_3)_4$ (0.05 Eq) was added, and the mixture was degassed with a flow of N_2 for 5 mins. The reaction mixture was then heated to 70-100 °C for 2-18 h. The

reaction was cooled to RT, and then diluted with EtOAc (10-30 Volumes). The solution was filtered through Celite and rinsed with additional EtOAc. The filtrate was then concentrated *in vacuo*, and the residue was purified by chromatography on silica gel (0-100% EtOAc/*iso*-hexane) to afford the desired products.

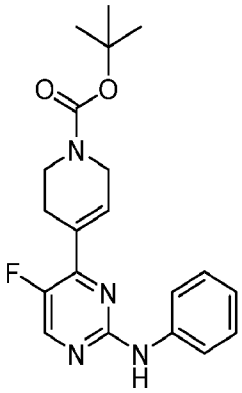
[1230] Compounds prepared according to the procedure of Example 1-A and corresponding characterization data are listed in Table A-4 below.

TABLE A-4.

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-A-1		UPLC Acidic 257.7 $[M-t\text{Bu}+H]^+$, (1.60)	8.83 (d, J = 3.5 Hz, 1H), 6.92 (s, 1H), 4.13 (s, 2H), 3.55 – 3.49 (m, 2H), 2.56 – 2.51 (m, 2H), 1.43 (s, 9H)
Int-A-2		UPLC Basic 319.2, (1.81)	10.87 (s, 1H), 8.79 (d, J = 1.3 Hz, 1H), 8.13 (d, J = 1.3 Hz, 1H), 6.90 (br.s, 1H), 4.12 – 4.03 (m, 2H), 3.53 (t, J = 5.7 Hz, 2H), 2.49 – 2.45 (m, 2H), 2.13 (s, 3H), 1.42 (s, 9H)
Int-A-3		UPLC Acidic 317.3, (1.49)	8.25 (d, J = 5.2 Hz, 1H), 7.30 – 6.99 (m, 1H), 6.91 – 6.66 (m, 2H), 4.07 – 4.00 (m, 2H), 3.53 – 3.43 (m, 2H), 2.76 – 2.63 (m, 1H), 2.47 (s, 2H), 1.42 (s, 9H), 0.70 – 0.56 (m, 2H), 0.49 – 0.41 (m, 2H).

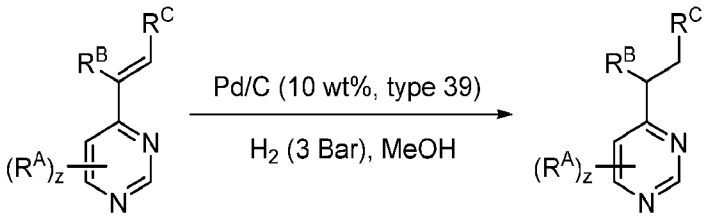
Int. No.	Chemical Structure	LCMS Method m/z (M+H)+, (Rt/min)	1H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-A-4		UPLC Basic 291.2, (2.01)	Not Determined

EXAMPLE 2-A – Synthesis of *tert*-Butyl 4-(5-fluoro-2-(phenylamino)pyrimidin-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (Int-A-5)



[1231] *tert*-Butyl 4-(2-chloro-5-fluoropyrimidin-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**Int-A-1**, 300 mg, 1 Eq, 0.96 mmol), aniline (134 mg, 131 µL, 1.5 Eq, 1.43 mmol), sodium 2-methylpropan-2-olate (276 mg, 3 Eq, 2.87 mmol) and PhMe (5 mL) were added to a microwave vial. The solution was purged with N_2 for 10 min. Pd-170 (19.3 mg, 0.03 Eq, 28.7 µmol) and XPhos (27.3 mg, 0.06 Eq, 0.057 mmol) were then added. The solution was further sparged with N_2 for 5 minutes, before heating to 100 °C overnight. The cooled reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (24 g cartridge, 0-20% EtOAc/iso-hexanes) to afford **Int-A-5** (210 mg, 0.57 mmol, 59 %) as an orange powder. Rt 1.85 min (UPLC Acidic); m/z 370.7 $(M+H)^+$ (ES^+).

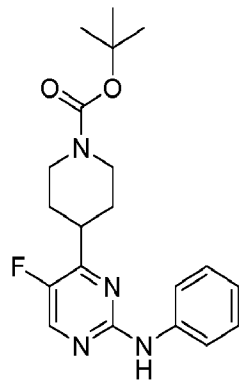
EXAMPLE 3-A -- Synthesis of 4-(Piperidinyl)-pyrimidines and Related Compounds via Hydrogenation

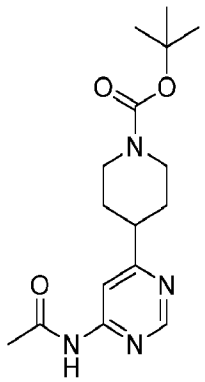
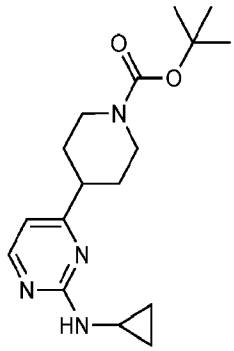
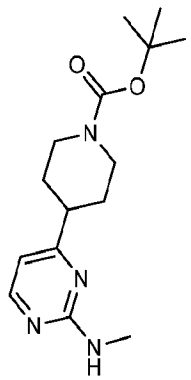


[1232] To a glass-lined steel pressure vessel was added a solution of alkene (1 Eq) in methanol (10-20 volumes) to which was added Pd/C (10 wt%, type-39, 0.11 Eq). The vessel was purged with N_2 and then purged with H_2. The reaction mixture was subjected to H_2 (3 bar) at RT for 22 h. The mixture was filtered through a glass fiber filter pad, and washed with ethanol (20-30 volume). The filtrate was then concentrated *in vacuo*, and the residue was purified by chromatography on silica gel (0-100% EtOAc/*iso*-hexane), to afford the desired product.

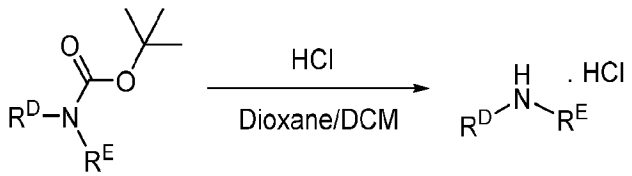
[1233] Compounds prepared according to the procedure of Example 3-A (from alkenes **Int-A-1** through **Int-A-4**, for example) and corresponding characterization data are listed in Table A-5 below.

TABLE A-5.

Int. No.	**Chemical Structure**	**LCMS Method m/z $(M+H)^+$, (Rt/min)**	**^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)**
Int-A-6		UPLC Acidic 373.4, (1.78)	Not Determined

Int. No.	Chemical Structure	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
Int-A-7		UPLC Basic 321.1, (1.74)	10.84 (s, 1H), 8.77 (d, *J* = 1.2 Hz, 1H), 7.96 (s, 1H), 4.08 – 3.99 (m, 2H), 2.94 – 2.72 (m, 3H), 2.12 (s, 3H), 1.80 (d, *J* = 12.8 Hz, 2H), 1.51 (qd, *J* = 12.5, 4.2 Hz, 2H), 1.41 (s, 9H).
Int-A-8		UPLC Acidic 319.5, (0.51)	Not Determined
Int-A-9		HPLC Acidic 293.3, (1.40)	Not Determined

EXAMPLE 4-A -- Acid Deprotection of Boc-Protected 4-(Piperidinyl)-pyrimidine and Related Compounds

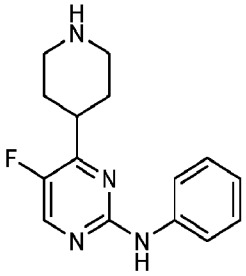
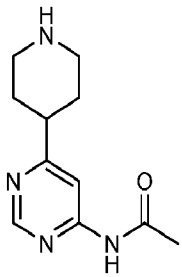
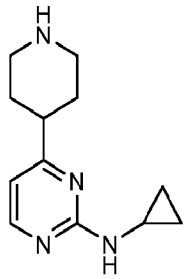
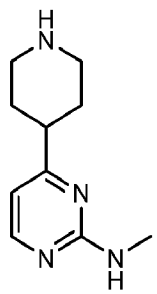


[1234] To a solution of Boc-protected amine (1.00 Eq) in DCM (5-20 Volumes) was added HCl 4M in dioxanes (4 molar, 2-20 Eq) and stirred at RT for 18 h. The reaction mixture was

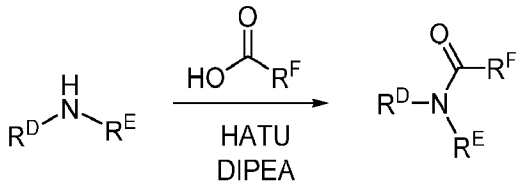
evaporated *in vacuo*. The residue was optionally sonicated in isohexanes (10-50 Volumes). The solid was isolated by filtration and dried under suction to afford the deprotected secondary amine as the HCl salt.

[1235] Compounds prepared according to the procedure of Example 4-A (from alkenes **Int-A-6** through **Int-A-9**, for example), and corresponding characterization data, are listed in Table A-6, below.

TABLE A-6.

Int. No.	**Chemical Structure**	**LCMS Method m/z $(M+H)^+$, (Rt/min)**	**^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)**
Int-A-10		UPLC Basic, 273.3, (0.647)	Not Determined
Int-A-11		UPLC Basic, 221.1, (0.96)	11.06 - 10.97 (m, 1H), 9.28 - 9.12 (m, 1H), 8.98 – 8.76 (m, 2H), 8.03 - 7.58 (d, *J* = 1.3 Hz, 3H), 3.34 (br.d, *J* = 12.6 Hz, 2H), 3.05 – 2.93 (m, 3H), 2.14 (s, 3H), 2.03 – 1.85 (m, 4H).
Int-A-12		UPLC Basic, 219.2, (1.20)	Not Determined
Int-A-13		UPLC Basic, 193.4, (0.60)	Not Determined

EXAMPLE 5-A – Amide Coupling in Deepwell Plates



[1236] To a well of a 96-deepwell plate were added amine (10-50 mg, 1 Eq) and carboxylic acid (1.2 Eq) reagents, which were dissolved in DMF (10-30 volumes). DIPEA (3-5 Eq) was added, followed by a solution of HATU (1.2 Eq) in DMF (20 volumes). The well plate was shaken at RT for 20 h. The samples were submitted for analysis by LCMS using the UPLC Basic method. The samples were filtered and submitted for purification by mass-directed preparative HPLC using the Basic prep method described above. The compounds were dried in a Genevac HT-12, dissolved in MeCN and submitted for analysis by LCMS using methods described. The compounds were dried in a Genevac HT-4X and then were further dried in a desiccator at 40 °C for 3 h. The compounds were analysed by ^{1}H NMR in DMSO-d6.

[1237] Compounds prepared according to the procedure of Example 5-A (from amine **Int-A-10** through **Int-A-13**, for example) and corresponding characterization data are listed in Table A-7 below. Chemical structures are presented in Table A-1, above, for the compounds presented in Table A-7.

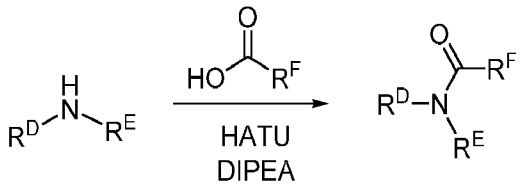
TABLE A-7.

Compound No.	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
I-A-1	UPLC Basic, 352.2, (1.17)	9.11 (d, *J* = 1.4 Hz, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.50 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.47 – 7.41 (m, 2H), 4.69 – 4.50 (m, 1H), 3.74 – 3.56 (m, 1H), 3.29 – 3.14 (m, 1H), 3.07 – 2.86 (m, 2H), 2.06 – 1.77 (m, 2H), 1.76 – 1.61 (m, 2H).
I-A-2	UPLC Basic, 367.2, (1.02)	9.11 (d, *J* = 1.4 Hz, 1H), 8.72 (d, *J* = 5.2 Hz, 1H), 7.49 (dd, *J* = 5.3, 1.4 Hz, 1H), 7.15 (dq, *J* = 8.3, 1.6 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.56 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.59 (s, 2H), 4.55 (s, 1H), 3.73 (s, 1H), 3.17 (s, 1H), 3.01 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.88 (s, 1H), 2.02 – 1.81 (m, 2H), 1.73 – 1.59 (m, 2H).

Compound No.	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
I-A-4	UPLC Basic, 407.2, (1.33)	8.20 (d, *J* = 5.0 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 3.6 Hz, 1H), 6.55 (d, *J* = 5.0 Hz, 1H), 4.60 – 4.49 (m, 1H), 3.65 – 3.56 (m, 1H), 3.22 – 3.11 (m, 1H), 2.94 – 2.85 (m, 1H), 2.79 – 2.72 (m, 1H), 2.71 – 2.64 (m, 1H), 1.97 – 1.85 (m, 1H), 1.83 – 1.73 (m, 1H), 1.71 – 1.56 (m, 2H), 0.63 (td, *J* = 6.9, 4.7 Hz, 2H), 0.47 – 0.41 (m, 2H).
I-A-5	UPLC Basic, 353.3, (1.11)	8.20 (d, *J* = 5.1 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.21 (d, *J* = 3.6 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.54 (d, *J* = 5.1 Hz, 1H), 4.68 – 4.22 (m, 1H), 4.14 – 3.57 (m, 1H), 3.79 (s, 3H), 3.21 – 2.82 (m, 2H), 2.78 – 2.71 (m, 1H), 2.68 (td, *J* = 6.9, 3.7 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.67 – 1.56 (m, 2H), 0.63 (td, *J* = 6.9, 4.7 Hz, 2H), 0.47 – 0.41 (m, 2H). Multiplet at 4.14 – 3.57 (m, 1H) partially obscured by methyl signal.
I-A-6	UPLC Basic, 391.2, (1.29)	8.21 (d, *J* = 5.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 3.7 Hz, 1H), 6.55 (d, *J* = 5.0 Hz, 1H), 4.62 – 4.51 (m, 1H), 3.58 – 3.52 (m, 1H), 3.22 – 3.12 (m, 1H), 2.96 – 2.85 (m, 1H), 2.81 – 2.72 (m, 1H), 2.72 – 2.66 (m, 1H), 1.97 – 1.88 (m, 1H), 1.82 – 1.72 (m, 1H), 1.73 – 1.54 (m, 2H), 0.67 – 0.60 (m, 2H), 0.47 – 0.41 (m, 2H).
I-A-7	UPLC 3 min Basic, 422.3, (1.28)	8.20 (d, *J* = 5.0 Hz, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.54 (d, *J* = 5.0 Hz, 1H), 6.50 – 6.46 (m, 1H), 5.56 (s, 2H), 4.63 – 3.47 (m, 2H), 3.00 (s, 2H), 2.76 – 2.63 (m, 2H), 1.90 – 1.79 (m, 2H), 1.68 – 1.56 (m, 2H), 0.63 (td, *J* = 6.8, 4.6 Hz, 2H), 0.47 – 0.40 (m, 2H). Signal at 4.63 – 3.47 (m, 2H) broadened considerably.
I-A-8	UPLC Basic, 381.3, (1.28)	^{1}H NMR (500 MHz, DMSO-d6) δ 8.23 – 8.10 (m, 1H), 7.59 – 7.51 (m, 2H), 7.48 – 7.39 (m, 2H), 6.95 – 6.87 (m, 1H), 6.50 (d, *J* = 5.1 Hz, 1H), 4.72 – 4.42 (m, 1H), 3.75 – 3.47 (m, 1H), 3.27 – 3.06 (m, 1H), 3.01 – 2.82 (m, 1H), 2.78 (d, *J* = 4.8 Hz, 3H), 2.76 – 2.70 (m, 1H), 2.02 – 1.70 (m, 2H), 1.71 – 1.50 (m, 2H).
I-A-9	UPLC Basic, 327.1, (1.05)	^{1}H NMR (500 MHz, DMSO-d6) δ 8.17 (d, *J* = 4.8 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.02 – 6.95 (m, 2H), 6.95 – 6.88 (m, 1H), 6.49 (d, *J* = 5.0 Hz, 1H), 4.92 – 4.13 (m, 1H), 4.07 – 3.62 (m, 4H), 3.20 – 2.82 (m, 2H), 2.77 (d, *J* = 4.8 Hz, 3H), 2.76 – 2.68 (m, 1H), 2.02 – 1.70 (m, 2H), 1.70 – 1.51 (m, 2H).
I-A-10	UPLC Basic, 365.3, (1.25)	^{1}H NMR (500 MHz, DMSO-d6) δ 8.18 (d, *J* = 4.3 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 6.95 – 6.89 (m, 1H), 6.50 (d, *J* = 5.0 Hz, 1H), 4.61 – 4.55 (m, 1H), 3.59 – 3.52 (m, 1H), 3.23 – 3.12 (m, 1H), 2.95 – 2.86 (m, 1H), 2.78 (d, *J* = 4.8 Hz, 3H), 2.76 – 2.71 (m, 1H), 1.96 – 1.90 (m, 1H), 1.80 – 1.74 (m, 1H), 1.70 – 1.54 (m, 2H). Multiplet at 2.76-2.71 ppm partially obscured by methyl peak.

Compound No.	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
I-A-11	UPLC Basic, 396.3, (1.24)	8.17 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.67 – 6.63 (m, 1H), 6.51 – 6.45 (m, 2H), 5.56 (s, 2H), 3.00 (s, 2H), 2.77 (d, *J* = 4.8 Hz, 3H), 2.72 – 2.69 (m, 1H), 1.87 – 1.80 (m, 2H), 1.64 – 1.58 (m, 2H), 2 x CH not observed
I-A-12	UPLC Basic, 424.3, (1.13)	10.85 (s, 1H), 8.77 (d, *J* = 1.2 Hz, 1H), 7.98 (d, *J* = 1.3 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.67 – 6.63 (m, 1H), 6.51 – 6.45 (m, 1H), 5.57 (s, 2H), 3.02 (s, 2H), 2.96 – 2.88 (m, 1H), 2.12 (s, 3H), 1.90 – 1.84 (m, 2H), 1.68 – 1.62 (m, 2H), 2 x CH not observed
I-A-13	UPLC Basic, 409.3, (1.17)	10.85 (s, 1H), 8.78 (d, *J* = 1.2 Hz, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.47 – 7.41 (m, 2H), 4.58 (s, 1H), 3.63 (s, 1H), 3.27 – 3.10 (m, 1H), 3.01 – 2.91 (m, 1H), 2.12 (s, 3H), 2.03 – 1.74 (m, 2H), 1.67 – 1.64 (m, 2H), 1 x CH not observed
I-A-14	UPLC Basic, 355.3, (0.94)	10.85 (s, 1H), 8.78 (d, *J* = 1.2 Hz, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.02 – 6.95 (m, 2H), 4.49 (s, 2H), 3.81 – 3.77 (m, 3H), 3.24 – 2.82 (m, 3H), 2.12 (s, 3H), 1.88 – 1.84 (m, 2H), 1.68 – 1.57 (m, 2H).
I-A-15	UPLC Basic, 393.3, (1.14)	10.86 (s, 1H), 8.79 (d, *J* = 1.2 Hz, 1H), 7.99 (d, *J* = 1.3 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.66 – 7.61 (m, 2H), 4.63 – 4.57 (m, 1H), 3.60 – 3.53 (m, 1H), 3.25 – 3.11 (m, 1H), 3.04 – 2.74 (m, 2H), 2.12 (s, 3H), 1.97 – 1.93 (m, 1H), 1.81 – 1.77 (m, 1H), 1.68 – 1.63 (m, 2H).

EXAMPLE 6-A – Amide Coupling in Stirred Vessel



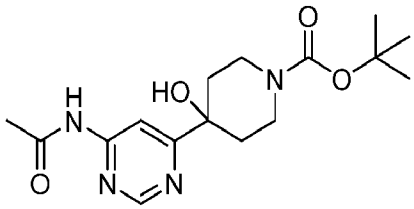
[1238] To a stirred mixture of amine (1 Eq), carboxylic acid (1 Eq) and DIPEA (3-5 Eq) in DMF (10-30 volumes), was added HATU (1.2 Eq). The reaction was left at RT for 1 h before being diluted with EtOAc (10-200 volumes). The diluted mixture was then washed with 1M HCl, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude compounds were purified by chromatography on silica gel (0-50% EtOAc/isohexane or DCM/MeOH/NH_3 solvent mixtures).

[1239] Compounds prepared according to the procedure of Example 6-A (from amine **Int-A-10**, for example) and corresponding characterization data are listed in Table A-8 below. The chemical structure of compound I-A-3 is provided in Table A-1 above.

TABLE A-8.

Compound No.	LCMS Method m/z $(M+H)^+$, (Rt/min)	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless Stated)
I-A-3	UPLC Acidic 461.3, (1.73)	9.61 (s, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.58 – 7.52 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.25 (m, 2H), 6.98 – 6.91 (m, 1H), 4.69 – 4.53 (m, 1H), 3.74 – 3.58 (m, 1H), 3.30 – 3.24 (m, 2H), 3.04 – 2.89 (m, 1H), 2.00 – 1.65 (m, 4H).

EXAMPLE 7-A -- Synthesis of *tert*-Butyl 4-(6-acetamidopyrimidin-4-yl)-4-hydroxypiperidine-1-carboxylate (Int-A-14)



[1240] A stirring mixture of tert-butyl 4-(6-acetamidopyrimidin-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**Int-A-2**, 409 mg, 1 Eq, 1.28 mmol) and tris(dipivaloylmethanato)manganese (233 mg, 0.3 Eq, 385 µmol) in 2-propanol (3 mL) at -5 °C in a 50 mL flask was degassed before introducing oxygen into the mixture with the aid of a balloon. The mixture was then degassed and back-fillled with oxygen two more times. Phenylsilane (695 mg, 0.793 mL, 5.00 Eq, 6.43 mmol) was added to the mixture and it stirred at -5 °C for 1 h. Saturated solution of sodium thiosulfate (6 mL) was added to the reaction mixture, and it was stirred overnight. More saturated sodium thiosulfate (20 mL) was added to the reaction mixture. The mixture was then extracted with DCM (5 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (24 g cartridge, 0-100% EtOAc/isohexane, followed by 0-10% MeOH/DCM) to afford tert-butyl 4-(6-acetamidopyrimidin-4-yl)-4-hydroxypiperidine-1-carboxylate (423 mg, 1.2 mmol, 93 %, 95% purity) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.78 (d, J = 1.2 Hz, 1H), 8.40 (d, J = 1.2 Hz, 1H), 5.50 (s, 1H), 3.85 (br.s, 2H), 3.19 – 3.00 (m, 2H), 2.13 (s, 3H), 1.95 (td, J = 13.2, 4.8 Hz, 2H), 1.49 – 1.44 (m, 2H), 1.41 (s, 9H).

EXAMPLE 8-A – Synthesis of Additional 4-Piperidinyl-pyrimidine-4-amines and Related Compounds

[1241] Additional compounds prepared according to the procedures of Examples 1-A through 7-A are listed in Table A-9, below, along with each compound's ^{1}H NMR characterization data and mass-to-charge ratio observed by LC/MS. Chemical structures are presented in Table A-1-A above.

TABLE A-9.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
I-A-20	458	9.51 (s, 1H), 8.54 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.11 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.57 (s, 2H), 3.08-2.94 (m, 1H), 2.82-2.71 (m, 1H), 1.93-1.82 (m, 2H), 1.71-1.55 (m, 2H), 0.88-0.78 (m, 1H). Missing 2 protons.
I-A-21	534	9.50 (s, 1H), 8.19 (q, J = 4.5 Hz, 1H), 8.09 (d, J = 6.4 Hz, 1H), 7.77-7.69 (m, 4H), 7.15 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 2.5, 1.2 Hz, 1H), 6.50 (ddd, J = 8.3, 2.5, 1.2 Hz, 1H), 5.66 (s, 2H), 3.77 (s, 4H), 3.60 (s, 4H), 2.75 (d, J = 4.6 Hz, 3H), 1H not observed
I-A-22	440	10.85 (s, 1H), 8.79 (d, J = 1.2 Hz, 1H), 8.41 (d, J = 1.2 Hz, 1H), 7.63 (d, J = 8.7 Hz, 0H), 7.12 (d, J = 8.4 Hz, 1H), 6.67-6.62 (m, 1H), 6.51-6.45 (m, 1H), 5.59 (d, J = 7.5 Hz, 3H), 2.13 (s, 3H), 2.06-2.02 (m, 2H), 1.57-1.51 (m, 2H), 4H not observed due to peak broadening
I-A-23	398	11.27 (s, 1H), 9.52 (s, 1H), 8.56 (s, 1H), 7.68-7.63 (m, 2H), 7.58 (d, J = 8.1 Hz, 1H), 7.48-7.43 (m, 2H), 7.35-7.28 (m, 2H), 7.07-6.97 (m, 2H), 6.66 (s, 1H), 6.50-6.45 (m, 1H), 3.36-3.31 (m, 2H), 3.03 (s, 2H), 2.86-2.76 (m, 1H), 1.89-1.85 (m, 2H), 1.71-1.59 (m, 2H).
I-A-24	425	10.86 (s, 1H), 8.80 (d, J = 1.2 Hz, 1H), 8.42 (d, J = 1.2 Hz, 1H), 7.60-7.53 (m, 2H), 7.44 (d, J = 8.2 Hz, 2H), 5.64 (s, 1H), 3.46 (s, 2H), 2.13 (s, 3H), 6H not observed
I-A-25	409	10.87 (s, 1H), 8.80 (s, 1H), 8.42 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H), 5.65 (s, 1H), 4.50-4.35 (m, 1H), 3.52-3.36 (m, 2H), 3.25-3.12 (m, 1H), 2.13 (s, 3H), 2.12-2.06 (m, 1H), 2.05-1.91 (m, 1H), 1.73-1.57 (m, 1H), 1.57-1.40 (m, 1H).
I-A-26	371	10.86 (s, 1H), 8.79 (d, J = 1.2 Hz, 1H), 8.42 (d, J = 1.2 Hz, 1H), 7.42-7.32 (m, 2H), 7.05-6.93 (m, 2H), 5.61 (s, 1H), 4.62-4.07 (m, 1H), 3.79 (s, 3H), 3.72-2.99 (m, 3H), 2.13 (s, 3H), 2.07-1.97 (m, 2H), 1.72-1.33 (m, 2H).
I-A-27	518	9.91 (s, 1H), 8.51 (d, J = 1.9 Hz, 1H), 8.27-8.21 (m, 1H), 7.83-7.75 (m, 4H), 7.59-7.53 (m, 2H), 7.49-7.43 (m, 2H), 4.68-4.54 (m, 1H), 3.73-3.58 (m, 1H), 3.30-3.23 (m, 1H), 3.05-2.92 (m, 1H), 2.76 (d, J = 4.5 Hz, 3H), 2.03-1.64 (m, 4H). 1 proton not observed.

Compound No.	Mass Spec. m/z	^{1}H NMR Chemical Shift Data (ppm, DMSO-d6, RT, unless stated)
I-A-28	480	9.69 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.69-6.64 (m, 1H), 6.53 (d, J = 2.2 Hz, 1H), 6.51-6.48 (m, 1H), 5.58 (s, 2H), 3.73 (s, 3H), 3.24-3.14 (m, 1H), 3.15-2.99 (m, 2H), 1.86-1.80 (m, 2H), 1.78-1.69 (m, 2H). 2 protons not observed.
I-A-29	465	9.70 (s, 1H), 8.37 (d, J = 2.0 Hz, 1H), 7.58-7.52 (m, 3H), 7.48-7.43 (m, 2H), 6.53 (d, J = 2.2 Hz, 1H), 4.70-4.52 (m, 1H), 3.73 (s, 3H), 3.70-3.58 (m, 1H), 3.28-3.20 (m, 2H), 3.04-2.92 (m, 1H), 1.97-1.85 (m, 1H), 1.82-1.59 (m, 3H).

EXAMPLE 9-A – Biological Assay for Inhibiting Isolated ERK5

[1242] Exemplary compounds were tested for ability to inhibit isolated ERK5 using the LANCE® Ultra time-resolved FRET assay. Assay procedures and results are described below.

Part I – Procedures for Time-Resolved FRET Assay

[1243] Recombinant human Erk5 catalytic domain (1-398 amino acids of accession number NP_002740.2) was purchased from Carna Biosciences (Product number 04-146, Lot 13CBS-0805 C). The protein was expressed as an N-terminal GST-fusion protein (73 kDa) in E.coli. GST-Erk5 was purified using glutathione Sepharose chromatography and activated using His-tagged MAP2K5. The activated GST-Erk5 was then purified using Ni-NTA chromatography resulting in 53% purity. The protein was stored at 515 µg/mL (7.05 µM) in storage buffer (50 mM Tris-HCl, 150 mM NaCl, 0.05% Brij35, 1 mM DTT, 10% v/v glycerol, pH 7.5), at -80°C.

[1244] The substrate for the kinase was LANCE® Ultra Europium-anti-phospho-eIF4E-binding protein 1 (Thr37/46) peptide (Perkin Elmer TRF0216-D). The sequence motif for the peptide was ST(pT)PGGTLFST(pT)PG, with (pT) denoting the two potential phospo-theronines. The peptide was stored as a 5 µM stock solution in 50 mM Tris-HCl (pH7.4), 0.9% w/v NaCl, 0.1% w/v BSA and 0.05% w/v sodium azide, at -20°C.

[1245] Test compounds were prepared as 30 mM stock solutions in DMSO, stored under dry nitrogen gas. Solutions were plated into Echo® Qualified 384-well low dead volume microplates (Labcyte LP-0200). Compounds were then dosed into white, low-volume 384-well assay plates (Greiner Bio-One Ltd 784075) using the Labcyte Echo® 650 acoustic dosing platform. Test compounds were dosed in a 12-point, 2-fold dilution series at 100 µM top concentration then

backfilled to 1% v/v DMSO. The top concentration was adjusted based on expected compound potency. A tool compound (BAY-885) was included in each assay plate as a standard. High controls (1% v/v DMSO) were included in rows A and O, with low controls (10 μM BAY-885) in rows B and P. Two identical sets of assay plates were prepared and tested in two independent experiments.

[1246] At the beginning of the assay, 3 μL of 2-fold concentrated peptide buffer (100 nM ULight-eIF4E-binding protein 1 (Thr37/46) peptide, 300 μM ATP, 10 mM $MgCl_2$, 1 mM EGTA, 50 mM HEPES, 1 mM DTT, 0.01% v/v Tween 20, pH 7.5) was added to each well using an electronic multichannel pipette. The reaction was initiated by adding 3 μL of 2-fold concentrated kinase buffer (15 nM Erk5, 10 mM $MgCl_2$, 1 mM EGTA, 50 mM HEPES, 1 mM DTT, 0.01% v/v Tween 20, pH 7.5), using an electronic multichannel pipette and mixing the assay volume three times. The final reaction composition was 7.5 nM Erk5, 50 nM ULight-eIF4E-binding protein 1 (Thr37/46) peptide, 150 μM ATP, 10 mM $MgCl_2$, 1 mM EGTA, 50 mM HEPES, 1 mM DTT, 0.01% v/v Tween 20, pH 7.5. As the protein purity was 53%, the true concentration of Erk5 was approximately 3.75 nM.

[1247] The reaction was allowed to progress for 1 hour at 22°C sealed and protected from light. To terminate the reaction and detect substrate phosphorylation, 6 μL of 2-fold concentrated detection buffer (12mM EDTA and 4 nM Eu-anti-phosphoeIF4E-binding protein 1 (Thr37/46) antibody in LANCE® Detection Buffer (Perkin Elmer CR97-100)) was added to each well using an electronic multichannel pipette. The assay volume was mixed three times.

[1248] The terminated reaction was allowed to incubate for 1 hour at 22°C sealed and protected from light. The level of resonance energy transfer was detected using an Envision Xcite plate reader (Perkin Elmer), with excitation at 350 nm and emission at 620 nm and 665 nm. The ratio of signal at 665 nm and 620 nm was taken as the level of phosphorylated substrate. The data was normalised to % inhibition by setting 0% as the signal from the high control and 100% as that from the low control. Values were plotted, and IC_{50} values were calculated using Dotmatics Studies (Dotmatics Knowledge Solutions).

Part II – Results

[1249] Experimental results are provided in Table A-10 and Table A-10-A, below. The symbol "++++" indicates an IC_{50} less than or equal to 0.05 μM. The symbol "+++" indicates an

IC_{50} in the range of 0.5 μM to greater than 0.05 μM. The symbol "++" indicates an IC_{50} in the range of 5 μM to greater than 0.5 μM. The symbol "+" indicates an IC_{50} in the range of 30 μM to greater than 5 μM.

TABLE A-10.

Compound No.	IC_{50}
I-A-1	++
I-A-2	++
I-A-3	+++
I-A-4	++
I-A-5	++
I-A-6	++
I-A-7	+++
I-A-8	++
I-A-9	+
I-A-10	+
I-A-11	++
I-A-12	+++
I-A-13	+++
I-A-14	++
I-A-15	++

TABLE A-10-A.

Compound No.	IC_{50}
I-A-16	++
I-A-17	+
I-A-20	+++
I-A-21	+
I-A-22	+++
I-A-23	++
I-A-24	+++

Compound No.	IC_{50}
I-A-25	++
I-A-26	++
I-A-27	+++
I-A-28	+++
I-A-29	++

EXAMPLE 10-A – Biological Assay for Inhibiting ERK5 in Cells

[1250] Exemplary compounds were tested for ability to inhibit ERK5 activity in SN12C cells using a MEF2-responsive transcription element and two luciferase reporter genes. Assay procedures and results are described below.

Part I – Procedures for Luciferase Reporter Gene Assay

[1251] The polyclonal SN12C-MEF2-luc cell line was generated by stably transducing SN12C cells with a MEF2-responsive transcription element upstream of a firefly luciferase gene and a cytomegalovirus (CMV) promoter element upstream of a renilla luciferase gene. Generation of this cell line was carried out at Sygnature Discovery. This cell line was grown in RPMI 1640 media (Gibco #11530406) without phenol red supplemented with 10 % FBS, 1 % L-glutamine, 1 % penicillin/streptomycin, 250 µg/mL Hygromycin B gold and 1.25 µg/mL puromycin. Cells were grown at 37 °C in a humidified environment with 5 % CO_2.

[1252] On day 1 cells were seeded in 384-well black-walled plates (Greiner 781091) at a density of 10,000 cells per well in 20 µL of culture media. On day 2, using an ECHO 650, test compounds were added in serial dilutions and trametinib was added to all wells at a final concentration of 125 nM. Plates were then incubated for 24 hours at 37 °C. On day 3, 20 µL of Dual-glo luciferase reagent (Promega, E2940) was added to each well, and the plates were incubated at room temperature for 10 minutes. Luminescence signal was then read on an EnVision Xcite multimode plate reader (Perkin-Elmer). Renilla luciferase substrate (Dual-glo stop & Glo Promega E2940) was added to all wells (20 µL per well), and the plates were incubated at room temperature for 10 minutes. Luminescence signal was then read on an EnVision Xcite multimode plate reader (Perkin-Elmer).

[1253] The firefly signal was then normalised to the renilla signal, and IC_{50} values were calculated using Dotmatics Studies (Dotmatics Knowledge Solutions) or GraphPad Prism. Values for cells treated only with DMSO were defined as the minimum control. Values for cells treated only with trametinib (125 nM) were defined as the maximum control.

Part II – Results

[1254] Experimental results are provided in Table A-11 and Table A-11-A, below. The symbol "***" indicates an IC_{50} less than or equal to 0.05 μM. The symbol "**" indicates an IC_{50} in the range of 0.5 μM to greater than 0.05 μM. The symbol "*" indicates an IC_{50} greater than 0.5 μM.

TABLE A-11.

Compound No.	IC_{50}
I-A-1	*
I-A-3	*

TABLE A-11-A.

Compound No.	IC_{50}
I-A-7	**
I-A-12	***
I-A-15	*
I-A-20	**
I-A-22	**

INCORPORATION BY REFERENCE

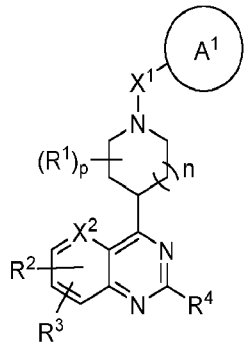
[1255] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[1256] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Claims:

1. A compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond;

R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and halo;

R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-;

X^2 is N or C(R^2);

A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

n is 1 or 2; and

m and p are each independently 0, 1, 2, or 3;

provided that if p is 0 and X^1 is -C(O)-, then n is 2.

2. The compound of claim 1, wherein the compound is a compound of Formula I.

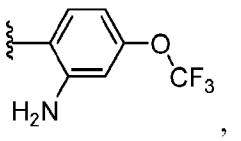
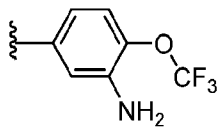
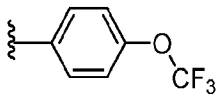
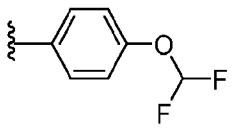
3. The compound of claim 1 or 2, wherein A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen,

oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

4. The compound of claim 1 or 2, wherein A^1 is phenyl substituted with m occurrences of R^7.

5. The compound of claim 1 or 2, wherein A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

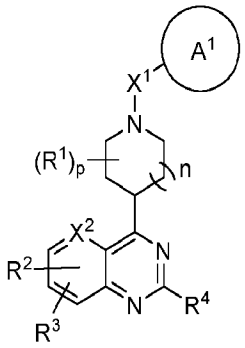
6. The compound of claim 1 or 2, wherein A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7.

7. The compound of claim 1 or 2, wherein A^1 is  ,  ,  , or  .

8. The compound of any one of claims 1-6, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

9. The compound of any one of claims 1-8, wherein p is 0, X^1 is -C(O)-, and n is 2.

10. A compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^5)(R^6)$, halo, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond;

R^2 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, hydrogen, a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and halo;

R^4 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X^1 is -C(O)-, -S(O)-, or -$S(O)_2$-;

X^2 is N or C(R^2);

A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or naphthyl; each of which is substituted with m occurrences of R^7; and when X^1 is -S(O)- or -$S(O)_2$-, A^1 is additionally selected from phenyl and a 6-membered monocyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

n is 1 or 2; and

m and p are each independently 0, 1, 2, or 3.

11. The compound of claim 10, wherein the compound is a compound of Formula II.

12. The compound of claim 10 or 11, wherein A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

13. The compound of claim 10 or 11, wherein A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^7.

14. The compound of any one of claims 10-13, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

15. The compound of any one of claims 10-14, wherein p is 0.

16. The compound of any one of claims 1-8 or 10-14, wherein p is 1 or 2.

17. The compound of any one of claims 1-8, 10-14, or 16, wherein n is 1.

18. The compound of any one of claims 1-8, 10-14, or 16, wherein n is 2.

19. The compound of any one of claims 1-8, 10-14, or 16-18, wherein R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or $-N(R^5)(R^6)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

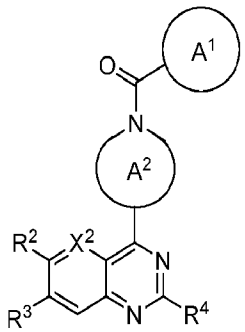
20. The compound of any one of claims 1-19, wherein R^2 represents independently for each occurrence hydrogen, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl.

21. The compound of any one of claims 1-20, wherein R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

22. The compound of any one of claims 1-21, wherein R^4 is hydrogen or C_{1-4} alkyl.

23. The compound of any one of claims 1-22, wherein X^1 is -C(O)-.

24. A compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

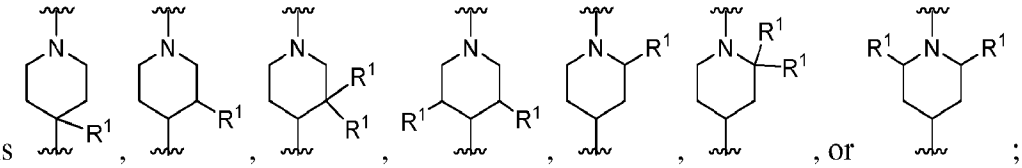
R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

X^2 is N or $C(R^2)$;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

A^2 is  ;

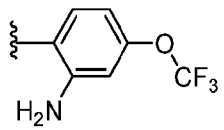
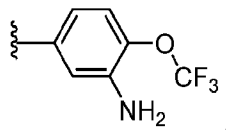
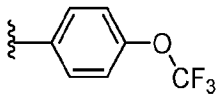
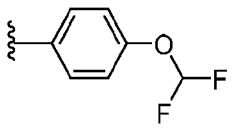
wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1; and

m is 0, 1, 2, or 3.

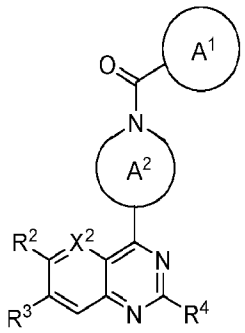
25. The compound of claim 24, wherein the compound is a compound of Formula I-A.

26. The compound of claim 24 or 25, wherein A^1 is phenyl substituted with m occurrences of R^7.

27. The compound of claim 24 or 25, wherein A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7.

28. The compound of claim 24 or 25, wherein A^1 is  ,  ,  , or  .

29. A compound represented by Formula II-A:



(II-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, hydrogen, or a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo;

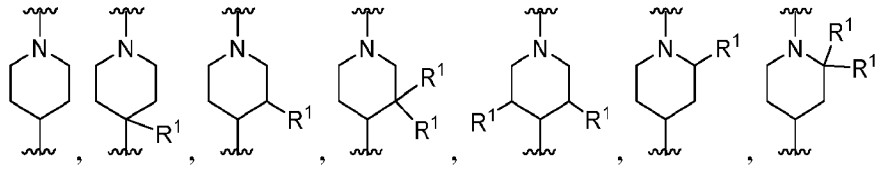
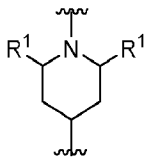
R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

X^2 is N or C(R^2);

A^1 is 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

A^2 is  , or  ; wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1; and

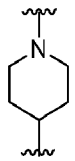
m is 0, 1, 2, or 3.

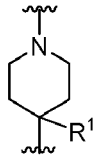
30. The compound of claim 29, wherein the compound is a compound of Formula II-A.

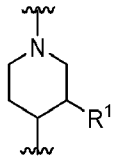
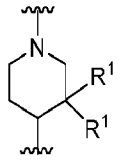
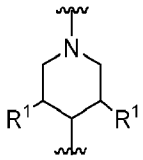
31. The compound of claim 29 or 30, wherein A^1 is a 5-membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

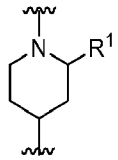
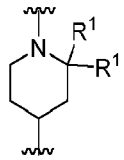
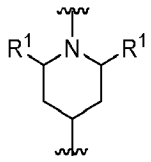
32. The compound of claim 29 or 30, wherein A^1 is a 6-membered monocyclic heteroaryl having 2 or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

33. The compound of claim 29 or 30, wherein A^1 is an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; which is substituted with m occurrences of R^7.

34. The compound of any one of claims 29-33, wherein A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

35. The compound of any one of claims 24-33, wherein A^2 is  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

36. The compound of any one of claims 24-33, wherein A^2 is  ,  , or  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

37. The compound of any one of claims 24-33, wherein A^2 is  ,  , or  wherein the piperidinylene nitrogen atom is attached to -C(O)-A^1.

38. The compound of any one of claims 1-33 or 35-37, wherein R^1 is hydroxyl.

39. The compound of any one of claims 1-33 or 35-37, wherein R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl.

40. The compound of any one of claims 1-33 or 35-37, wherein R^1 represents independently for each occurrence C_{1-4} alkoxyl or C_{1-4} haloalkoxyl.

41. The compound of any one of claims 1-33 or 35-37, wherein R^1 represents independently for each occurrence C_{1-4} alkyl.

42. The compound of any one of claims 1-41, wherein R^2 is hydrogen.

43. The compound of any one of claims 1-41, wherein R^2 represents independently for each occurrence C_{1-4} alkoxyl.

44. The compound of any one of claims 1-43, wherein R^3 is C_{1-4} alkoxyl.

45. The compound of any one of claims 1-43, wherein R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

46. The compound of any one of claims 1-43, wherein R^3 is piperazinyl substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and halo.

47. The compound of any one of claims 1-46, wherein R^4 is hydrogen.

48. The compound of any one of claims 1-47, wherein R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

49. The compound of any one of claims 1-48, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano.

50. The compound of any one of claims 1-48, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^5)(R^6)$, or C_{1-6} alkyl.

51. The compound of any one of claims 1-48, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl or $-N(R^5)(R^6)$.

52. The compound of any one of claims 1-48, wherein R^7 represents independently for each occurrence $-OCF_3$ or $-NH_2$.

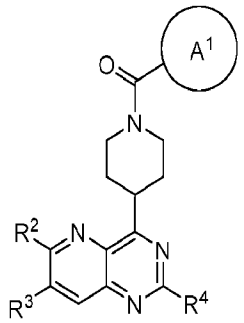
53. The compound of any one of claims 1-6, 10-13, or 29-34, wherein R^7 is phenyl.

54. The compound of any one of claims 1-53, wherein X^2 is N.

55. The compound of any one of claims 1-53, wherein X^2 is $C(R^2)$.

56. The compound of any one of claims 1-55, wherein m is 1 or 2.

57. A compound represented by Formula III:



(III)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{0-4} alkylene)-(C_{1-4} alkoxyl), -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, or halo;

R^2 represents independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^3 is:

(i) a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-$C(O)N(R^5)(R^6)$, and (b) p occurrences of R^1; or

(ii) a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with p occurrences of R^1;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 represents independently for each occurrence C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl; wherein R^7 is additionally selected from C_{1-6} haloalkoxyl when (i) m is 3, or (ii) m is 1 or 2, and q is 1;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^7;

m is 0, 1, 2, or 3;

p is 0, 1, or 2; and

q is 0 or 1.

58. The compound of claim 57, wherein the compound is a compound of Formula III.

59. The compound of claim 57 or 58, wherein R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, or halo.

60. The compound of any one of claims 57-59, wherein R^2 is hydrogen.

61. The compound of any one of claims 57-60, wherein R^4 is hydrogen.

62. The compound of any one of claims 57-61, wherein R^5 and R^6 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

63. The compound of any one of claims 57-62, wherein R^3 is a 4-7 membered saturated monocyclic heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said heterocyclyl is substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1.

64. The compound of any one of claims 57-62, wherein R^3 is piperazinyl substituted with (a) q occurrences of C_{1-4} haloalkyl, -(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), or -(C_{0-4} alkylene)-C(O)N(R^5)(R^6), and (b) p occurrences of R^1.

65. The compound of any one of claims 57-62, wherein R^3 is a 4-7 membered saturated or partially unsaturated monocyclic oxo-heterocyclyl having one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heterocyclyl is substituted with p occurrences of R^1.

66. The compound of any one of claims 57-65, wherein m is 3.

67. The compound of any one of claims 57-64, wherein m is 1 or 2, and q is 1.

68. The compound of any one of claims 57-65, wherein m is 1 or 2.

69. The compound of any one of claims 57-66, wherein q is 1.

70. The compound of claim 66 or 67, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), or phenyl; or two occurrences of R^7 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

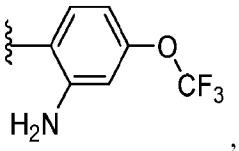
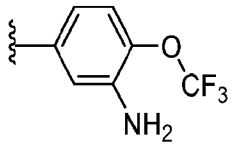
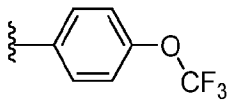
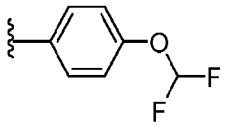
71. The compound of claim 66 or 67, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^5)(R^6), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, -S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl).

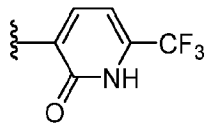
72. The compound of claim 66 or 67, wherein R^7 represents independently for each occurrence C_{1-6} haloalkoxyl, $-N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo.

73. The compound of any one of claims 57-69, wherein R^7 represents independently for each occurrence $-N(R^5)(R^6)$, C_{1-6} haloalkyl, or halo.

74. The compound of any one of claims 57-73, wherein A^1 is phenyl substituted with m occurrences of R^6.

75. The compound of any one of claims 57-73, wherein A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^6.

76. The compound of claim 67, wherein A^1 is  ,  ,  , or  .

77. The compound of any one of claims 57-69, wherein A^1 is  .

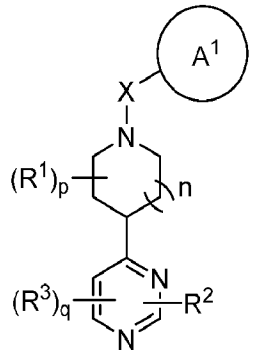
78. The compound of any one of claims 57-77, wherein p is 1.

79. A compound in Table 1, 1-A, 2, 2-A, 3, 4, 5, 6, or 7 herein, or a pharmaceutically acceptable salt thereof.

80. A compound in Table 1, 2, 3, 4, or 5 herein, or a pharmaceutically acceptable salt thereof.

81. A pharmaceutical composition comprising a compound of any one of claims 1-80 and a pharmaceutically acceptable carrier.

82. A compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} hydroxyalkoxyl, -(C_{1-4} alkoxylene)-$N(R^4)(R^5)$, halo, or $-N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms; or two occurrences of R^1 attached to adjacent carbon atoms are taken together with said carbon atoms to form a carbon-carbon double bond;

R^2 is $-N(R^4)C(O)(R^7)$, $-N(R^6)(R^7)$, $-C(O)N(R^6)(R^7)$, or hydrogen

R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or cyano;

R^4 and R^5 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^6 is hydrogen, C_{1-4} alkyl, or C_{3-5} cycloalkyl;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of $-C(O)N(R^4)(R^5)$, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, -S-(C_{1-6} haloalkyl), -S-(C_{1-6} alkyl), -$S(O)_2$-(C_{1-6} alkyl), C_{3-6} cycloalkyl, phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered saturated or partially unsaturated monocyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and oxo;

X is -C(O)-, -S(O)-, or -$S(O)_2$-;

A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

n is 1 or 2;

m and p are each independently 0, 1, 2, or 3; and

q is 0, 1, or 2.

83. The compound of claim 82, wherein the compound is a compound of Formula I.

84. The compound of claim 82 or 83, wherein R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or -$N(R^4)(R^5)$; or two occurrences of R^1 attached to the same carbon atom are taken together with said carbon atom to form a cyclopropyl ring.

85. The compound of any one of claims 82-84, wherein R^2 is -$N(R^4)C(O)(R^7)$ or -$N(R^6)(R^7)$.

86. The compound of any one of claims 82-84, wherein R^2 is -$C(O)N(R^6)(R^7)$, and m is 1, 2, or 3.

87. The compound of any one of claims 82-86, wherein R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl.

88. The compound of any one of claims 82-87, wherein R^6 is hydrogen.

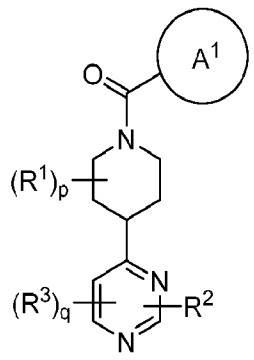
89. The compound of any one of claims 82-88, wherein R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, $-N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, or 2 heteroatoms independently selected from nitrogen and oxygen, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

90. The compound of any one of claims 82-89, wherein X is -C(O)-.

91. The compound of any one of claims 82-90, wherein A^1 is phenyl; naphthyl; a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

92. The compound of any one of claims 82-91, wherein n is 1.

93. A compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl; or two occurrences of R^1 attached to different carbon atoms are taken together to form a C_{1-3} alkylene group connecting said carbon atoms;

R^2 is -N(H)C(O)(C_{1-6} alkyl) or -N(H)(R^7);

R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl;

R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, phenyl, or pyrazolyl; wherein said phenyl and pyrazolyl are substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -O-(C_{0-4} alkylene)-(C_{3-6} cycloalkyl), -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, cyano, S-(C_{1-6} haloalkyl), or -S-(C_{1-6} alkyl); or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

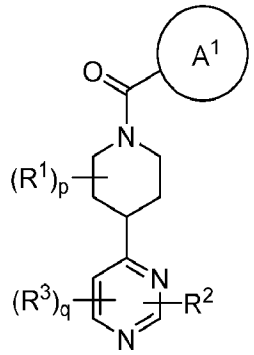
A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

m is 0, 1, 2, or 3; and

p and q are each independently 0, 1, or 2.

94. The compound of claim 93, wherein the compound is a compound of Formula I-A.

95. A compound represented by Formula I-A1:



(I-A1)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 represents independently for each occurrence hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyl, or C_{1-4} haloalkoxyl;

R^2 is -N(H)C(O)(C_{1-6} alkyl) or -N(H)(R^7);

R^3 represents independently for each occurrence halo, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, or C_{1-4} alkyl;

R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 4-7 membered saturated ring having one nitrogen atom;

R^7 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or phenyl; wherein said phenyl is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano;

R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -N(R^4)(R^5), hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano; or two occurrences of R^8 are taken together with the intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

A^1 is phenyl, a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic

heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8;

m is 0, 1, 2, or 3; and

p and q are each independently 0, 1, or 2.

96. The compound of claim 95, wherein the compound is a compound of Formula I-A1.

97. The compound of any one of claims 82-96, wherein R^1 is hydroxyl.

98. The compound of any one of claims 82-96, wherein p is 0.

99. The compound of any one of claims 82-97, wherein p is 1.

100. The compound of any one of claims 82-99, wherein R^2 is -N(H)(R^7).

101. The compound of any one of claims 82-100, wherein R^7 is C_{1-6} alkyl or C_{1-6} haloalkyl.

102. The compound of any one of claims 82-100, wherein R^7 is C_{3-6} cycloalkyl.

103. The compound of any one of claims 82-100, wherein R^7 is phenyl substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano.

104. The compound of any one of claims 82-94, wherein R^7 is phenyl or pyrazolyl; each of which is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of -C(O)N(R^4)(R^5), halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, and cyano.

105. The compound of any one of claims 82-99, wherein R^2 is -N(H)C(O)(C_{1-6} alkyl).

106. The compound of any one of claims 82-105, wherein R^2 is attached at the 2-position of the pyrimidine.

107. The compound of any one of claims 82-105, wherein R^2 is attached at the 4-position of the pyrimidine.

108. The compound of any one of claims 82-107, wherein R^3 represents independently for each occurrence halo.

109. The compound of any one of claims 82-107, wherein q is 0.

110. The compound of any one of claims 82-108, wherein q is 1.

111. The compound of any one of claims 82-110, wherein R^4 and R^5 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

112. The compound of any one of claims 82-111, wherein R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, halo, or cyano.

113. The compound of any one of claims 82-111, wherein R^8 represents independently for each occurrence C_{1-6} haloalkoxyl, C_{1-6} alkoxyl, -$N(R^4)(R^5)$, or C_{1-6} alkyl.

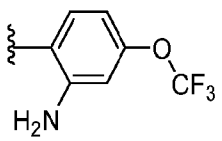
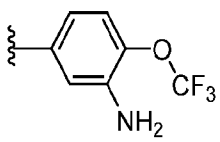
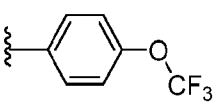
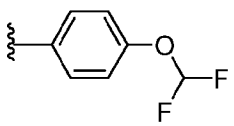
114. The compound of any one of claims 82-111, wherein R^8 represents independently for each occurrence C_{1-6} haloalkoxyl or -$N(R^4)(R^5)$.

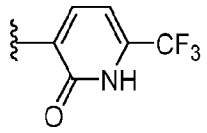
115. The compound of any one of claims 82-111, wherein R^8 represents independently for each occurrence $-OCF_3$ or $-NH_2$.

116. The compound of any one of claims 82-115, wherein A^1 is phenyl substituted with m occurrences of R^8.

117. The compound of any one of claims 82-115, wherein A^1 is a 5-6 membered monocyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with m occurrences of R^8.

118. The compound of any one of claims 82-114, wherein A^1 is a 5-6 membered monocyclic partially unsaturated oxo-heterocyclyl having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said oxo-heterocyclyl is substituted with m occurrences of R^8.

119. The compound of any one of claims 82-111, wherein A^1 is  ,  ,  , or  .

120. The compound of any one of claims 82-94, wherein A^1 is  .

121. The compound of any one of claims 82-118, wherein m is 1 or 2.

122. A compound in Table A-1, A-1-A, A-2, or A-3 herein, or a pharmaceutically acceptable salt thereof.

123. A compound in Table A-1, A-2, or A-3 herein, or a pharmaceutically acceptable salt thereof.

124. A pharmaceutical composition comprising a compound of any one of claims 82-123 and a pharmaceutically acceptable carrier.

125. A method of treating a disorder mediated by ERK5, comprising administering a therapeutically effective amount of a compound of any one of claims 1-80 or 82-123 to a subject in need thereof to treat the disorder.

126. The method of claim 125, wherein the disorder is cancer.

127. A method of treating cancer in a subject, comprising administering to a subject in need thereof (i) a therapeutically effective amount of a compound of any one of claims 1-80 or 82-123 and (ii) a second anti-cancer agent, in order to treat the cancer.

128. The method of claim 127, wherein the second anti-cancer agent is a MEK inhibitor.

129. The method of any one of claims 126-128, wherein the cancer is an adenocarcinoma, melanoma, carcinoma, or neuroblastoma.

130. The method of any one of claims 126-128, wherein the cancer is breast cancer, lung cancer, pancreas cancer, cervical cancer, colorectal cancer, prostate cancer, gastric cancer, skin cancer, lung cancer, liver cancer, bile duct cancer, or nervous system cancer.

131. The method of any one of claims 126-128, wherein the cancer is breast adenocarcinoma, lung adenocarcinoma, pancreas adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, prostate adenocarcinoma, gastric adenocarcinoma, melanoma, lung squamous cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, glioblastoma, or neuroblastoma.

132. The method of any one of claims 126-128, wherein the cancer is non-small cell lung cancer (NSCLC), pancreatic cancer, or colorectal cancer.

133. The method of any one of claims 125-133, wherein the subject is a human.

134. A method of inhibiting ERK5 activity, comprising contacting ERK5 with an effective amount of a compound of any one of claims 1-80 or 82-123 to inhibit ERK5 activity.

135. The method of any one of claims 125-134, wherein the compound is a compound of any one of claims 1-80.

136. The method of any one of claims 125-134, wherein the compound is a compound of any one of claims 82-123.

137. Use of a compound of any one of claims 1-80 or 82-123 or the pharmaceutical composition of claim 81 or 124 for the treatment of a disorder mediated by ERK5.

138. The use of claim 137, wherein the disorder is cancer.

139. Use of (i) a compound of any one of claims 1-80 or 82-123 or the pharmaceutical composition of claim 81 or 124 and (ii) a second anti-cancer agent, for the treatment of cancer.

140. The use of claim 139, wherein the second anti-cancer agent is a MEK inhibitor.

141. The use of any one of claims 138-140, wherein the cancer is a melanoma, carcinoma, or neuroblastoma.

142. The use of any one of claims 138-140, wherein the cancer is breast cancer, lung cancer, pancreas cancer, cervical cancer, colorectal cancer, prostate cancer, gastric cancer, skin cancer, liver cancer, bile duct cancer, or nervous system cancer.

143. The use of any one of claims 138-140, wherein the cancer is breast adenocarcinoma, lung adenocarcinoma, pancreas adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, prostate adenocarcinoma, gastric adenocarcinoma, melanoma, lung squamous cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, glioblastoma, or neuroblastoma.

144. The use of any one of claims 138-140, wherein the cancer is non-small cell lung cancer (NSCLC), pancreatic cancer, or colorectal cancer.

Figure 1.

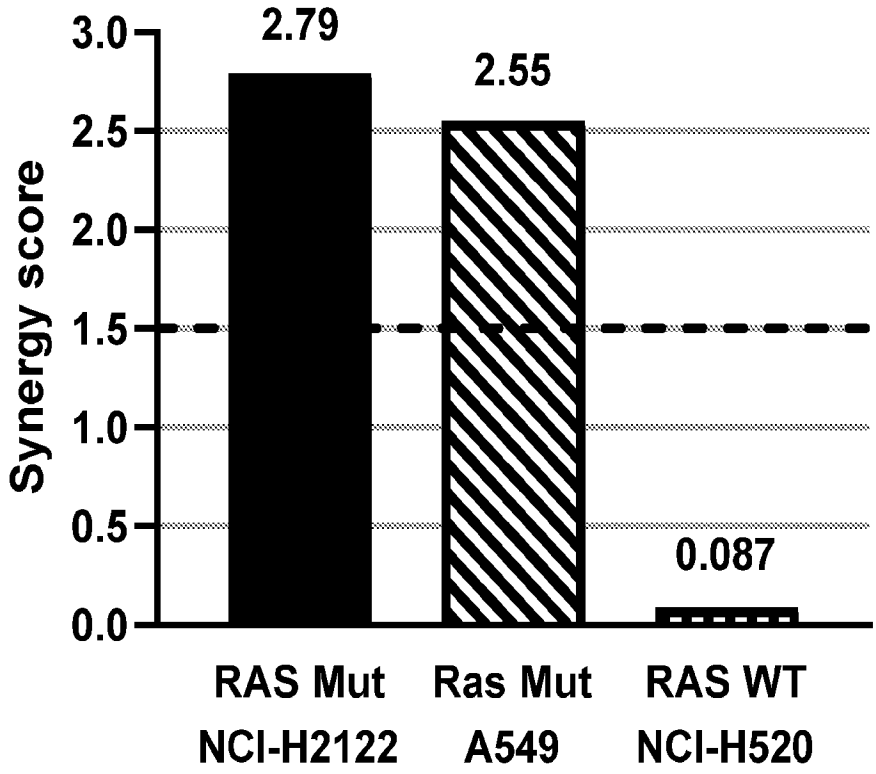

Synergy score
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.79
2.55
0.087
RAS Mut
NCI-H2122
Ras Mut
A549
RAS WT
NCI-H520

Figure 2.

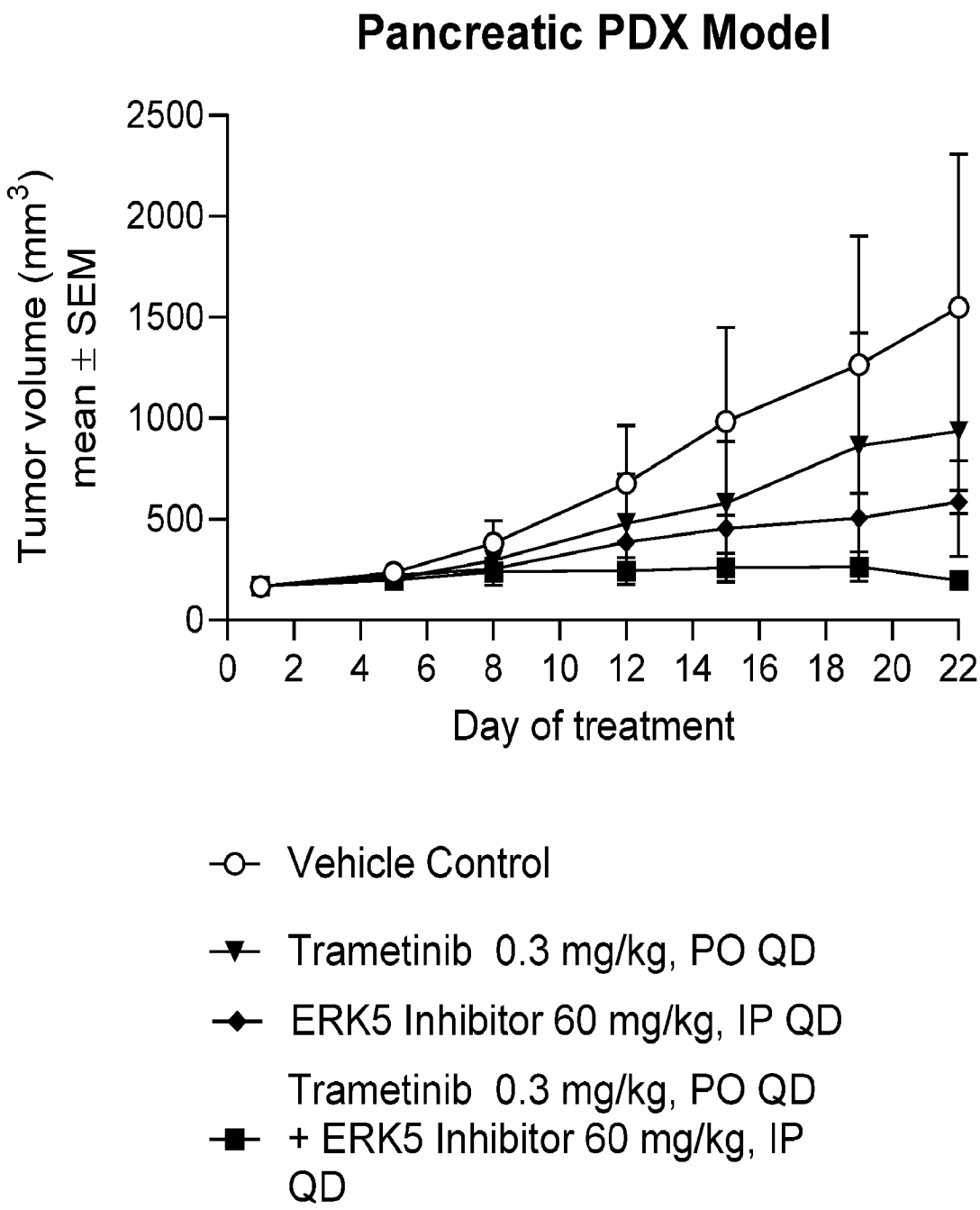
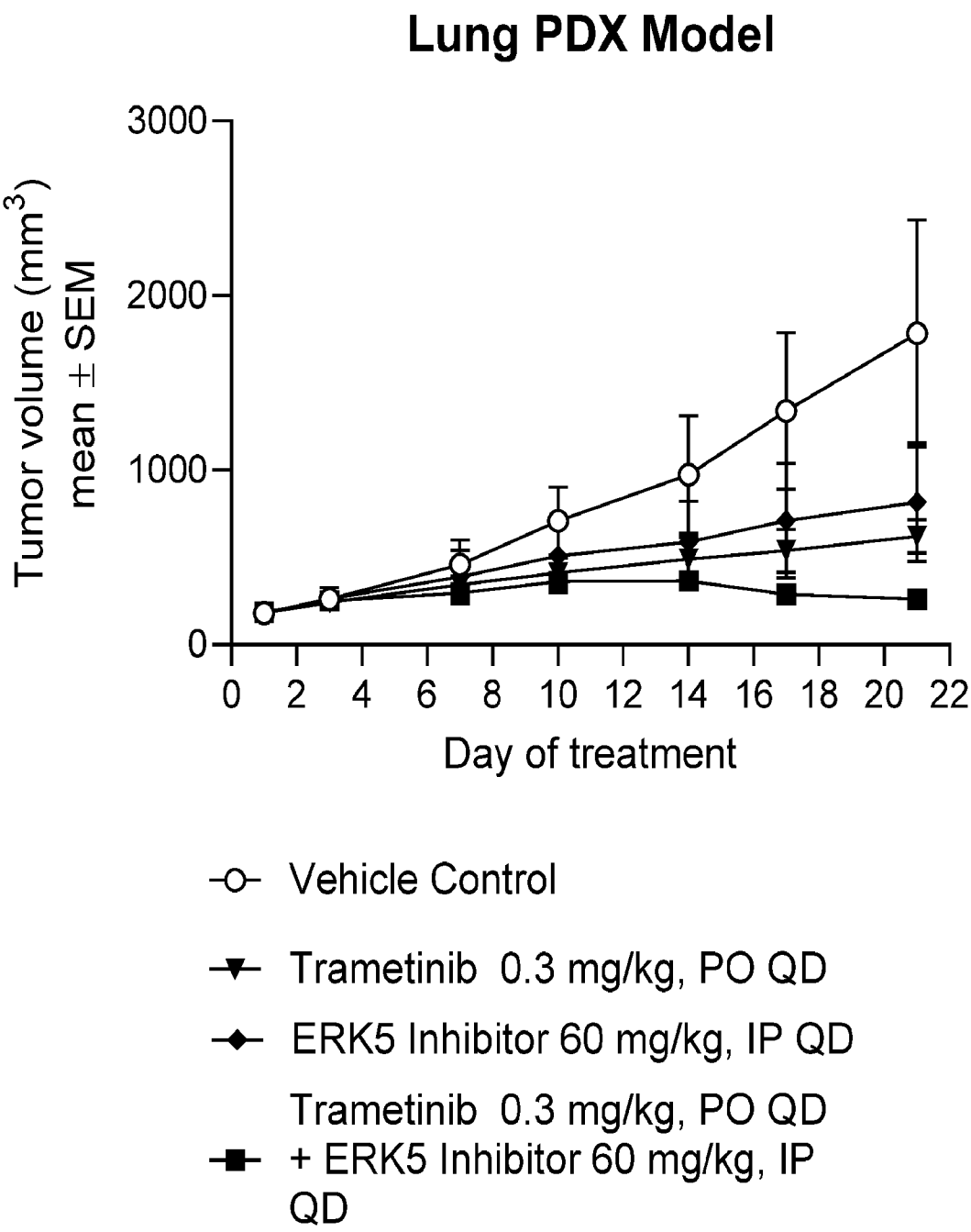

Pancreatic PDX Model
Tumor volume (mm3) mean ± SEM
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22
Day of treatment
Vehicle Control
Trametinib 0.3 mg/kg, PO QD
ERK5 Inhibitor 60 mg/kg, IP QD
Trametinib 0.3 mg/kg, PO QD + ERK5 Inhibitor 60 mg/kg, IP QD

Figure 3.


Lung PDX Model
Tumor volume (mm^3) mean ± SEM
3000
2000
1000
0
0 2 4 6 8 10 12 14 16 18 20 22
Day of treatment
Vehicle Control
Trametinib 0.3 mg/kg, PO QD
ERK5 Inhibitor 60 mg/kg, IP QD
Trametinib 0.3 mg/kg, PO QD + ERK5 Inhibitor 60 mg/kg, IP QD

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/048968

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04 (2006.01) C07D 239/74 (2006.01) C07D 249/14 (2006.01) C07D 277/40 (2006.01) C07D 295/13 (2006.01) C07D 333/34 (2006.01) C07D 333/62 (2006.01) C07D 513/04 (2006.01) A61K 31/498 (2006.01) A61K 31/4985 (2006.01) A61K 31/5375 (2006.01) A61K 31/538 (2006.01) A61K 31/55 (2006.01) A61P 35/00 (2006.01)

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)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN (Registry/CAPlus): Substructure search based upon formulas (I), (II), (I-A), (II-A), (III) of claims 1-78, and formulas (I), (I-A), (I-A1) of claims 82-121.

Database DOCDB and DWPI: Applicant/Inventor search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"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 establish the publication date of another citation or other special reason (as specified)

"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	Date of mailing of the international search report
4 November 2021	04 November 2021

Name and mailing address of the ISA/AU

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Telephone No. +61262832070

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/US2021/048968
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/170543 A1 (BAYER AKTIENGESELLSCHAFT ET AL) 12 September 2019 Abstract, 3rd paragraph page 4, compound of example 81 page 121, compound of example 23 page 64, page 125-129, lines 26-28 page 35, pages 36, 42-43, Formula (I)	10-11, 14-15, 17, 20-23, 42-52, 54-56, 81, 125-135, 137-144
X	Nguyen, D. et al., 'Discovery and Characterization of the Potent and Highly Selective (Piperidin-4-yl)pyrido[3,2-d]pyrimidine Based in Vitro Probe BAY885 for the Kinase ERK5', Journal of Medicinal Chemistry. 2019, vol.62, pages 928-940 Tables 1-5, Introduction 2nd paragraph, Cellular Assays page 931, compound 16 in table 2, Introduction page 928	10-11, 14-17, 20-23, 42, 44-52, 54-56, 81, 125-126, 129-135, 137-138, 141-144
X	WO 2019/043372 A1 (E-THERAPEUTICS PLC) 07 March 2019 Compound 71 page 159, abstract, pages 69, 72, 28	82-83, 89, 91-92, 98, 106-107, 109, 112-113, 116, 121, 124, 127, 129-133, 136, 139, 141-144
X	WO 2016/077375 A1 (GENENTECH, INC. ET AL) 19 May 2016 Second compound in row 2 on page 235, pages 57, 58-61, 51	82-83, 89-92, 98, 106-107, 109, 117-118, 121, 124, 127, 129-133, 136, 139, 141-144
X	WO 2011/135276 A1 (THE UNIVERSITY OF EDINBURGH) 03 November 2011 Compounds XX-23 and XX-21 page 64	82-84, 87, 90-92, 97, 106-110, 117, 121, 124
X	Sakai, H. et al., 'Cross-Electrophile Coupling of Unactivated Alkyl Chlorides', Journal of the American Chemical Society. 2020, vol.142, pages 11691-11697 Compound 42 page 11694	82-83, 87, 89-92, 98, 107, 110, 112, 117, 121
X	EP 3456716 A1 (NIPPON SODA CO., LTD.) 20 March 2019 Compound 1-210 on page 44	82-83, 90-92, 98, 106-107, 109, 117, 124
X	WO 2006/117669 A1 (PFIZER INC.) 09 November 2006 Compound 83 on page 61, pages 22-23, 31	82-83, 89-92, 98, 107, 110, 112, 116, 121, 124, 127-133, 136, 139-144
X	CAS Registry Number 2395297-79-5; Entry Date 2019-12-20; (2-aminopyrazolo[1,5-a]pyridin-3-yl)[4-(4-pyrimidinyl)-1-piperidinyl]-methanone Whole citation	82-83, 89-92, 98, 106-107, 109, 111-115, 117, 121
X	CAS Registry Number 2096263-96-4; Entry Date 2017-05-19; 4-[1-(1H-imidazol-5-ylcarbonyl)-4-piperidinyl]-2-methyl-N-propyl-5-pyrimidinecarboxamide Whole citation	82-83, 87-88, 90-92, 98, 101, 110, 117
X	CAS Registry Number 2096042-00-9; Entry Date 2017-05-19; 2-methyl-N-phenyl-4-[1-(1H-pyrazol-4-ylcarbonyl)-4-piperidinyl]-5-pyrimidinecarboxamide Whole citation	82-83, 87-88, 90-92, 98, 103-104, 110, 117

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/US2021/048968**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

Supplemental Box

Continuation of **Box II**

Claims 79-80 and 122-123 do not comply with Rule 6.2(a) because they rely on references to the description.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/048968

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:

the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **79-80, 122-123**

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:

See Supplemental Box

3. ☐ Claims Nos:

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:

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.:

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.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2021/048968**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2019/170543 A1	12 September 2019	WO 2019170543 A1	12 Sep 2019
		AU 2019232437 A1	08 Oct 2020
		CA 3093189 A1	12 Sep 2019
		EP 3762379 A1	13 Jan 2021
		JP 2021515767 A	24 Jun 2021
		US 2021017174 A1	21 Jan 2021
WO 2019/043372 A1	07 March 2019	WO 2019043372 A1	07 Mar 2019
WO 2016/077375 A1	19 May 2016	WO 2016077375 A1	19 May 2016
		CN 107108613 A	29 Aug 2017
		CN 107108613 B	25 Feb 2020
		EP 3218376 A1	20 Sep 2017
		EP 3218376 B1	25 Dec 2019
		HK 1243072 A1	06 Jul 2018
		JP 2017533250 A	09 Nov 2017
		JP 6639497 B2	05 Feb 2020
		US 2017340604 A1	30 Nov 2017
		US 10258603 B2	16 Apr 2019
WO 2011/135276 A1	03 November 2011	WO 2011135276 A1	03 Nov 2011
		AU 2011247116 A1	22 Nov 2012
		AU 2011247116 B2	03 Dec 2015
		BR 112012027640 A2	08 Aug 2017
		BR 112012027640 B1	03 Aug 2021
		CA 2796297 A1	03 Nov 2011
		CN 102947295 A	27 Feb 2013
		CN 102947295 B	20 Jan 2016
		EP 2563780 A1	06 Mar 2013
		EP 2563780 B1	06 May 2015
		IL 222417 A	31 Aug 2016
		JP 2013527162 A	27 Jun 2013
		JP 5899202 B2	06 Apr 2016
		KR 20130079379 A	10 Jul 2013
		KR 101714820 B1	09 Mar 2017

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2021/048968**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		MX 2012012413 A	26 Feb 2013
		MX 344142 B	07 Dec 2016
		RU 2012143502 A	10 Jun 2014
		US 2013123268 A1	16 May 2013
		US 9365564 B2	14 Jun 2016
		US 2016251346 A1	01 Sep 2016
		US 9834549 B2	05 Dec 2017
EP 3456716 A1	20 March 2019	EP 3456716 A1	20 Mar 2019
		JP WO2017195703 A1	14 Feb 2019
		JP 6710273 B2	17 Jun 2020
		US 2019191702 A1	27 Jun 2019
		WO 2017195703 A1	16 Nov 2017
WO 2006/117669 A1	09 November 2006	WO 2006117669 A1	09 Nov 2006
		WO 2006117669 B1	11 Jan 2007
		CA 2605985 A1	09 Nov 2006
		EP 1879863 A1	23 Jan 2008
		JP 2008540395 A	20 Nov 2008
		US 2009215742 A1	27 Aug 2009

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.