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(54) Title: IRAK DEGRADERS AND USES THEREOF

(57) Abstract: The present invention provides compounds, compositions thereof, and methods of using the same.

IRAK DEGRADERS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Appl. No. 63/380,925, filed October 25, 2022, the entirety of which, is herein incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds and methods useful for the modulation of one or more interleukin-1 receptor-associated kinases ("IRAK") via ubiquitination and/or degradation by compounds according to the present invention. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] Ubiquitin-Proteasome Pathway (UPP) or Ubiquitin-Proteasome System (UPS) is a critical pathway that regulates key regulator proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, it leads to pathogenesis of a variety of diseases. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases.

[0004] Cullin RING E3 ligases (CRLs) are the largest family of E3 ubiquitin ligases. In the CRL ligase complexes, cullin serves as a scaffold to bind small RING finger protein ROC1 or ROC2 (RBX1 or RBX2) through a C-terminal domain and a linker-substrate receptor dimer or a substrate receptor directly through an N-terminal domain. Mammalian cells express nine distinct cullins, including two cullin 4 (CUL4) proteins: CUL4A and CUL4B, which use DNA damage-binding protein 1 (DDB1) as the linker. DDB1 bridges the interaction between CUL4 and a subset of DDB1 binding WD40 repeat proteins (DWD or DCAFs for DDB1 cullin associated factors). These DCAF proteins function as substrate receptors to target specific substrates to the CRL4 E3 complexes. One of the most abundant DCAF proteins is DDB1- and CUL4-associated factor 1 or DCAF1 (also known as VprBP).

[0005] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a

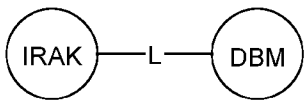
protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0006] An ongoing need exists in the art for effective treatments for disease, especially cancer. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage DCAF1 E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases ("IRAK") hold promise as therapeutic agents. Accordingly, there remains a need to find bifunctional compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0007] The present application relates novel bifunctional compounds, which function to recruit IRAK kinases to DCAF1 E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of IRAK kinases, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of IRAK kinases. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer.

[0008] The present application further relates to bifunctional molecules, including bifunctional molecules that link a DCAF1-binding moiety to a ligand that binds IRAK kinases that are effective for the modulation of targeted ubiquitination. Such compounds have the general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein,

IRAK is a IRAK binding moiety capable of binding to IRAK protein, such as IRAK4;

L is a bivalent moiety that connects IRAK to DBM; and

DBM is a DCAF binding moiety capable of binding to DCAF1 protein.

[0009] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling

pathways implicating IRAK kinases. Such diseases, disorders, or conditions include those described herein.

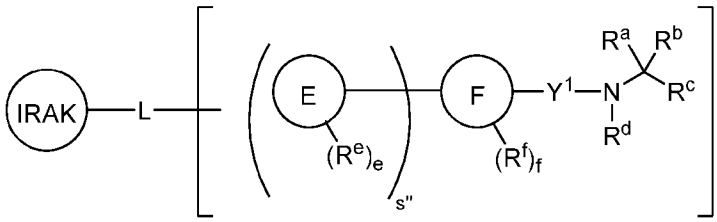
[0010] Compounds provided by this invention are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators of kinases, signaling pathways, and cytokine levels *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

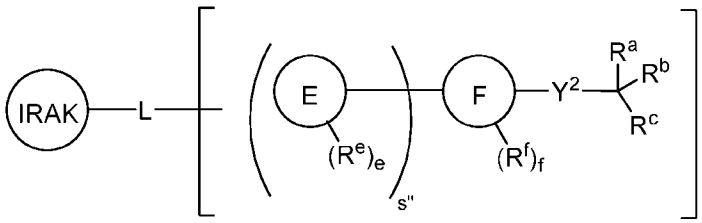
1. General Description of Certain Embodiments of the Invention:

[0011] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of one or more IRAK protein kinases. In some embodiments, a provided compound degrades and/or inhibits IRAK4.

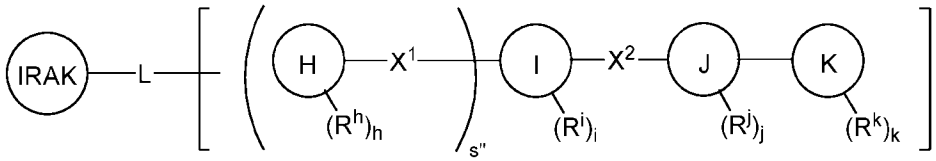
[0012] In certain embodiments, the present invention provides a compound of formula **I** as a compound of any one of the following formulae:



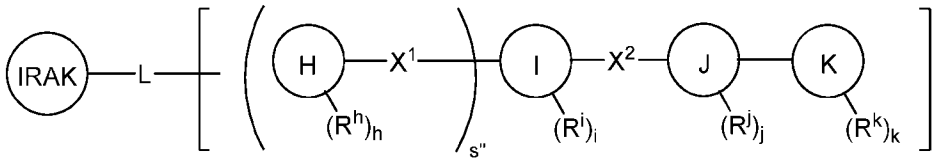
I-a



I-a'



I-b



I-b'

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined and described herein.

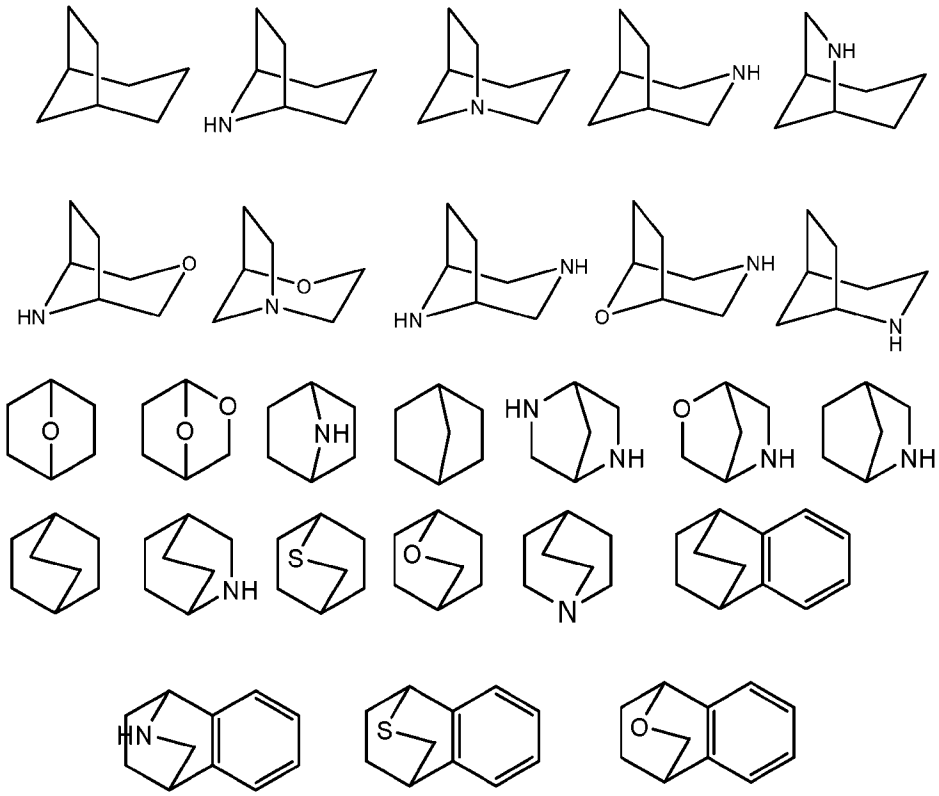
2. Compounds and Definitions:

[0013] 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. 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.

[0014] 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 "carbocycle," "cycloaliphatic" or "cycloalkyl"), 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" (or "carbocycle" or "cycloalkyl") 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.

[0015] 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, and 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 bridged bicyclics include:



[0016] 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.

[0017] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[0018] 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)).

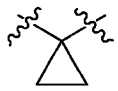
[0019] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0024] The term "halogen" means F, Cl, Br, or I.

[0025] 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.

[0026] 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 the radical or point of attachment is on the heteroaromatic ring. 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, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. 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.

[0027] 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).

[0028] 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, 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.

[0029] 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.

[0030] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted" 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.

[0031] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently 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; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene)$O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene)$C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and 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, and 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, and sulfur, which may be substituted as defined below.

[0032] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, -(haloR•), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; -O(haloR•), –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•, $-(C_{1-4}$ straight or branched alkylene)$C(O)OR^\bullet$, or -SSR• wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and 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, and sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0033] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, –

$O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0034] Suitable substituents on the aliphatic group of R^* include 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 unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently 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, and sulfur.

[0035] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or, notwithstanding the definition above, 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, and sulfur.

[0036] Suitable substituents on the aliphatic group of $R^\dagger$ are independently 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 unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently 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, and sulfur.

[0037] As used herein, the term "provided compound" refers to any genus, subgenus, and/or species set forth herein.

[0038] 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.

[0039] 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.

[0040] 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, and R_a (or M) and S_a (or P) atropisomers. 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

[0041] As used herein, the term "inhibitor" is defined as a compound that binds to and /or inhibits an IRAK kinase with measurable affinity. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of 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.

[0042] As used herein, the term "degrader" is defined as a heterobifunctional compound that binds to and /or inhibits both an IRAK kinase and an E3 ligase with measurable affinity resulting in the ubiqitination and subsequent degradation of the IRAK kinase. In certain embodiments, a degrader has an DC_{50} of 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.

[0043] A compound of the present invention may be tethered to a detectable moiety. It will be appreciated that such compounds are useful as imaging agents. One of ordinary skill in the art will recognize that a detectable moiety may be attached to a provided compound *via* a suitable substituent. As used herein, the term "suitable substituent" refers to a moiety that is capable of covalent attachment to a detectable moiety. Such moieties are well known to one of ordinary skill in the art and include groups containing, e.g., a carboxylate moiety, an amino moiety, a thiol moiety, or a hydroxyl moiety, to name but a few. It will be appreciated that such moieties may be directly attached to a provided compound or *via* a tethering group, such as a bivalent saturated or unsaturated hydrocarbon chain. In some embodiments, such moieties may be attached via click chemistry. In some embodiments, such moieties may be attached via a 1,3-cycloaddition of an azide with an alkyne, optionally in the presence of a copper catalyst. Methods of using click chemistry are known in the art and include those described by Rostovtsev *et al.*, Angew. Chem. Int. Ed. 2002, 41:2596-99 and Sun *et al.*, Bioconjugate Chem., 2006, 17:52-57.

[0044] As used herein, the term "detectable moiety" is used interchangeably with the term "label" and relates to any moiety capable of being detected, e.g., primary labels and secondary labels. Primary labels, such as radioisotopes (e.g., tritium, ^{32}P, ^{33}P, ^{35}S, or ^{14}C), mass-tags, and fluorescent labels are signal generating reporter groups which can be detected without further modifications. Detectable moieties also include luminescent and phosphorescent groups.

[0045] The term "secondary label" as used herein refers to moieties such as biotin and various protein antigens that require the presence of a second intermediate for production of a detectable signal. For biotin, the secondary intermediate may include streptavidin-enzyme conjugates. For antigen labels, secondary intermediates may include antibody-enzyme conjugates. Some fluorescent groups act as secondary labels because they transfer energy to another group in the process of nonradiative fluorescent resonance energy transfer (FRET), and the second group produces the detected signal.

[0046] The terms "fluorescent label", "fluorescent dye", and "fluorophore" as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY

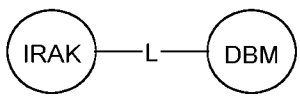
576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD 800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine (TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X.

[0047] The term "mass-tag" as used herein refers to any moiety that is capable of being uniquely detected by virtue of its mass using mass spectrometry (MS) detection techniques. Examples of mass-tags include electrophore release tags such as N-[3-[4`-[(p-Methoxytetrafluorobenzyl)oxy]phenyl]-3-methylglyceronyl]isonipecotic Acid, 4`-[2,3,5,6-Tetrafluoro-4-(pentafluorophenoxyl)]methyl acetophenone, and their derivatives. The synthesis and utility of these mass-tags is described in United States Patents 4,650,750, 4,709,016, 5,360,8191, 5,516,931, 5,602,273, 5,604,104, 5,610,020, and 5,650,270. Other examples of mass-tags include, but are not limited to, nucleotides, dideoxynucleotides, oligonucleotides of varying length and base composition, oligopeptides, oligosaccharides, and other synthetic polymers of varying length and monomer composition. A large variety of organic molecules, both neutral and charged (biomolecules or synthetic compounds) of an appropriate mass range (100-2000 Daltons) may also be used as mass-tags.

[0048] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change in an IRAK protein kinase activity between a sample comprising a compound of the present invention, or composition thereof, and an IRAK protein kinase, and an equivalent sample comprising an IRAK protein kinase, in the absence of said compound, or composition thereof.

3. Description of Exemplary Embodiments:

[0049] The compounds of the present application include bifunctional molecules that link a DCAF binding moiety to a ligand that binds IRAK kinases having the following general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein,

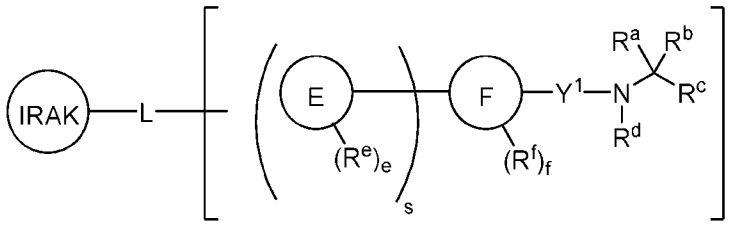
IRAK is a IRAK binding moiety capable of binding to IRAK protein, such as IRAK4;

L is a bivalent moiety that connects IRAK to DBM; and

DBM is a DCAF binding moiety capable of binding to DCAF1 protein.

DCAF1 Binding Moiety (DBM)

[0050] As described above and in certain embodiments, the present invention provides a compound of formula **I-a**:



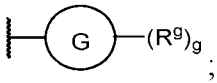
I-a

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined and described herein, and wherein:

Ring E is phenyl, a 4-7 membered partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring F is phenylenyl, a 4-10 membered partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, -S(O)-, or $-S(O)_2-$;

R^a is an optionally substituted C_{1-6} aliphatic or 

;

Ring G is phenyl, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^b is hydrogen, an optionally substituted C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur, or:

R^a and R^b are optionally taken together with their intervening atoms to form an optionally substituted 9-10 membered saturated or partially unsaturated bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

when Y^1 is -C(NR)-, R^b is optionally taken together with R of -C(NR)- with their intervening atoms

to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 nitrogen atoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur;

R^c is $-CR_2CONR_2$, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^d is hydrogen, or:

when R^c is $-CR_2CONR_2$, R^d is optionally taken together with a single R of $-CR_2CONR_2$ with their intervening atoms to form a 5-7 membered saturated or partially unsaturated heterocyclyl with 0-3 heteroatoms, in addition to the nitrogen atom to which R^d is attached, independently selected from nitrogen, oxygen, and sulfur;

R^e, R^f, and R^g are each independently selected from hydrogen, oxo, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$;

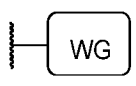
each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

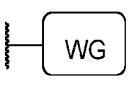
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

s is 0 or 1; and

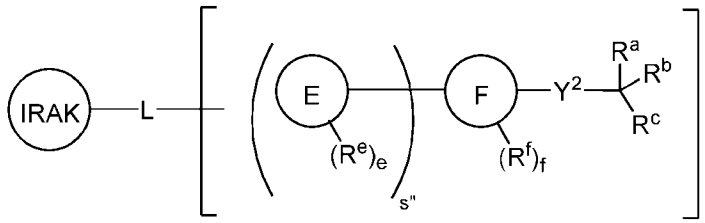
each of e, f, and g are independently 0, 1, 2, 3, or 4;

wherein said compound of formula **I-a** is optionally substituted with 

, and wherein 

is a warhead group.

[0051] As described above and in certain embodiments, the present invention provides a compound of formula **I** as a compound of formula **I-a'**:



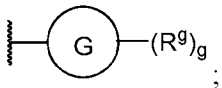
I-a'

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined and described herein, and wherein:

Ring E is phenyl, naphthyl, a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring F is phenyl, a 4-11 membered partially unsaturated monocyclic or bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Y^2 is a C_{1-4} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, $-S(O)-$, $-S(O)_2-$, -C(OR)=N-, $-N(R^d)-$, or -O-;

R^a is hydrogen, an optionally substituted C_{1-6} aliphatic, or 

;

Ring G is phenyl, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^b is hydrogen, an optionally substituted C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur, or:

R^a and R^b are taken together with their intervening atoms to form an optionally substituted 9-10 membered saturated or partially unsaturated bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

when Y^1 is -C(NR)-, R^b is taken together with R of -C(NR)- with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 heteroatoms within the heterocyclyl, independently selected from nitrogen, oxygen, and

sulfur;

R^c is halogen, -CN, -CFR_2, -CF_2R, -CF_3, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)(NR)R, -S(O)R, -C(O)R, -CR=NOR, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, -$P(O)R_2$, -$P(O)(OR)_2$, -$P(O)(OR)NR_2$, -$P(O)(NR_2)_2$, -CR_2CN, -CR_2CFR_2, -CR_2CF_2R, -CR_2CF_3, -CR_2NO_2, -CR_2OR, -CR_2SR, -CR_2NR_2, -CR_2SiR_3, -$CR_2S(O)_2R$, -$CR_2S(O)_2NR_2$, -$CR_2S(O)(NR)R$, -$CR_2S(O)R$, -$CR_2C(O)R$, -CR_2CR=NOR, -$CR_2C(O)OR$, -$CR_2C(O)NR_2$, -$CR_2C(O)NROR$, -$CR_2C(NOR)R$, -$CR_2OC(O)R$, -$CR_2OC(O)NR_2$, -$CR_2OP(O)R_2$, -$CR_2OP(O)(OR)_2$, -$CR_2OP(O)(OR)NR_2$, -$CR_2OP(O)(NR_2)_2$, -$CR_2NRC(O)OR$, -$CR_2NRC(O)R$, -$CR_2NRC(O)N(R)_2$, -$CR_2NRS(O)_2R$, -$CR_2NP(O)R_2$, -$CR_2NRP(O)(OR)_2$, -$CR_2NRP(O)(OR)NR_2$, -$CR_2NRP(O)(NR_2)_2$, -$CR_2P(O)R_2$, -$CR_2P(O)(OR)_2$, -$CR_2P(O)(OR)NR_2$, -$CR_2P(O)(NR_2)_2$, -CR_2CR_2CN, -$CR_2CR_2CFR_2$, -$CR_2CR_2CF_2R$, -$CR_2CR_2CF_3$, -$CR_2CR_2NO_2$, -CR_2CR_2OR, -CR_2CR_2SR, -$CR_2CR_2NR_2$, -$CR_2CR_2SiR_3$, -$CR_2CR_2S(O)_2R$, -$CR_2CR_2S(O)_2NR_2$, -$CR_2CR_2S(O)(NR)R$, -$CR_2CR_2S(O)R$, -$CR_2CRC(O)R$, -CR_2CR_2CR=NOR, -$CR_2CR_2C(O)OR$, -$CR_2CR_2C(O)NR_2$, -$CR_2CR_2C(O)NROR$, -$CR_2CR_2C(NOR)R$, -$CR_2CR_2OC(O)R$, -$CR_2CR_2OC(O)NR_2$, -$CR_2CR_2OP(O)R_2$, -$CR_2CR_2OP(O)(OR)_2$, -$CR_2CR_2OP(O)(OR)NR_2$, -$CR_2CR_2OP(O)(NR_2)_2$, -$CR_2CR_2NRC(O)OR$, -$CR_2CR_2NRC(O)R$, -$CR_2CR_2NRC(O)N(R)_2$, -$CR_2CR_2NRS(O)_2R$, -$CR_2CR_2NP(O)R_2$, -$CR_2CR_2NRP(O)(OR)_2$, -$CR_2CR_2NRP(O)(OR)NR_2$, -$CR_2CR_2NRP(O)(NR_2)_2$, -$CR_2CR_2P(O)R_2$, -$CR_2CR_2P(O)(OR)_2$, -$CR_2CR_2P(O)(OR)NR_2$, -$CR_2CR_2P(O)(NR_2)_2$, -$CR_2CR(OR)CR_2OR$, or an optionally substituted group selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or:

–$(CR_2)_{1-2}$-X^a, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or:

-$(CR_2)_{0-2}C(O)R^{cc}$ or -$(CR_2)_{0-2}S(O)_{0-2}R^{cc}$; or:

R^b and R^c are taken together with their intervening atoms to form an optionally substituted 4-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or:

R^a is absent and R^b and R^c are taken together with their intervening atoms to form an optionally

substituted phenyl;

R^d is hydrogen or an optionally substituted C_{1-6} aliphatic, or:

when R^c is $-CR_2CONR_2$, R^d is taken together with a single R of $-CR_2CONR_2$ with their intervening atoms to form a 5-7 membered saturated or partially unsaturated heterocyclyl with 0-3 heteroatoms, in addition to the nitrogen atom to which R^d is attached, independently selected from nitrogen, oxygen, and sulfur;

R^e, R^f, and R^g are each independently selected from hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

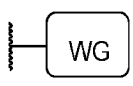
R^{cc} is R^A, halogen, -CN, -OR, -SR, $-NR_2$, -NROR, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$;

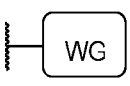
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, naphthyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom, or on different atoms, are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

s is 0 or 1; and

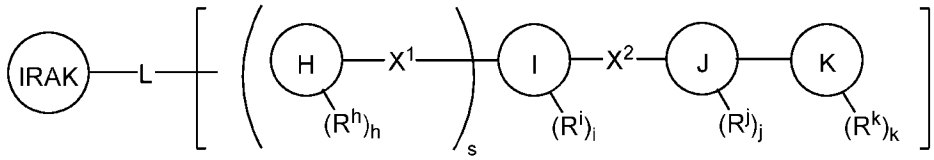
each of e, f, and g are independently 0, 1, 2, 3, or 4;

wherein said compound of formula **I-a'** is optionally substituted with 

, and wherein 

is a warhead group.

[0052] As described above and in certain embodiments, the present invention provides a compound of formula **I-b**:



I-b

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined and described herein, and wherein:

Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring I is phenylenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring J is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring K is phenyl, naphthyl, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-13 membered monocyclic, bicyclic, or tricyclic heteroarylenyl with 1-5 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^h, R^i, R^j, and R^k are each independently selected from hydrogen, oxo, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$, or:

an R^i group on Ring I and an R^j group or Ring J are optionally taken together with their intervening atoms to form a 5-8 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2

heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

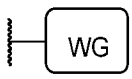
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

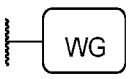
two R groups on the same atom are optionally taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each of X^1 and X^2 is independently a covalent bond, spiro-fusion between the two rings that X^1 or X^2 connect, $-CR_2-$, $-CR(OR)-$, $-CRF-$, $-CF_2-$, $-NR-$, $-O-$, $-S-$, or $-S(O)_2-$;

s is 0 or 1; and

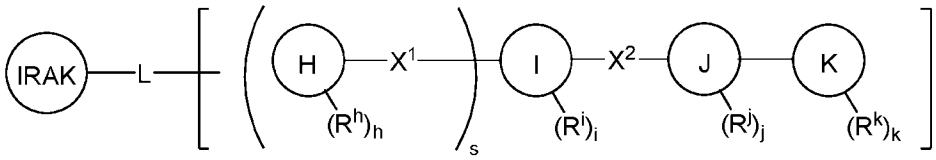
each of w, x, y, and z are independently 0, 1, 2, 3, or 4;

wherein said compound of formula **I-b** is optionally substituted with 

, and wherein 

is a warhead group.

[0053] As described above and in certain embodiments, the present invention provides a compound of formula **I** as a compound of formula **I-b'**:



I-b'

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined and described herein, and wherein:

Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring I is phenylenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic

heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring J is phenylenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring K is phenyl, naphthyl, a 3-7 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-13 membered monocyclic, bicyclic, or tricyclic heteroarylenyl with 1-5 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^h, R^i, R^j, and R^k are each independently selected from hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, -$P(O)R_2$, -$P(O)(OR)_2$, -$P(O)(OR)NR_2$, and -$P(O)(NR_2)_2$, or:

an R^i group on Ring I and an R^j group or Ring J are optionally taken together with their intervening atoms to form a 5-8 membered saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

an R^j group on Ring J and an R^k group or Ring K are optionally taken together with their intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, naphthyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom, or on different atoms, are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are

attached, independently selected from nitrogen, oxygen, and sulfur;

each of X^1 and X^2 are independently a covalent bond, spiro-fusion between the two rings that X^1 or X^2 connect, or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, $-CR(OR)-$, $-CRF-$, $-CF_2-$, $-C(NR)-$, $-C(O)-$, $-O-$, $-N(R)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

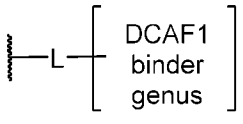
s is 0 or 1; and

each of w, x, y, and z are independently 0, 1, 2, 3, or 4;

wherein said compound of formula **I-b'** is optionally substituted with

, and wherein

is a warhead group.

[0054] As defined herein and described below, wherein a formula is depicted using square brackets, e.g., 

, L is attached to a modifiable carbon, oxygen, or nitrogen atom within the referenced DCAF1 binder genus including substitution on or replacement of a defined variable within the referenced DCAF1 binder genus.

[0055] As described above and defined herein, Ring E is phenyl, naphthyl, a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0056] In some embodiments, Ring E is phenyl. In some embodiments, Ring E is naphthyl. In some embodiments, Ring E is a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic carbocyclyl. In some embodiments, Ring E is a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring E is a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0057] In some embodiments, Ring E is phenyl, naphthyl, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0058] In some embodiments, Ring E is phenyl or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0059] In some embodiments, Ring E is phenyl or a 5-6 membered monocyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0060] In some embodiments, Ring E is phenyl or a 5-6-membered heteroaryl with 1-2 heteroatoms

independently selected from nitrogen, oxygen and sulfur.

[0061] In some embodiments, Ring E is cyclobutyl, azetinyl, cyclohexyl, cyclohexenyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, pyrrolidinyl, imidazolyl, 4,5-dihydro-1H-pyrazolyl, piperidinyl, phenyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, 2,3-dihydro-1H-indenyl, indolyl, benzoimidazolyl, pyrazolo[1,5-a]pyridyl, [1,2,4]triazolo[1,5-a]pyridyl, bicyclo[2.2.2]octane, or naphthyl.

[0062] In some embodiments, Ring E is as depicted in the compounds of **Table 1**, below.

[0063] As described above and defined herein, Ring F is phenylenyl, a 4-11 membered partially unsaturated monocyclic or bicyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;.

[0064] In some embodiments, Ring F is phenylenyl. In some embodiments, Ring F is a 4-11 membered partially unsaturated monocyclic or bicyclic carbocyclylenyl. In some embodiments, Ring F is a 4-11 membered partially unsaturated monocyclic or bicyclic heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring F is a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0065] In some embodiments, Ring F is phenyl or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0066] In some embodiments, F is phenyl or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0067] In some embodiments, Ring F is a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0068] In some embodiments, Ring F is a 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0069] In some embodiments, Ring F is a 5-membered heteroaryl with 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0070] In some embodiments, Ring F is a 5-membered heteroaryl with 1-2 nitrogen heteroatoms.

[0071] In some embodiments, Ring F is cyclobutylenyl, azetinylenyl, cyclopentylenyl cyclohexylenyl, phenylenyl, pyrrolylenyl, imidazolylenyl, pyrazolylenyl, isoxazolylenyl, thiophenylenyl, 2,5-dihydro-1H-pyrrolylenyl, 1,2,3-triazolylenyl, 1,2,4-triazolylenyl, 1,2-dihydro-3H-pyrazol-3-onylenyl, thiazolylenyl, pyridylenyl, indazolylenyl, 1,2,3,6-tetrahydropyridinylenyl, benzoimidazolylenyl, 3,4-dihydroquinolinylenyl, 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridylenyl, 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepanylenyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidinylenyl, 1,3,4,5-

tetrahydro-2H-benzo[b][1,4]diazepin-2-onylenyl, or 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridylenyl.

[0072] In some embodiments, Ring F is as depicted in the compounds of **Table 1**, below.

[0073] As described above and defined herein, Ring G is phenyl, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0074] In some embodiments, Ring G is phenyl. In some embodiments, Ring G is a 5-7 membered saturated or partially unsaturated carbocyclyl. In some embodiments, Ring G is a 5-7 membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring G is a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0075] In some embodiments, Ring G is phenyl or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0076] In some embodiments, Ring G is phenyl or a 6-membered heteroaryl with 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0077] In some embodiments, Ring G is cyclohexyl, cyclohexenyl, isothiazolyl, phenyl, or pyridyl.

[0078] In some embodiments, Ring G is as depicted in the compounds of **Table 1**, below.

[0079] As described above and defined herein, Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0080] In some embodiments, Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl. In some embodiments, Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0081] In some embodiments, Ring H is a 3-7 membered saturated or partially unsaturated monocyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0082] In some embodiments, Ring H is a 6-membered saturated or partially unsaturated monocyclic heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0083] In some embodiments, Ring H is a 6-membered saturated monocyclic heterocyclyl with 1-2 heteroatoms independently selected from nitrogen and oxygen.

[0084] In some embodiments, Ring H is cyclopropyl, cyclobutyl, azetinyl, cyclopentyl, pyrrolidinyl, cyclohexyl, piperidinyl, piperazinyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-pyranyl, morpholinyl, piperzinyl, isoindolinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, azepanyl, 2-3-azabicyclo[3.2.2]nonanyl, azaspiro[3.3]heptanyl, 5-

azaspiro[2.5]octanyl, 2,7-diazaspiro[3.5]nonanyl, 3-azaspiro[5.5]undecanyl, 2-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, octahydrocyclopenta[c]pyrrolyl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, or 2-oxa-5-azabicyclo[2.2.2]octanyl.

[0085] In some embodiments, Ring H is as depicted in the compounds of **Table 1**, below.

[0086] As described above and defined herein, Ring I is phenylenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0087] In some embodiments, Ring I is phenylenyl. In some embodiments, Ring I is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl. In some embodiments, Ring I is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring I is a 5-10 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0088] In some embodiments, Ring I is phenyl or a 5-10 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0089] In some embodiments, Ring I is phenyl or a 5-6 membered monocyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0090] In some embodiments, Ring I is phenyl or a 6-membered monocyclic heteroaryl with 1-2 nitrogen heteroatoms.

[0091] In some embodiments, Ring I is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0092] In some embodiments, Ring I is a 3-11 membered saturated or partially unsaturated monocyclic or bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0093] In some embodiments, Ring I is a 9-membered saturated or partially unsaturated bicyclic heterocyclyl with 1-2 nitrogen heteroatoms.

[0094] In some embodiments, Ring I is cyclohexylenyl, phenylenyl, imidazolylenyl, pyrazolylenyl, oxazolylenyl, thiazolylenyl, 1,2-thiazinanylenyl, pyridylenyl, pyridazinylenyl, pyrimidinylenyl, indolinylenyl, 2,6-diazaspiro[3.5]nonanylenyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridylenyl, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridylenyl, 1H-pyrrolo[2,3-b]pyridylenyl, 7H-pyrrolo[2,3-d]pyrimidinylenyl, 1H-imidazo[4,5-b]pyridinylenyl, 3H-imidazo[4,5-b]pyridylenyl, 9H-purinylenyl, octahydro-1H-pyrrolo[3,2-

b]pyridinylenyl, decahydroisoquinolinylenyl, quinolinylenyl, isoquinolinylenyl, 3,4-dihydroquinoxalin-2(1H)-onylenyl, 1,2,3,4-tetrahydroquinoxalinylenyl, 1,2,3,4-tetrahydropyrido[2,3-b]pyrazinylenyl, 1,2,3,4-tetrahydro-1,8-naphthyridinylenyl, or 1,2,3,4-tetrahydro-1,6-naphthyridinylenyl.

[0095] In some embodiments, Ring I is as depicted in the compounds of **Table 1**, below.

[0096] As described above and defined herein, phenylenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0097] In some embodiments, Ring J is phenylenyl. In some embodiments, Ring J is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl. In some embodiments, Ring J is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring J is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0098] In some embodiments, Ring J is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0099] In some embodiments, Ring J is a 6-9 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 9-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00100] In some embodiments, Ring J is a 6-membered saturated monocyclic carbocyclyl or heterocyclyl with 1 nitrogen heteroatom.

[00101] In some embodiments, Ring J is a 9-membered saturated monocyclic heterocyclyl with 1-2 nitrogen heteroatoms.

[00102] In some embodiments, Ring J is a 10-membered bicyclic heteroaryl ring having 1-2 nitrogen heteroatoms.

[00103] In some embodiments, Ring J is cyclohexylenyl, azetidinylenyl, pyrrolidinylenyl, imidazolylenyl, thiazolylenyl, piperidinylenyl, piperzinylenyl, azepanylenyl, phenylenyl, pyridinylenyl, isoindolinyl, quinazolinylenyl, octahydro-1H-indolylenyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridylenyl, 8-azabicyclo[3.2.1]octanylenyl, 2-azabicyclo[3.2.1]octanylenyl, 2,7-diazaspiro[4.4]nonanylenyl, octahydropyrrolo[3,2-b]pyrrolylenyl, 2-azabicyclo[3.2.2]nonanylenyl, octahydro-1H-pyrrolo[3,2-b]pyridylenyl, octahydro-1H-pyrrolo[3,4-b]pyridinylenyl, decahydro-1,5-naphthyridinylenyl, 9-

azabicyclo[3.3.1]nonanylenyl, 5-azaspiro[3.5]nonanylenyl, 2-oxa-5-azaspiro[3.5]nonanylenyl, or 2,6-diazaspiro[3.5]nonanylenyl.

[00104] In some embodiments, Ring J is as depicted in the compounds of **Table 1**, below.

[00105] As described above and defined herein, Ring K is phenyl, naphthyl, a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-13 membered monocyclic, bicyclic, or tricyclic heteroaryl with 1-5 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00106] In some embodiments, Ring K is phenyl. In some embodiments, Ring K is naphthyl. In some embodiments, Ring K is a 3-7 membered saturated or partially unsaturated carbocyclyl. In some embodiments, Ring K is a 3-7 membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring K is a 9-10 membered saturated or partially unsaturated bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring K is a 5-13 membered monocyclic, bicyclic, or tricyclic heteroaryl with 1-5 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00107] In some embodiments, Ring K is phenyl, a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00108] In some embodiments, Ring K is phenyl or a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

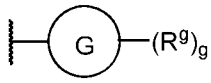
[00109] In some embodiments, Ring K is phenyl or a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00110] In some embodiments, Ring K is phenyl or a 6-membered saturated carbocyclyl or heterocyclyl with 1-2 nitrogen heteroatoms.

[00111] In some embodiments, Ring K is 1,2,3-triazolyl, thiazolyl, pyrazolyl, cyclohexyl, piperdinyl, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, 2,3-dihydro-1H-indenyl, purinyl, indazolyl, benzo[d]imidazoyl, benzo[d][1,3]dioxolyl, benzo[b]thiophenyl, benzo[d]isoxazolyl, benzo[d]isothiazolyl, pyrrolo[3,2-c]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyrimidinyl,

pyrrolo[2,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 2,3-dihydro-1H-pyrrolo[2,3-c]pyridinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, naphthyl, 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, quinolinyl, isoquinolinyl, isoquinolin-3(2H)-onyl, 1,6-naphthyridinyl, phthalazinyl, quinazolinyl, 2,7-naphthyridinyl, or tetrazolo[1,5-a]quinoxalinyl.

[00112] In some embodiments, Ring K is as depicted in the compounds of **Table 1**, below.

[00113] As described above and defined herein, R^a is hydrogen, an optionally substituted C_{1-6} aliphatic or 

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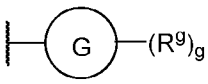
[00114] In some embodiments, R^a is hydrogen. In some embodiments, R^a is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^a is 

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[00115] In some embodiments, Ring R^a is methyl, -CH(Me)OH, benzyl, -CH_2tolyl, or -CH_2indolyl.

[00116] In some embodiments, Ring R^a is as depicted in the compounds of **Table 1**, below.

[00117] As described above and defined herein, R^b is hydrogen, an optionally substituted C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur, or R^a and R^b are optionally taken together with their intervening atoms to form an optionally substituted 9-10 membered saturated or partially unsaturated bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or when Y is -C(NR)-, R^b is optionally taken together with R of -C(NR)- with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 nitrogen atoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur.

[00118] In some embodiments, R^b is hydrogen. In some embodiments, R^b is hydrogen is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^b is hydrogen is phenyl. In some embodiments, R^b is hydrogen is a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R^a and R^b are optionally taken together with their intervening atoms to form an optionally substituted 9-10 membered saturated or partially unsaturated bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, when Y is -C(NR)-, R^b is optionally taken together with R of -C(NR)- with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 nitrogen atoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur.

[00119] In some embodiment, R^b is methyl, -CH(Me)OH, cyclopropyl, phenyl, -CO_2H, -CH_2cyclopropyl, -CH_2OH, -CH_2OMe, or -CH_2CO_2H.

[00120] In some embodiments, Ring R^b is as depicted in the compounds of **Table 1**, below.

[00121] As described above and defined herein, R^c is $-CO_2R$, $-CONR_2$, $-CR_2CF_2R$, $-CR_2CONR_2$, $-CR_2C(O)R$, $-CR_2CO_2R$, $-CR_2NR_2$, $-CR_2OR$, $-CR_2SO_2NR_2$, $-CR_2S(O)R$, $-CR_2SO_2R$, $-CR_2S(O)(NR)R$, $-CR_2CN$, $-CR_2CR_2NR_2$, $-CR_2CR_2OR$, $-CR_2CR{=}NOR$, $-CR_2CR(OR)CR_2OR$, or an optionally substituted group selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or: $-(CR_2)_{1-2}-X^a$, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or: R^b and R^c are taken together with their intervening atoms to form an optionally substituted 4-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or: R^a is absent and R^b and R^c are taken together with their intervening atoms to form an optionally substituted phenyl; or: when Y^1 is $-C(OR)=$, R^c is taken together with R of $-C(OR)=$ with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 heteroatoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur.

[00122] As described above and defined herein, R^c is halogen, $-CN$, $-CFR_2$, $-CF_2R$, $-CF_3$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)(NR)R$, $-S(O)R$, $-C(O)R$, $-CR{=}NOR$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-C(NOR)R$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, $-P(O)(NR_2)_2$, $-CR_2CN$, $-CR_2CFR_2$, $-CR_2CF_2R$, $-CR_2CF_3$, $-CR_2NO_2$, $-CR_2OR$, $-CR_2SR$, $-CR_2NR_2$, $-CR_2SiR_3$, $-CR_2S(O)_2R$, $-CR_2S(O)_2NR_2$, $-CR_2S(O)(NR)R$, $-CR_2S(O)R$, $-CR_2C(O)R$, $-CR_2CR{=}NOR$, $-CR_2C(O)OR$, $-CR_2C(O)NR_2$, $-CR_2C(O)NROR$, $-CR_2C(NOR)R$, $-CR_2OC(O)R$, $-CR_2OC(O)NR_2$, $-CR_2OP(O)R_2$, $-CR_2OP(O)(OR)_2$, $-CR_2OP(O)(OR)NR_2$, $-CR_2OP(O)(NR_2)_2$, $-CR_2NRC(O)OR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)N(R)_2$, $-CR_2NRS(O)_2R$, $-CR_2NP(O)R_2$, $-CR_2NRP(O)(OR)_2$, $-CR_2NRP(O)(OR)NR_2$, $-CR_2NRP(O)(NR_2)_2$, $-CR_2P(O)R_2$, $-CR_2P(O)(OR)_2$, $-CR_2P(O)(OR)NR_2$, $-CR_2P(O)(NR_2)_2$, $-CR_2CR_2CN$, $-CR_2CR_2CFR_2$, $-CR_2CR_2CF_2R$, $-CR_2CR_2CF_3$, $-CR_2CR_2NO_2$, $-CR_2CR_2OR$, $-CR_2CR_2SR$, $-CR_2CR_2NR_2$, $-CR_2CR_2SiR_3$, $-CR_2CR_2S(O)_2R$, $-CR_2CR_2S(O)_2NR_2$, $-CR_2CR_2S(O)(NR)R$, $-CR_2CR_2S(O)R$, $-CR_2CRC(O)R$, $-CR_2CR_2CR{=}NOR$, $-CR_2CR_2C(O)OR$, $-CR_2CR_2C(O)NR_2$, $-CR_2CR_2C(O)NROR$, $-CR_2CR_2C(NOR)R$, $-CR_2CR_2OC(O)R$, $-CR_2CR_2OC(O)NR_2$, $-CR_2CR_2OP(O)R_2$, $-CR_2CR_2OP(O)(OR)_2$, $-CR_2CR_2OP(O)(OR)NR_2$, $-CR_2CR_2OP(O)(NR_2)_2$, $-CR_2CR_2NRC(O)OR$, $-CR_2CR_2NRC(O)R$, $-CR_2CR_2NRC(O)N(R)_2$, $-CR_2CR_2NRS(O)_2R$, -

$CR_2CR_2NP(O)R_2$, $-CR_2CR_2NRP(O)(OR)_2$, $-CR_2CR_2NRP(O)(OR)NR_2$, $-CR_2CR_2NRP(O)(NR_2)_2$, $-CR_2CR_2P(O)R_2$, $-CR_2CR_2P(O)(OR)_2$, $-CR_2CR_2P(O)(OR)NR_2$, $-CR_2CR_2P(O)(NR_2)_2$, $-CR_2CR(OR)CR_2OR$, or an optionally substituted group selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or $-(CR_2)_{1-2}-X^a$, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or $-(CR_2)_{0-2}C(O)R^{cc}$ or $-(CR_2)_{0-2}S(O)_{0-2}R^{cc}$; or: R^b and R^c are taken together with their intervening atoms to form an optionally substituted 4-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or R^a is absent and R^b and R^c are taken together with their intervening atoms to form an optionally substituted phenyl.

[00123] As described above and defined herein, R^c is halogen, $-CN$, $-CFR_2$, $-CF_2R$, $-CF_3$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)(NR)R$, $-S(O)R$, $-C(O)R$, $-CR{=}NOR$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-C(NOR)R$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, $-P(O)(NR_2)_2$, $-CR_2CN$, $-CR_2CFR_2$, $-CR_2CF_2R$, $-CR_2CF_3$, $-CR_2NO_2$, $-CR_2OR$, $-CR_2SR$, $-CR_2NR_2$, $-CR_2SiR_3$, $-CR_2S(O)_2R$, $-CR_2S(O)_2NR_2$, $-CR_2S(O)(NR)R$, $-CR_2S(O)R$, $-CR_2C(O)R$, $-CR_2CR{=}NOR$, $-CR_2C(O)OR$, $-CR_2C(O)NR_2$, $-CR_2C(O)NROR$, $-CR_2C(NOR)R$, $-CR_2OC(O)R$, $-CR_2OC(O)NR_2$, $-CR_2OP(O)R_2$, $-CR_2OP(O)(OR)_2$, $-CR_2OP(O)(OR)NR_2$, $-CR_2OP(O)(NR_2)_2$, $-CR_2NRC(O)OR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)N(R)_2$, $-CR_2NRS(O)_2R$, $-CR_2NP(O)R_2$, $-CR_2NRP(O)(OR)_2$, $-CR_2NRP(O)(OR)NR_2$, $-CR_2NRP(O)(NR_2)_2$, $-CR_2P(O)R_2$, $-CR_2P(O)(OR)_2$, $-CR_2P(O)(OR)NR_2$, $-CR_2P(O)(NR_2)_2$, $-CR_2CR_2CN$, $-CR_2CR_2CFR_2$, $-CR_2CR_2CF_2R$, $-CR_2CR_2CF_3$, $-CR_2CR_2NO_2$, $-CR_2CR_2OR$, $-CR_2CR_2SR$, $-CR_2CR_2NR_2$, $-CR_2CR_2SiR_3$, $-CR_2CR_2S(O)_2R$, $-CR_2CR_2S(O)_2NR_2$, $-CR_2CR_2S(O)(NR)R$, $-CR_2CR_2S(O)R$, $-CR_2CRC(O)R$, $-CR_2CR_2CR{=}NOR$, $-CR_2CR_2C(O)OR$, $-CR_2CR_2C(O)NR_2$, $-CR_2CR_2C(O)NROR$, $-CR_2CR_2C(NOR)R$, $-CR_2CR_2OC(O)R$, $-CR_2CR_2OC(O)NR_2$, $-CR_2CR_2OP(O)R_2$, $-CR_2CR_2OP(O)(OR)_2$, $-CR_2CR_2OP(O)(OR)NR_2$, $-CR_2CR_2OP(O)(NR_2)_2$, $-CR_2CR_2NRC(O)OR$, $-CR_2CR_2NRC(O)R$, $-CR_2CR_2NRC(O)N(R)_2$, $-CR_2CR_2NRS(O)_2R$, $-CR_2CR_2NP(O)R_2$, $-CR_2CR_2NRP(O)(OR)_2$, $-CR_2CR_2NRP(O)(OR)NR_2$, $-CR_2CR_2NRP(O)(NR_2)_2$, $-CR_2CR_2P(O)R_2$, $-CR_2CR_2P(O)(OR)_2$, $-CR_2CR_2P(O)(OR)NR_2$, $-CR_2CR_2P(O)(NR_2)_2$, $-CR_2CR(OR)CR_2OR$, , or an optionally substituted group selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-9 membered monocyclic or

bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or: –$(CR_2)_{1-2}$-X^a, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00124] In some embodiments, R^c is -CO_2R, -$CONR_2$, -CR_2CN, -CR_2CFR_2, -CR_2CF_2R, -CR_2CF_3, -CR_2NO_2, -CR_2OR, -CR_2SR, -CR_2NR_2, -CR_2SiR_3, -$CR_2S(O)_2R$, -$CR_2S(O)_2NR_2$, -$CR_2S(O)(NR)R$, -$CR_2S(O)R$, -$CR_2C(O)R$, -CR_2CR=NOR, -$CR_2C(O)OR$, -$CR_2C(O)NR_2$, -$CR_2C(O)NROR$, -$CR_2C(NOR)R$, -$CR_2OC(O)R$, -$CR_2OC(O)NR_2$, -$CR_2NRC(O)OR$, -$CR_2NRC(O)R$, -$CR_2NRC(O)N(R)_2$, -$CR_2NRS(O)_2R$, -CR_2CR_2CN, -$CR_2CR_2CFR_2$, -$CR_2CR_2CF_2R$, -$CR_2CR_2CF_3$, -$CR_2CR_2NO_2$, -CR_2CR_2OR, -CR_2CR_2SR, -$CR_2CR_2NR_2$, -$CR_2CR_2SiR_3$, -$CR_2CR_2S(O)_2R$, -$CR_2CR_2S(O)_2NR_2$, -$CR_2CR_2S(O)(NR)R$, -$CR_2CR_2S(O)R$, -$CR_2CRC(O)R$, -CR_2CR_2CR=NOR, -$CR_2CR_2C(O)OR$, -$CR_2CR_2C(O)NR_2$, -$CR_2CR_2C(O)NROR$, -$CR_2CR_2C(NOR)R$, -$CR_2CR_2OC(O)R$, -$CR_2CR_2OC(O)NR_2$, -$CR_2CR_2NRC(O)OR$, -$CR_2CR_2NRC(O)R$, -$CR_2CR_2NRC(O)N(R)_2$, -$CR_2CR_2NRS(O)_2R$, -$CR_2CR(OR)CR_2OR$; or: –$(CR_2)_{1-2}$-X^a, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00125] In some embodiments, R^c is -CO_2R, -$CONR_2$, -CR_2CN, -CR_2CF_2R, -CR_2OR, -CR_2SR, -CR_2NR_2, -$CR_2S(O)_2R$, -$CR_2S(O)_2NR_2$, -$CR_2S(O)(NR)R$, -$CR_2S(O)R$, -$CR_2C(O)R$, -CR_2CR=NOR, -$CR_2C(O)OR$, -$CR_2C(O)NR_2$, -CR_2CR_2CN, -$CR_2CR_2CF_2R$, -CR_2CR_2OR, -CR_2CR_2SR, -$CR_2CR_2NR_2$, -$CR_2CR_2S(O)_2R$, -$CR_2CR_2S(O)_2NR_2$, -$CR_2CR_2S(O)(NR)R$, -$CR_2CR_2S(O)R$, -$CR_2CRC(O)R$, -CR_2CR_2CR=NOR, -$CR_2CR_2C(O)OR$, -$CR_2CR_2C(O)NR_2$, -$CR_2CR_2C(O)NROR$, -$CR_2CR_2C(NOR)R$, -$CR_2CR(OR)CR_2OR$; or: –$(CR_2)_{1-2}$-X^a, wherein X^a is an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

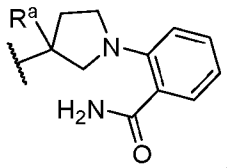
[00126] In some embodiments, R^c is -CO_2R, -$CONR_2$, -CR_2CN, -CR_2CF_2R, -CR_2CONR_2, -$CR_2C(O)R$, -CR_2CO_2R, -CR_2NR_2, -CR_2OR, -$CR_2S(O)NR_2$, -$CR_2SO_2NR_2$, -$CR_2S(O)R$, -CR_2SO_2R, -$CR_2S(O)(NR)R$, -CR_2CN, -$CR_2CR_2NR_2$, -CR_2CR_2OR, -CR_2CR=NOR, -$CR_2CR(OR)CR_2OR$.

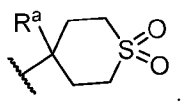
[00127] In some embodiments, R^c is -CR_2CN, -CR_2CF_2R, -CR_2CONR_2, -$CR_2C(O)R$, -CR_2CO_2R, -CR_2NR_2, -CR_2OR, -CR_2SONR_2, -$CR_2SO_2NR_2$, -$CR_2S(O)R$, -CR_2SO_2R, -$CR_2S(O)(NR)R$, or -CR_2CN.

[00128] In some embodiments, R^c is -CR_2CN, -CR_2CONR_2, -$CR_2C(O)R$, -CR_2CO_2R, -$CR_2S(O)NR_2$, -

$CR_2SO_2NR_2$, $-CR_2S(O)R$, $-CR_2SO_2R$, or $-CR_2CR_2NR_2$.In some embodiments, R^c is $-CO_2R$. In some embodiments, R^c is $-CONR_2$. In some embodiments, R^c is $-CR_2CF_2R$. In some embodiments, R^c is $-CR_2CONR_2$. In some embodiments, R^c is $-CR_2C(O)R$. In some embodiments, R^c is $-CR_2CO_2R$. In some embodiments, R^c is $-CR_2NR_2$. In some embodiments, R^c is $-CR_2OH$. In some embodiments, R^c is $-CR_2SO_2NR_2$. In some embodiments, R^c is $-CR_2S(O)R$. In some embodiments, R^c is $-CR_2SO_2R$. In some embodiments, R^c is $-CR_2S(O)(NR)R$. In some embodiments, R^c is $-CR_2CN$. In some embodiments, R^c is $-CR_2CR_2NR_2$. In some embodiments, R^c is $-CR_2CR_2OR$. In some embodiments, R^c is $-CR_2CR{=}NOR$. In some embodiments, R^c is $-CR_2CR(OR)CR_2OR$. In some embodiments, R^c is an optionally substituted phenyl. In some embodiments, R^c is an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclyl. In some embodiments, R^c is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^c is an optionally substituted 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00129] In some embodiments, R^c is $-(CR_2)_{1-2}$-X^a, wherein X^a is halogen. In some embodiments, R^c is $-(CR_2)_{1-2}$-X^a, wherein X^a is an optionally substituted phenyl. In some embodiments, R^c is $-(CR_2)_{1-2}$-X^a, wherein X^a is an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclyl. In some embodiments, R^c is $-(CR_2)_{1-2}$-X^a, wherein X^a is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^c is $-(CR_2)_{1-2}$-X^a, wherein X^a is an optionally substituted 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

[00130] In some embodiments, R^b and R^c are taken together with their intervening atoms to form an optionally substituted 4-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^b and R^c are taken together with their intervening atoms to form an optionally substituted pyrrolyl. In some embodiments, R^b and R^c are taken together with their intervening atoms to form oxetanyl, tetrahydrothiophenyl dioxide, 

, 

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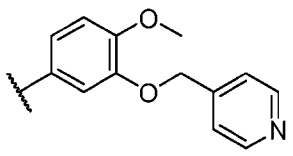
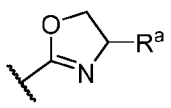
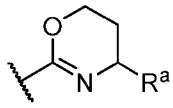
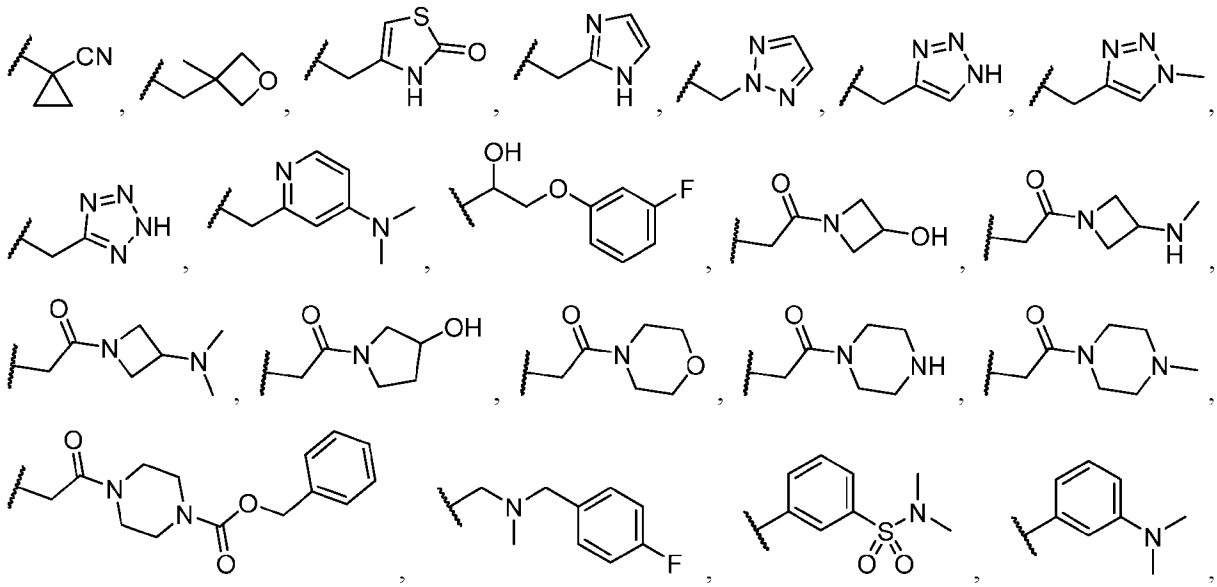
[00131] In some embodiments, R^a is absent and R^b and R^c are taken together with their intervening atoms to form an optionally substituted phenyl. In some embodiments, R^a is absent and R^b and R^c are taken

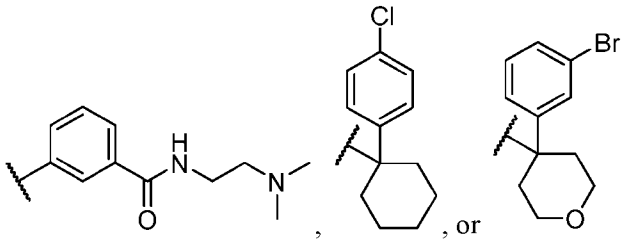


together with their intervening atoms to form

[00132] In some embodiments, when Y^1 is -C(OR)=, R^c is taken together with R of -C(OR)= with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 heteroatoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur. In some embodiments, when Y^1 is -C(OR)=, R^c is taken together with R of -C(OR)= with their intervening atoms to form  or 

[00133] In some embodiments, R^c is $-CO_2Bn$, $-CONHPh$, $-CR_2CF_2Me$, $-CH_2CONH_2$, $-CH(Me)CONH_2$, $-CH_2CONHMe$, $-CH_2CONHEt$, $-CH_2COMe$, $-CH_2CON(Me)CH_2CH_2NH_2$, $-CH_2CONHCONH_2$, $-CH_2CONHCH_2Ph$, $-CH_2CONHcyclopropyl$, $-CH_2OH$, $-CH_2Cl$, $-CH_2NMe_2$, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CH_2COCH_2CH_2OMe$, $-CH_2COCH_2CH_2CH_2OMe$, $-CH(Ph)OH$, $-CH(PhF)OH$, $-CH(Ph)NH_2$, $-CH(PhMe)NH_2$, $-CH_2SOMe$, $-CH_2SO_2NHEt$, $-CH_2SO_2NHMe$, $-CH_2SO_2Me$, $-CH_2SO_2Et$, $-CH_2SO_2iPr$, $-CH_2S(O)(NH)Me$, $-CH_2S(O)(NMe)Me$, $-CH_2C(Me)=NOH$, $-CH_2C(Me)=NOMe$, oxetanyl, thietanyl, theitanyl dioxide, pyrrolidin-2-onyl, piperidin-2-onyl, isoxazolyl, imidazolyl, pyrrolyl, tetrahydrofuranyl, tetrahydrothiophenyl dioxide, pyridine-2-onyl, phenyl, tolyl, indolyl, $-CH_2CN$, $-CH(Me)CN$, $-CH_2CH_2Cl$, $-CH_2CH_2NH_2$, $-CH_2CH_2NMe_2$, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2$pyrrolyl, $-CH_2$pyridyl, $-CH_2$indolyl,





[00134] In some embodiments, R^c is $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONHEt$, $-CH_2CON(Me)CH_2CH_2NH_2$, $-CH_2CONHCONH_2$, $-CH_2CONHCH_2Ph$, $-CH_2CONHcyclopropyl$, $-CH_2SO_2Me$, $-CH_2SO_2Et$, $-CH_2SO_2iPr$, $-CH_2CH_2NH_2$, or $-CH_2CH_2NMe_2$.

[00135] In some embodiments, R^c is $-CH_2CONH_2$, $-CH_2SO_2Me$, or $-CH_2CH_2NH_2$.

[00136] In some embodiments, R^c is $-CH_2CONH_2$. In some embodiments, R^c is $-CH_2SO_2Me$. In some embodiments, is $-CH_2CH_2NH_2$.

[00137] In some embodiments, Ring R^c is as depicted in the compounds of **Table 1**, below.

[00138] As described above and defined herein, R^d is hydrogen or an optionally substituted C_{1-6} aliphatic, or when R^c is $-CR_2CONR_2$, R^d is optionally taken together with a single R of $-CR_2CONR_2$ with their intervening atoms to form a 5-7 membered saturated or partially unsaturated heterocyclyl with 0-3 heteroatoms, in addition to the nitrogen atom to which R^d is attached, independently selected from nitrogen, oxygen, and sulfur.

[00139] In some embodiments, R^d is hydrogen. In some embodiments, R^d is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^d is a C_{1-6} alkyl. In some embodiments, R^d is benzyl. In some embodiments, R^d is methyl.

[00140] In some embodiments, R^d is absent.

[00141] In some embodiments, Ring R^d is as depicted in the compounds of **Table 1**, below.

[00142] As described above and defined herein, R^{cc}, R^e, R^r, R^g, R^h, R^i, R^j, and R^k are each independently selected from hydrogen, oxo, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, -NROR, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$; or an R^i group on Ring I and an R^j group or Ring J are optionally taken together with their intervening atoms to form a 5-8 membered saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an R^j group on Ring J and an R^k group or Ring K are optionally taken together with their intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00143] In some embodiments, R^{cc} is is R^A. In some embodiments, R^{cc} is halogen. In some

embodiments, R^{cc} is -CN. In some embodiments, R^{cc} is $-NO_2$. In some embodiments, R^{cc} is -OR. In some embodiments, R^{cc} is -SR. In some embodiments, R^{cc} is $-NR_2$. In some embodiments, R^{cc} is -NROR. In some embodiments, R^{cc} is $-SiR_3$. In some embodiments, R^{cc} is $-S(O)_2R$. In some embodiments, R^{cc} is $-S(O)_2NR_2$. In some embodiments, R^{cc} is -S(O)R. In some embodiments, R^{cc} is -C(O)R. In some embodiments, R^{cc} is -C(O)OR. In some embodiments, R^{cc} is $-C(O)NR_2$. In some embodiments, R^{cc} is -C(O)NROR. In some embodiments, R^{cc} is -C(NOR)R. In some embodiments, R^{cc} is -OC(O)R. In some embodiments, R^{cc} is $-OC(O)NR_2$. In some embodiments, R^{cc} is $-OP(O)R_2$. In some embodiments, R^{cc} is $-OP(O)(OR)_2$. In some embodiments, R^{cc} is $-OP(O)(OR)NR_2$. In some embodiments, R^{cc} is $-OP(O)(NR_2)_2$. In some embodiments, R^{cc} is -NRC(O)OR. In some embodiments, R^{cc} is -NRC(O)R. In some embodiments, R^{cc} is $-NRC(O)N(R)_2$. In some embodiments, R^{cc} is $-NRS(O)_2R$. In some embodiments, R^{cc} is $-NP(O)R_2$. In some embodiments, R^{cc} is $-NRP(O)(OR)_2$. In some embodiments, R^{cc} is $-NRP(O)(OR)NR_2$. In some embodiments, R^{cc} is $-NRP(O)(NR_2)_2$. In some embodiments, R^{cc} is $-P(O)R_2$. In some embodiments, R^{cc} is $-P(O)(OR)_2$. In some embodiments, R^{cc} is $-P(O)(OR)NR_2$. In some embodiments, R^{cc} is $-P(O)(NR_2)_2$.

[00144] In some embodiments, R^e is hydrogen. In some embodiments, R^e is oxo. In some embodiments, R^e is is R^A. In some embodiments, R^e is halogen. In some embodiments, R^e is -CN. In some embodiments, R^e is $-NO_2$. In some embodiments, R^e is -OR. In some embodiments, R^e is -SR. In some embodiments, R^e is $-NR_2$. In some embodiments, R^e is $-SiR_3$. In some embodiments, R^e is $-S(O)_2R$. In some embodiments, R^e is $-S(O)_2NR_2$. In some embodiments, R^e is -S(O)R. In some embodiments, R^e is -C(O)R. In some embodiments, R^e is -C(O)OR. In some embodiments, R^e is $-C(O)NR_2$. In some embodiments, R^e is -C(O)NROR. In some embodiments, R^e is -C(NOR)R. In some embodiments, R^e is -OC(O)R. In some embodiments, R^e is $-OC(O)NR_2$. In some embodiments, R^e is $-OP(O)R_2$. In some embodiments, R^e is $-OP(O)(OR)_2$. In some embodiments, R^e is $-OP(O)(OR)NR_2$. In some embodiments, R^e is $-OP(O)(NR_2)_2$. In some embodiments, R^e is -NRC(O)OR. In some embodiments, R^e is -NRC(O)R. In some embodiments, R^e is $-NRC(O)N(R)_2$. In some embodiments, R^e is $-NRS(O)_2R$. In some embodiments, R^e is $-NP(O)R_2$. In some embodiments, R^e is $-NRP(O)(OR)_2$. In some embodiments, R^e is $-NRP(O)(OR)NR_2$. In some embodiments, R^e is $-NRP(O)(NR_2)_2$. In some embodiments, R^e is $-P(O)R_2$. In some embodiments, R^e is $-P(O)(OR)_2$. In some embodiments, R^e is $-P(O)(OR)NR_2$. In some embodiments, R^e is $-P(O)(NR_2)_2$.

[00145] In some embodiments, R^e is R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

[00146] In some embodiments, R^e is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R,

-OC(O)R, -OC(O)NR_2, -NRC(O)OR, -NRC(O)R, -NRC(O)$N(R)_2$, or -NRS(O)$_2$R.

[00147] In some embodiments, R^e is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -C(O)NR_2.

[00148] In some embodiments, R^e is hydrogen, oxo, fluoro, chloro, -CN, methyl, -CF_3, isopropyl, cyclopropyl, ethynyl, -CO_2H, -CO_2Me, -$CONH_2$, -C(O)$CHCH_2$, -OH, -OMe, -CH_2CHF_2, -CH_2OMe, -CH_2CO_2H, -CH_2CONH_2, -CH_2SO_2Me, -$CH_2CH_2CO_2$H, -$CH_2CH_2CONH_2$, -$CH_2CH_2SO_2$Me, -CH_2CH_2OMe, -NHC(O)$CHCH_2$, tetrazolyl, or N-methyltetrazolyl.

[00149] In some embodiments, R^f is hydrogen. In some embodiments, R^f is oxo. In some embodiments, R^f is is R^A. In some embodiments, R^f is halogen. In some embodiments, R^f is -CN. In some embodiments, R^f is -NO_2. In some embodiments, R^f is -OR. In some embodiments, R^f is -SR. In some embodiments, R^e is -NR_2. In some embodiments, R^f is -SiR_3. In some embodiments, R^f is -S(O)$_2$R. In some embodiments, R^f is -S(O)$_2$$NR_2$. In some embodiments, R^f is -S(O)R. In some embodiments, R^f is -C(O)R. In some embodiments, R^f is -C(O)OR. In some embodiments, R^f is -C(O)NR_2. In some embodiments, R^f is -C(O)NROR. In some embodiments, R^f is -C(NOR)R. In some embodiments, R^f is -OC(O)R. In some embodiments, R^f is -OC(O)NR_2. In some embodiments, R^f is -OP(O)R_2. In some embodiments, R^f is -OP(O)$(OR)_2$. In some embodiments, R^f is -OP(O)(OR)NR_2. In some embodiments, R^f is -OP(O)$(NR_2)_2$. In some embodiments, R^f is -NRC(O)OR. In some embodiments, R^f is -NRC(O)R. In some embodiments, R^f is -NRC(O)$N(R)_2$. In some embodiments, R^f is -NRS(O)$_2$R. In some embodiments, R^f is -NP(O)R_2. In some embodiments, R^f is -NRP(O)$(OR)_2$. In some embodiments, R^f is -NRP(O)(OR)NR_2. In some embodiments, R^f is -NRP(O)$(NR_2)_2$. In some embodiments, R^f is -P(O)R_2. In some embodiments, R^f is -P(O)$(OR)_2$. In some embodiments, R^f is -P(O)(OR)NR_2. In some embodiments, R^f is -P(O)$(NR_2)_2$.

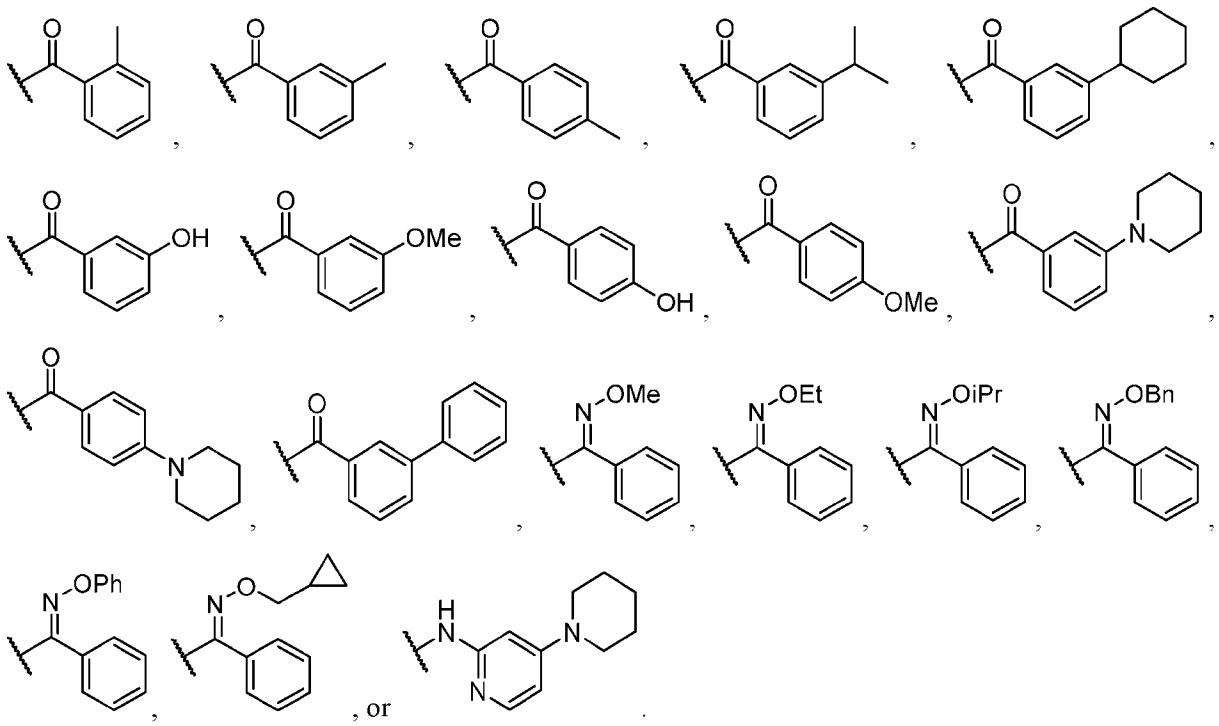
[00150] In some embodiments, R^f is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -S(O)$_2$R, -S(O)$_2$$NR_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR_2, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR_2, -NRC(O)OR, -NRC(O)R, -NRC(O)$N(R)_2$, or -NRS(O)$_2$R.

[00151] In some embodiments, R^f is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -S(O)$_2$R, -S(O)$_2$$NR_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR_2, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR_2, -NRC(O)OR, -NRC(O)R, -NRC(O)$N(R)_2$, or -NRS(O)$_2$R.

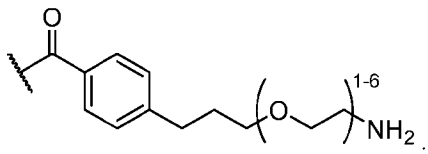
[00152] In some embodiments, R^f is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -C(O)NR_2.

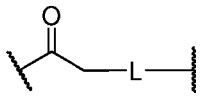
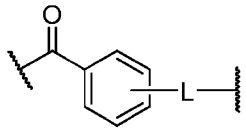
[00153] In some embodiments, R^f is hydrogen, oxo, -CN, methyl, ethyl, isopropyl, -CF_3, phenyl, pyrrolyl, pyridinyl, -$CONH_2$, -COcyclohexyl, -CH_2cyclopropyl, -CH_2cyclopentyl, -CH_2cyclohexyl, -CH_2morpholinyl, -CH_2Ph, -CH_2thiazolyl, -CH_2pyrimidinyl, -CH_2CH_2OMe, -CH_2CH_2Ph, -C(O)Me, -C(O)$CHCH_2$, -C(O)CH_2CH_2OMe, -C(O)$CH_2OCH_2CH_2$OMe, -$CH_2CH_2OCH_2CH_2$OMe, -C(O)Ph, -C(O)pyridinyl, -C(O)naphthyl, -C(O)CH_2Ph, -C(O)pyrimidinyl, -NH_2, -NHC(O)$CHCH_2$, -

$CH_2NHC(O)CHCH_2$, -CCNHC(O)$CHCH_2$, -NHcyclohexyl, -NHphenyl, -NHpyrimidinyl, -SO_2Me, tosyl,



[00154] In some embodiments, R^f is -$CO(CH_2)_{1-30}NH_2$, -$COCH_2(OCH_2CH_2)_{1-10}NH_2$, or



[00155] In some embodiments, R^f is attached to L, e.g.,  or  .

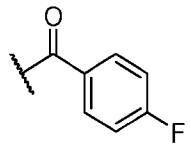
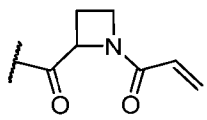
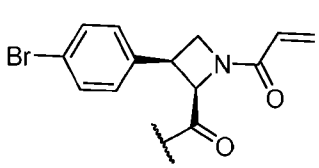
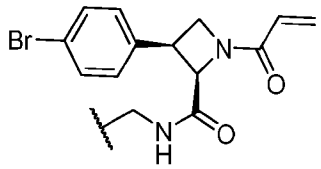
[00156] In some embodiments, R^h is hydrogen. In some embodiments, R^h is oxo. In some embodiments, R^h is is R^A. In some embodiments, R^h is halogen. In some embodiments, R^h is -CN. In some embodiments, R^h is -NO_2. In some embodiments, R^h is -OR. In some embodiments, R^h is -SR. In some embodiments, R^h is -NR_2. In some embodiments, R^h is -SiR_3. In some embodiments, R^h is -$S(O)_2R$. In some embodiments, R^h is -$S(O)_2NR_2$. In some embodiments, R^h is -S(O)R. In some embodiments, R^h is -C(O)R. In some embodiments, R^h is -C(O)OR. In some embodiments, R^h is -$C(O)NR_2$. In some embodiments, R^h is -C(O)NROR. In some embodiments, R^h is -C(NOR)R. In some embodiments, R^h is -OC(O)R. In some embodiments, R^h is -$OC(O)NR_2$. In some embodiments, R^h is -$OP(O)R_2$. In some embodiments, R^h is -$OP(O)(OR)_2$. In some embodiments, R^h is -OP(O)(OR)NR_2. In some embodiments, R^h is -$OP(O)(NR_2)_2$. In some embodiments, R^h is -NRC(O)OR. In some embodiments, R^h is -NRC(O)R.

In some embodiments, R^h is -NRC(O)N(R)$_2$. In some embodiments, R^h is -NRS(O)$_2$R. In some embodiments, R^h is -NP(O)R$_2$. In some embodiments, R^h is -NRP(O)(OR)$_2$. In some embodiments, R^h is -NRP(O)(OR)NR$_2$. In some embodiments, R^h is -NRP(O)(NR$_2$)$_2$. In some embodiments, R^h is -P(O)R$_2$. In some embodiments, R^h is -P(O)(OR)$_2$. In some embodiments, R^h is -P(O)(OR)NR$_2$. In some embodiments, R^h is -P(O)(NR$_2$)$_2$.

[00157] In some embodiments, R^h is R^A, halogen, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

[00158] In some embodiments, R^h is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

[00159] In some embodiments, R^h is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR$_2$, -C(O)R, -C(O)OR, or -C(O)NR$_2$.

[00160] In some embodiments, R^h is hydrogen, oxo, fluoro, methyl, ethyl, n-propyl, n-butyl, -CH$_2$N(Me)CH$_2$CH$_2$OMe, -CH$_2$CH$_2$OMe, -CH$_2$CH$_2$OCH$_2$CH$_2$OMe, -C(O)Me, -C(O)CHCH$_2$, -OH, -NHC(O)CHCH$_2$, -N(Me)C(O)CHCH$_2$, -NHC(O)Me, -CH$_2$NHC(O)CHCH$_2$, -(CH$_2$)$_2$-$_6$NHC(O)CHCH$_2$, -(CH$_2$)$_{2-6}$NMeC(O)CHCH$_2$,  ,  ,  ,  .

[00161] In some embodiments, R^g is hydrogen. In some embodiments, R^g is oxo. In some embodiments, R^g is is R^A. In some embodiments, R^g is halogen. In some embodiments, R^g is -CN. In some embodiments, R^g is -NO$_2$. In some embodiments, R^g is -OR. In some embodiments, R^g is -SR. In some embodiments, R^g is -NR$_2$. In some embodiments, R^g is -SiR$_3$. In some embodiments, R^g is -S(O)$_2$R. In some embodiments, R^g is -S(O)$_2$NR$_2$. In some embodiments, R^g is -S(O)R. In some embodiments, R^g is -C(O)R. In some embodiments, R^g is -C(O)OR. In some embodiments, R^g is -C(O)NR$_2$. In some embodiments, R^g is -C(O)NROR. In some embodiments, R^g is -C(NOR)R. In some embodiments, R^g is -OC(O)R. In some embodiments, R^g is -OC(O)NR$_2$. In some embodiments, R^g is -OP(O)R$_2$. In some embodiments, R^g is -OP(O)(OR)$_2$. In some embodiments, R^g is -OP(O)(OR)NR$_2$. In some embodiments, R^g is -OP(O)(NR$_2$)$_2$. In some embodiments, R^g is -NRC(O)OR. In some embodiments, R^g is -NRC(O)R.

In some embodiments, R^g is -NRC(O)N(R)$_2$. In some embodiments, R^g is -NRS(O)$_2$R. In some embodiments, R^g is -NP(O)R$_2$. In some embodiments, R^g is -NRP(O)(OR)$_2$. In some embodiments, R^g is -NRP(O)(OR)NR$_2$. In some embodiments, R^g is -NRP(O)(NR$_2$)$_2$. In some embodiments, R^g is -P(O)R$_2$. In some embodiments, R^g is -P(O)(OR)$_2$. In some embodiments, R^g is -P(O)(OR)NR$_2$. In some embodiments, R^g is -P(O)(NR$_2$)$_2$.

[00162] In some embodiments, R^g is R^A, halogen, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

[00163] In some embodiments, R^g is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

[00164] In some embodiments, R^g is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR$_2$, -C(O)R, -C(O)OR, or -C(O)NR$_2$.

[00165] In some embodiments, R^g is hydrogen, oxo, fluoro, chloro, bromo, -CN, methyl, ethyl, -CONH$_2$, -OH, or -OMe.

[00166] In some embodiments, R^i is hydrogen. In some embodiments, R^i is oxo. In some embodiments, R^i is is R^A. In some embodiments, R^i is halogen. In some embodiments, R^i is -CN. In some embodiments, R^i is -NO$_2$. In some embodiments, R^i is -OR. In some embodiments, R^i is -SR. In some embodiments, R^i is -NR$_2$. In some embodiments, R^i is -SiR$_3$. In some embodiments, R^i is -S(O)$_2$R. In some embodiments, R^i is -S(O)$_2$NR$_2$. In some embodiments, R^i is -S(O)R. In some embodiments, R^i is -C(O)R. In some embodiments, R^i is -C(O)OR. In some embodiments, R^i is -C(O)NR$_2$. In some embodiments, R^i is -C(O)NROR. In some embodiments, R^i is -C(NOR)R. In some embodiments, R^i is -OC(O)R. In some embodiments, R^i is -OC(O)NR$_2$. In some embodiments, R^i is -OP(O)R$_2$. In some embodiments, R^i is -OP(O)(OR)$_2$. In some embodiments, R^i is -OP(O)(OR)NR$_2$. In some embodiments, R^i is -OP(O)(NR$_2$)$_2$. In some embodiments, R^i is -NRC(O)OR. In some embodiments, R^i is -NRC(O)R. In some embodiments, R^i is -NRC(O)N(R)$_2$. In some embodiments, R^i is -NRS(O)$_2$R. In some embodiments, R^i is -NP(O)R$_2$. In some embodiments, R^i is -NRP(O)(OR)$_2$. In some embodiments, R^i is -NRP(O)(OR)NR$_2$. In some embodiments, R^i is -NRP(O)(NR$_2$)$_2$. In some embodiments, R^i is -P(O)R$_2$. In some embodiments, R^i is -P(O)(OR)$_2$. In some embodiments, R^i is -P(O)(OR)NR$_2$. In some embodiments, R^i is -P(O)(NR$_2$)$_2$.

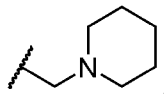
[00167] In some embodiments, R^i is R^A, halogen, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

[00168] In some embodiments, R^i is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R,

-OC(O)R, -OC(O)NR_2, -NRC(O)OR, -NRC(O)R, -NRC(O)$N(R)_2$, or -NRS(O)$_2$R.

[00169] In some embodiments, R^i is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -C(O)NR_2.

[00170] In some embodiments, R^i is hydrogen, oxo, fluoro, chloro, methyl, -CF_3, -CH_2OH, -CN, -CH_2C(O)NH_2, -CH_2NH_2, -$CH_2NHCH_2CH_2NH_2$, -$CONHCH_2CH_2NH_2$, -$CH_2NHCOCH_2NH_2$, -C(O)isobutyl, -C(O)CH_2NH_2, -C(O)CH_2OCONH_2, -CO_2H, -$CONH_2$, -C(O)cyclopropyl, -C(O)$(CH_2)_{1-6}SO_2$Me, -OH, -OMe, -NH_2, -NMe_2, -$NHCH_2CH_2NH_2$, -N(Me)$CH_2CH_2CH_2$N(Me)C(O)$CHCH_2$, or



[00171] In some embodiments, R^j is hydrogen. In some embodiments, R^j is oxo. In some embodiments, R^j is is R^A. In some embodiments, R^j is halogen. In some embodiments, R^j is -CN. In some embodiments, R^j is -NO_2. In some embodiments, R^j is -OR. In some embodiments, R^j is -SR. In some embodiments, R^j is -NR_2. In some embodiments, R^j is -SiR_3. In some embodiments, R^j is -S(O)$_2$R. In some embodiments, R^j is -S(O)$_2$$NR_2$. In some embodiments, R^j is -S(O)R. In some embodiments, R^j is -C(O)R. In some embodiments, R^j is -C(O)OR. In some embodiments, R^j is -C(O)NR_2. In some embodiments, R^j is -C(O)NROR. In some embodiments, R^j is -C(NOR)R. In some embodiments, R^j is -OC(O)R. In some embodiments, R^j is -OC(O)NR_2. In some embodiments, R^j is -OP(O)R_2. In some embodiments, R^j is -OP(O)$(OR)_2$. In some embodiments, R^j is -OP(O)(OR)NR_2. In some embodiments, R^j is -OP(O)$(NR_2)_2$. In some embodiments, R^j is -NRC(O)OR. In some embodiments, R^j is -NRC(O)R. In some embodiments, R^j is -NRC(O)$N(R)_2$. In some embodiments, R^j is -NRS(O)$_2$R. In some embodiments, R^j is -NP(O)R_2. In some embodiments, R^j is -NRP(O)$(OR)_2$. In some embodiments, R^j is -NRP(O)(OR)NR_2. In some embodiments, R^j is -NRP(O)$(NR_2)_2$. In some embodiments, R^j is -P(O)R_2. In some embodiments, R^j is -P(O)$(OR)_2$. In some embodiments, R^j is -P(O)(OR)NR_2. In some embodiments, R^j is -P(O)$(NR_2)_2$.

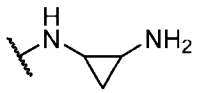
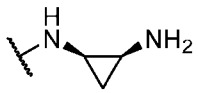
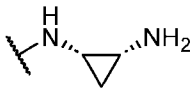
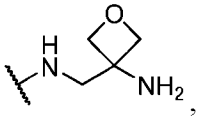
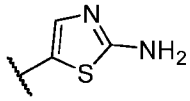
[00172] In some embodiments, R^j is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -S(O)$_2$R, -S(O)$_2$$NR_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR_2, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR_2, -NRC(O)OR, -NRC(O)R, -NRC(O)$N(R)_2$, or -NRS(O)$_2$R.

[00173] In some embodiments, R^j is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -S(O)$_2$R, -S(O)$_2$$NR_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR_2, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR_2, -NRC(O)OR, -NRC(O)R, -NRC(O)$N(R)_2$, or -NRS(O)$_2$R.

[00174] In some embodiments, R^j is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -C(O)NR_2.

[00175] In some embodiments, R^j is hydrogen, oxo, fluoro, chloro, methyl, -CH_2F, -CH_2OH, -CH_2C(O)NH_2, -CH_2NH_2, -$CH_2NHCH_2CH_2NH_2$, -$CONHCH_2CH_2NH_2$, -$CH_2NHCOCH_2NH_2$, -

$CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_2CH_2OMe$, $-CH_2CH_2OCH_2CH_2OCH_2CH_2OMe$, $-C(O)CH_2NH_2$, $-C(O)CH_2OCONH_2$, $-CO_2H$, $-C(O)CHCH_2$, $-C(O)Et$, $-C(O)NH_2$, $-NH_2$, $-OH$, $-OMe$, or $-S(O)_2NH_2$.

[00176] In some embodiments, R^j is $-OCH_2CH_2NH_2$, $-NHCH_2CH_2OH$, $-NHCH_2CONH_2$, $-NHCH_2SO_2NH_2$, $-NHC(O)CH_2NH_2$, $-OCH_2CH(CF_3)NH_2$,  ,  ,  ,  , or  .

[00177] In some embodiments, an R^i group on Ring I and an R^j group or Ring J are taken together with their intervening atoms to form a 5-8 membered saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00178] In some embodiments, R^i and R^j, are taken together by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$.

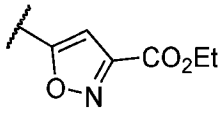
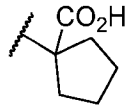
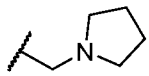
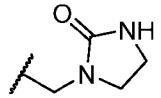
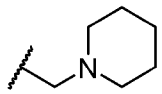
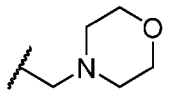
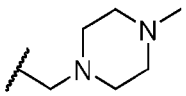
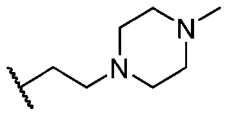
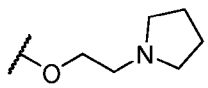
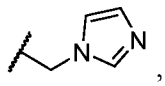
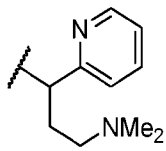
[00179] In some embodiments, R^k is hydrogen. In some embodiments, R^k is oxo. In some embodiments, R^k is is R^A. In some embodiments, R^k is halogen. In some embodiments, R^k is -CN. In some embodiments, R^k is $-NO_2$. In some embodiments, R^k is -OR. In some embodiments, R^k is -SR. In some embodiments, R^k is $-NR_2$. In some embodiments, R^k is $-SiR_3$. In some embodiments, R^k is $-S(O)_2R$. In some embodiments, R^k is $-S(O)_2NR_2$. In some embodiments, R^k is -S(O)R. In some embodiments, R^k is -C(O)R. In some embodiments, R^k is -C(O)OR. In some embodiments, R^k is $-C(O)NR_2$. In some embodiments, R^k is -C(O)NROR. In some embodiments, R^k is -C(NOR)R. In some embodiments, R^k is $-OC(O)R$. In some embodiments, R^k is $-OC(O)NR_2$. In some embodiments, R^k is $-OP(O)R_2$. In some embodiments, R^k is $-OP(O)(OR)_2$. In some embodiments, R^k is $-OP(O)(OR)NR_2$. In some embodiments, R^k is $-OP(O)(NR_2)_2$. In some embodiments, R^k is -NRC(O)OR. In some embodiments, R^k is -NRC(O)R. In some embodiments, R^k is $-NRC(O)N(R)_2$. In some embodiments, R^k is $-NRS(O)_2R$. In some embodiments, R^k is $-NP(O)R_2$. In some embodiments, R^k is $-NRP(O)(OR)_2$. In some embodiments, R^k is $-NRP(O)(OR)NR_2$. In some embodiments, R^k is $-NRP(O)(NR_2)_2$. In some embodiments, R^k is $-P(O)R_2$. In some embodiments, R^k is $-P(O)(OR)_2$. In some embodiments, R^k is $-P(O)(OR)NR_2$. In some embodiments, R^k is $-P(O)(NR_2)_2$.

[00180] In some embodiments, R^k is R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, $-OC(O)R$, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

[00181] In some embodiments, R^k is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, $-OC(O)R$, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

[00182] In some embodiments, R^k is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -

OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

[00183] In some embodiments, R^k is hydrogen, oxo, fluoro, chloro, bromo, -CN, -NO_2, methyl, ethyl, n-propyl, isobutyl, cyclopropyl, benzyl, -CF_3, -CO_2H, -CO_2Me, -CH_2CF_3, -CH_2OH, -CH_2OCONH_2, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CO_2H, -CH_2CO_2Me, -CH_2CO_2Et, -$C(O)NH_2$, -$C(O)NMe_2$, -$CH_2C(O)NH_2$, -$CH_2CH_2C(O)NH_2$, -CH_2NH_2, -$CH_2NHCONH_2$, -CH_2OCONH_2, -$CH_2CH_2NH_2$, -$CH_2CH_2CH_2NH_2$, -CH(OH)Me, -$CH(OH)CF_3$, -$CH(NH_2)$cyclopropyl, -CH_2Ph, -OH, -OMe, -OCF_3, -OiPr, -Ocyclopropyl, -OPh, -OBn, -NH_2, -NHiBu, -NHC(O)H, -NHC(O)Me, -$NHC(O)CHCH_2$, -SMe, -S(O)Me, -$S(O)_2NH_2$, -$CH_2CH_2S(O)_2NH_2$, 1,2,3-triazolyl, thiophenyl, pyrrolidinyl, piperdinyl, N-methylpiperdinyl, piperazinyl, phenyl, pyridinyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

[00184] In some embodiments, an R^j group on Ring J and an R^k group or Ring K are optionally taken together with their intervening atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00185] In some embodiments, R^j and R^k, are taken together by -NH-.

[00186] In some embodiments, R^{cc}, R^e, R^r, R^g, R^h, R^i, R^j, and R^k are as depicted in the compounds of **Table 1**, below.

[00187] As described above and defined herein, each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00188] In some embodiments, R^A is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^A is an optionally substituted phenyl. In some embodiments, R^A is an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic. In some embodiments, R^A is an optionally substituted saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^A is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00189] In some embodiments, R^A is C_{1-6} alkyl (e.g., methyl, ethyl, isopropyl). In some embodiments, R^A is C_{1-6} haloalkyl (e.g., $-CF_3$, $-CHF_2$).

[00190] In some embodiment, R^A is as depicted in the compounds of **Table 1**, below.

[00191] As described above and defined herein, each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, naphthyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same atom are optionally taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same atom, or on different atoms, are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur.

[00192] In some embodiments, R is hydrogen. In some embodiments, R is an optionally substituted C_{1-6} aliphatic. In some embodiments, R is an optionally substituted phenyl. In some embodiments, R is an optionally substituted naphthyl. In some embodiments, R is an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclic. In some embodiments, R is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same atom are optionally taken together with their intervening atoms to form optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same atom, or on different atoms, are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur.

[00193] In some embodiment, R is as depicted in the compounds of **Table 1**, below.

[00194] As described above and defined herein, each of each of X^1 and X^2 are independently a covalent bond, spiro-fusion between the two rings that X^1 or X^2 connect, or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, $-CR(OR)-$, $-CRF-$, $-CF_2-$, $-C(NR)-$, $-C(O)-$, $-O-$, $-N(R)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$.

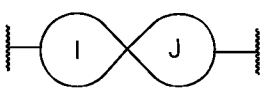
[00195] In some embodiments, X^1 is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$.

[00196] In some embodiments, X^1 is a covalent bond. In some embodiments, X^1 is a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$. In some embodiments, X^1 is $-CR_2-$. In some embodiments, X^1 is -CR(OR)-. In some embodiments, X^1 -CRF-. In some embodiments, X^1 is $-CF_2-$. In some embodiments, X^1 is $-(CR_2)_{0-2}-C(O)-$. In some embodiments, X^1 is $-CR_2NRCR_2-$. In some embodiments, X^1 is $-NRCR_2-$. In some embodiments, X^1 is -C(O)NR-. In some embodiments, X^1 is -C(NR)NR-. In some embodiments, X^1 is -C(S)NR-. In some embodiments, X^1 is -NR-. In some embodiments, X^1 is -O-. In some embodiments, X^1 is -S-. In some embodiments, X^1 is $-S(O)_2-$. In some embodiments, X^1 represents spiro-fusion between the two rings that X^1 connect.

[00197] In some embodiments, X^1 is a covalent bond, $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$.

[00198] In some embodiments, X^1 is a covalent bond, -NH-, -NMe-.

[00199] In some embodiments, X^2 is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$.

[00200] In some embodiments, X^2 is a covalent bond. In some embodiments, X^2 is a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$. In some embodiments, X^2 is $-CR_2-$. In some embodiments, X^2 is -CR(OR)-. In some embodiments, X^2 -CRF-. In some embodiments, X^2 is $-CF_2-$. In some embodiments, X^2 is $-(CR_2)_{0-2}-C(O)-$. In some embodiments, X^2 is $-CR_2NRCR_2-$. In some embodiments, X^2 is $-NRCR_2-$. In some embodiments, X^2 is -C(O)NR-. In some embodiments, X^2 is -C(NR)NR-. In some embodiments, X^2 is -C(S)NR-. In some embodiments, X^2 is -NR-. In some embodiments, X^2 is -O-. In some embodiments, X^2 is -S-. In some embodiments, X^2 is $-S(O)_2-$. In some embodiments, X^2 represents spiro-fusion between the two rings that X^2 connects, e.g., 

.

[00201] In some embodiments, X^2 is a covalent bond, $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$.

[00202] In some embodiments, X^2 is a covalent bond, $-CH_2-$, -CMe(OMe)-, -CMe(F)-, $-CMe(CF_3)-$, cyclopropylenyl, difluorocyclopropylenyl, -C(O)-, $-CH_2CH_2C(O)-$, $-CH_2NHCH(Me)-$, $-NHCH_2-$, -

N(Me)CH_2-, -C(O)NH-, -NH-, -NMe-, -N(COMe)-, -N(CF_3)-, -NEt-, -N(nPr)-, -N(nBu)-, -N(Ph)-, -N(3-pyridyl)-, -N(4-pyridyl)-, -N(SO_2Me)-, -N(CH_2CHF_2)-, -N(CH_2cyclopropyl)-, -N(CH_2Ph)-, -N(CH_2CONH_2)-, -N(CH_2SO_2Me)-, -N($CH_2CH_2CHF_2$)-, -N(CH_2CH_2Ph)-, -N($CH_2CH_2CO_2H$)-, -N($CH_2CH_2CONH_2$)-, -N(CH_2CH_2CN)-, -N(CH_2CH_2OMe)-, -N($CH_2CH_2SO_2Me$)-, -O-, -S-, or -S(O)$_2$-.

[00203] In some embodiment, X^1 and X^2 are as depicted in the compounds of **Table 1**, below.

[00204] As described above and defined herein, Y^2 is a C_{1-4} hydrocarbon chain wherein each methylene is optionally substituted with -CR_2-, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, -S(O)-, -S(O)$_2$-, -C(OR)=N-, -N(R^d)-, or -O-.

[00205] In some embodiments, Y^2 is -CR_2N(R^d)-, -CR(OR)N(R^d)-, -C(O)N(R^d)-, -C(NR)N(R^d)-, -C(NOR)N(R^d)-, -S(O)N(R^d)-, -S(O)$_2$N(R^d)-, -C(OR)=N-, -N(R^d)-, or -CO_2-.

[00206] In some embodiment, Y^2 is as depicted in the compounds of **Table 1**, below.

[00207] As described above and defined herein, Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with -CR_2-, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, -S(O)-, or -S(O)$_2$-.

[00208] In some embodiments, Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with -CR_2-, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, -S(O)-, -S(O)$_2$-, or Y^1 is -C(OR)= in formula **I-a'** where R^d is absent.

[00209] In some embodiments, Y^1 is a C_{1-3} hydrocarbon chain. In some embodiments, Y^1 is -CR_2-. In some embodiments, Y^1 is -CR(OR)-. In some embodiments, Y^1 is -C(O)-. In some embodiments, Y^1 is -C(NR)-. In some embodiments, Y^1 is -C(NOR)-. In some embodiments, Y^1 is -S(O)-. In some embodiments, Y^1 is -S(O)$_2$-. In some embodiments, Y^1 is -C(OR)= in formula **I-a'** where R^d is absent.

[00210] In some embodiments, Y^1 is -CH_2-, -CH_2C(O)-, -NHCH_2C(O)-, -CH_2CH_2C(O)-, -CH_2CH(OH)C(O)-, -C(O)-, -C(NH)-, -C(NOH)-, -S(O)-, or -S(O)$_2$-.

[00211] In some embodiment, Y^1 is as depicted in the compounds of **Table 1**, below.

[00212] As described above and defined herein, each of s is 0 or 1.

[00213] In some embodiments, s is 0. In some embodiments, s is 1.

[00214] In some embodiment, s is as depicted in the compounds of **Table 1**, below.

[00215] As described above and defined herein, each of e, f, g, h, i, j, and k are independently 0, 1, 2, 3, or 4.

[00216] In some embodiments, e is 0. In some embodiments, e is 1. In some embodiments, e is 2. In some embodiments, e is 3. In some embodiments, e is 4.

[00217] In some embodiments, e is 0 or 1. In some embodiments, e is 1 or 2. In some embodiments, e is 2 or 3. In some embodiments, e is 3 or 4. In some embodiments, e is 1, 2, or 3.

[00218] In some embodiments, f is 0. In some embodiments, f is 1. In some embodiments, f is 2. In some embodiments, f is 3. In some embodiments, f is 4.

[00219] In some embodiments, f is 0 or 1. In some embodiments, f is 1 or 2. In some embodiments, f is 1, 2, or 3.

[00220] In some embodiments, g is 0. In some embodiments, g is 1. In some embodiments, g is 2. In some embodiments, g is 3. In some embodiments, g is 4.

[00221] In some embodiments, g is 0 or 1. In some embodiments, g is 1 or 2. In some embodiments, g is 1, 2, or 3.

[00222] In some embodiments, h is 0. In some embodiments, h is 1. In some embodiments, h is 2. In some embodiments, h is 3. In some embodiments, h is 4.

[00223] In some embodiments, h is 0 or 1. In some embodiments, h is 1 or 2. In some embodiments, h is 1, 2, or 3.

[00224] In some embodiments, i is 0. In some embodiments, i is 1. In some embodiments, i is 2. In some embodiments, i is 3. In some embodiments, i is 4.

[00225] In some embodiments, i is 0 or 1. In some embodiments, i is 1 or 2. In some embodiments, i is 1, 2, or 3.

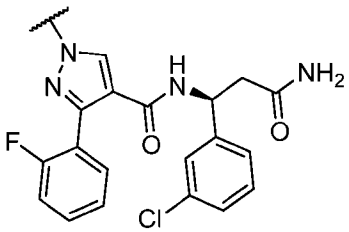
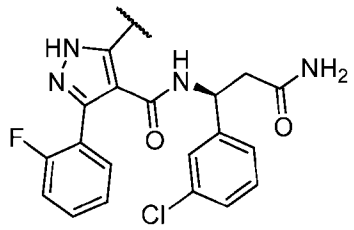
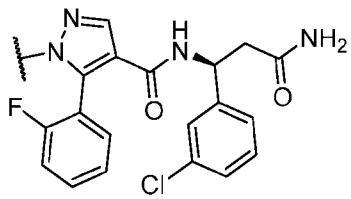
[00226] In some embodiments, j is 0. In some embodiments, j is 1. In some embodiments, j is 2. In some embodiments, j is 3. In some embodiments, j is 4.

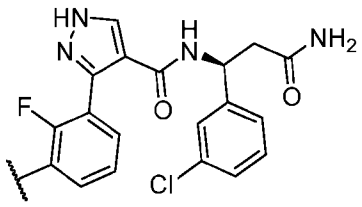
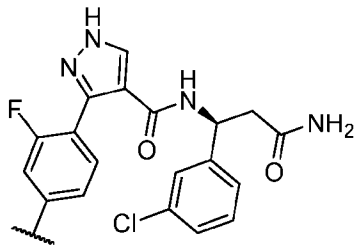
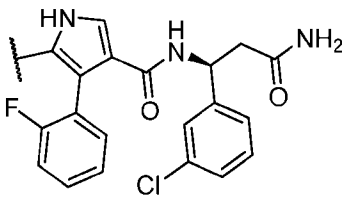
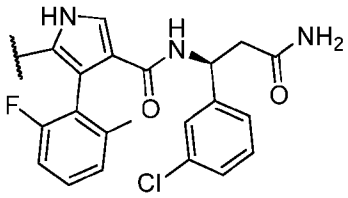
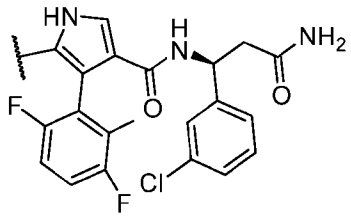
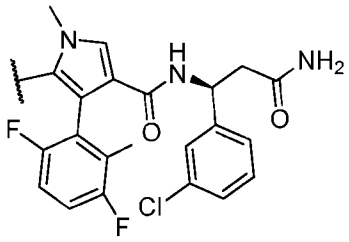
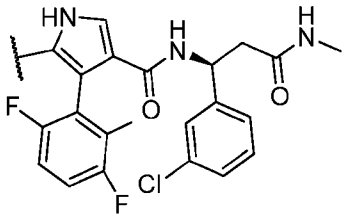
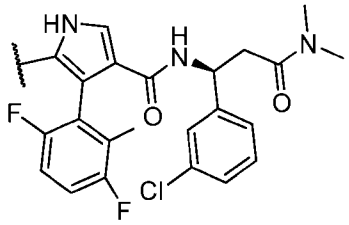
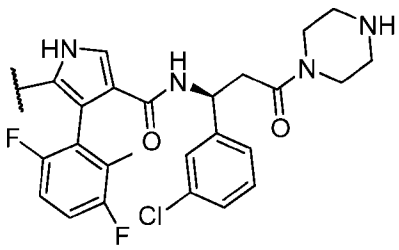
[00227] In some embodiments, j is 0 or 1. In some embodiments, j is 1 or 2. In some embodiments, j is 1, 2, or 3.

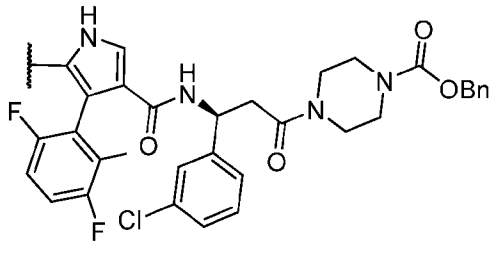
[00228] In some embodiments, k is 0. In some embodiments, k is 1. In some embodiments, k is 2. In some embodiments, k is 3. In some embodiments, k is 4.

[00229] In some embodiments, k is 0 or 1. In some embodiments, k is 1 or 2. In some embodiments, k is 1, 2, or 3.

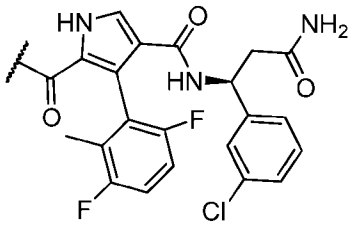
[00230] In some embodiment, e, f, g, h, i, j, and k are as depicted in the compounds of **Table 1**, below.

[00231] In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some

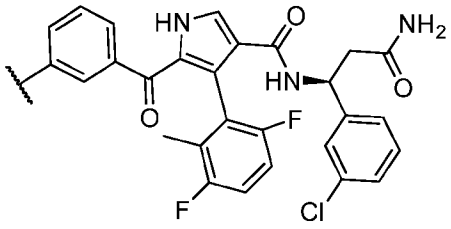
embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In some embodiments, DBM is  . In



some embodiments, DBM is . In some embodiments, DBM is



. In some embodiments, DBM is



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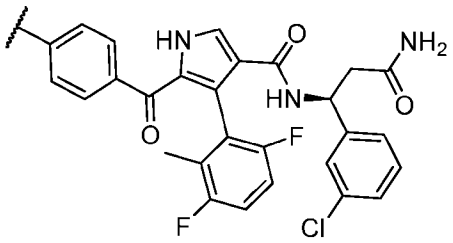
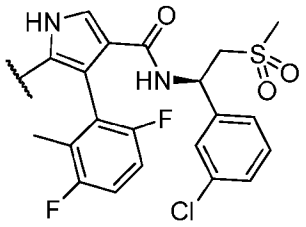
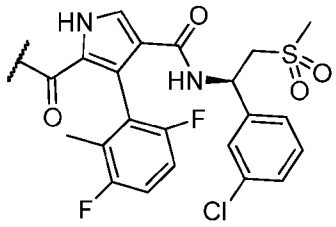


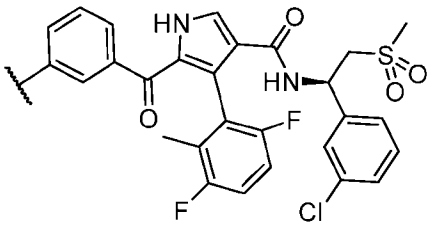
In some embodiments, DBM is . In some embodiments, DBM is



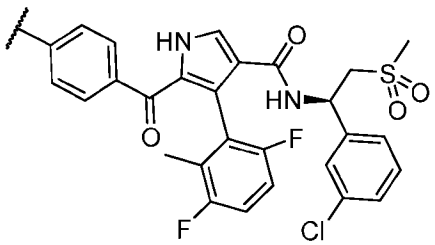
. In some embodiments, DBM is



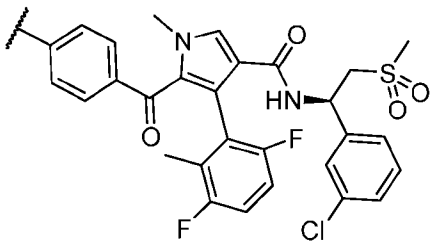
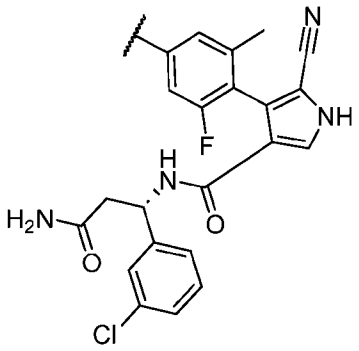
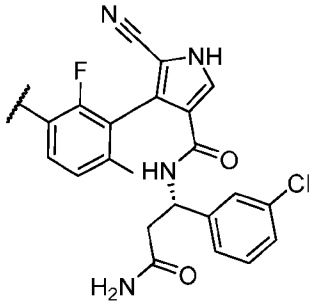
. In some



embodiments, DBM is . In some embodiments, DBM is



. In some embodiments, DBM is


. In some embodiments, DBM is 
. In some embodiments, DBM is 
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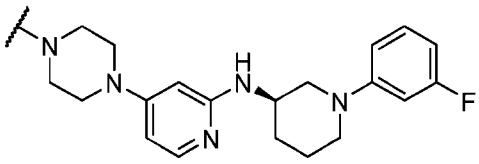
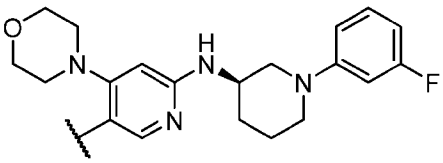
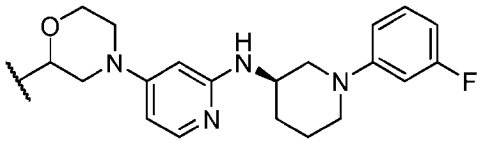
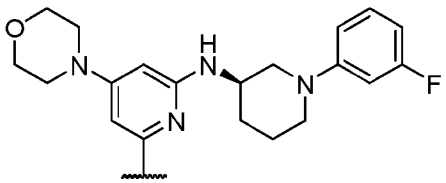
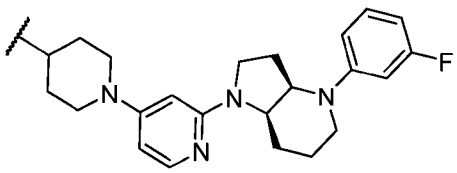
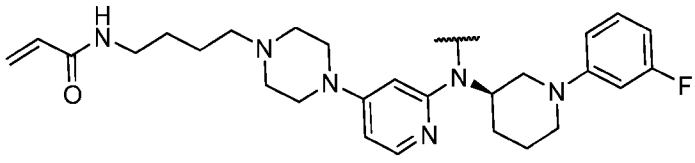
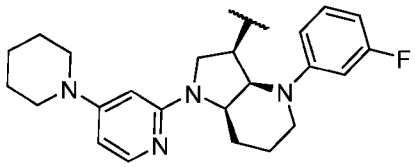
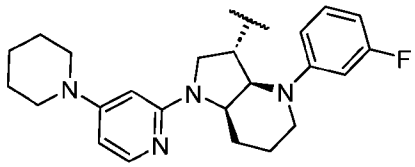
[00232] In some embodiments, DBM is 
. In some embodiments, DBM is 
. In some embodiments, DBM is 
. In some embodiments, DBM is 
. In some embodiments, DBM is 
. In some embodiments, DBM is



. In some embodiments, DBM is

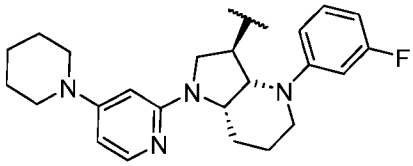


. In some embodiments, DBM is

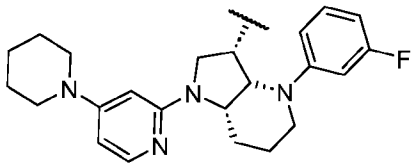


.

In some embodiments, DBM is

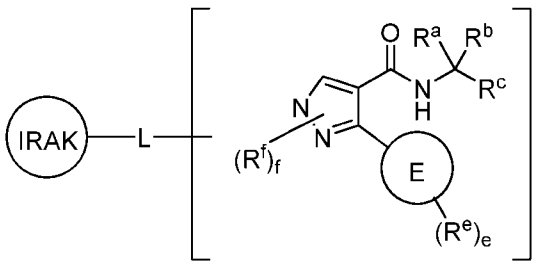


. In some embodiments, DBM is

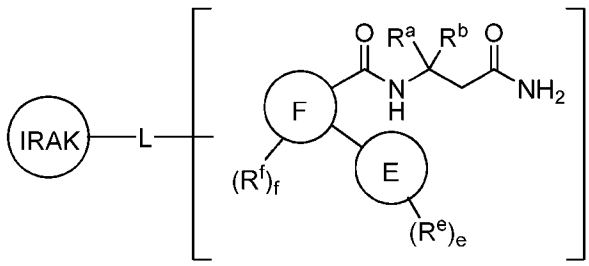


.In some embodiment, DBM as depicted in the compounds of **Table 1**, below.

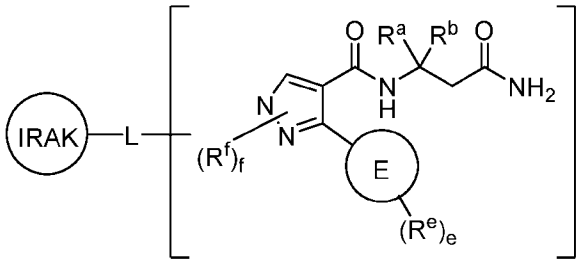
[00233] In certain embodiments, the present invention provides a compound of formula **I-a** or **I-a'** represented by any one of the following formulae:



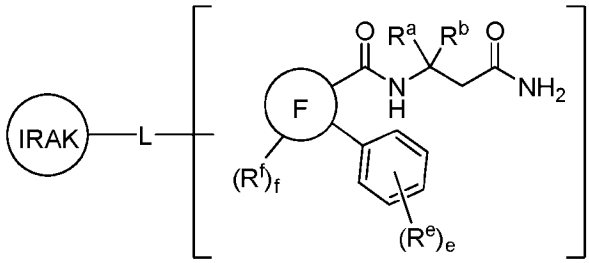
I-a-1



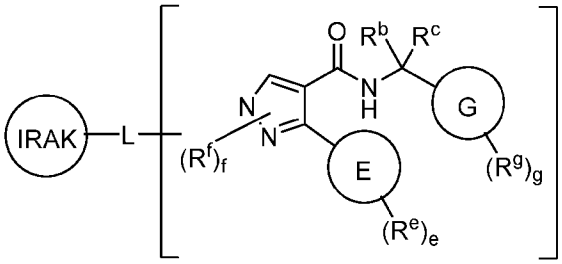
I-a-2



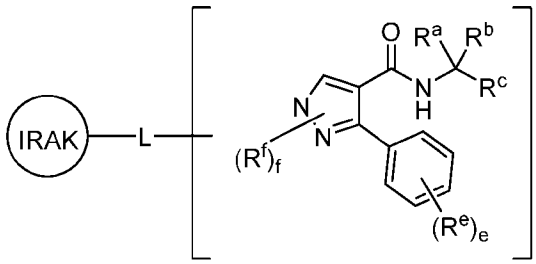
I-a-3



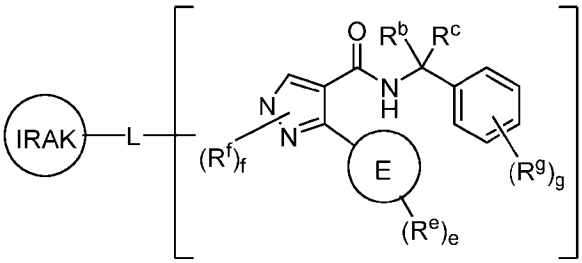
I-a-4



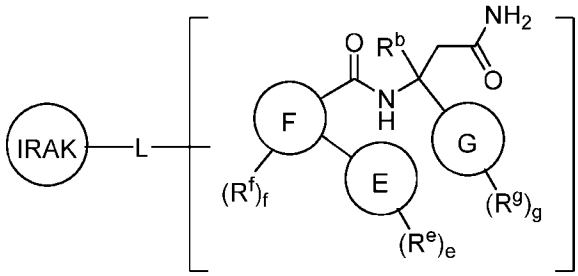
I-a-5



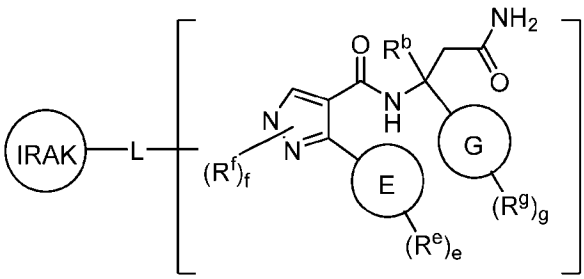
I-a-6



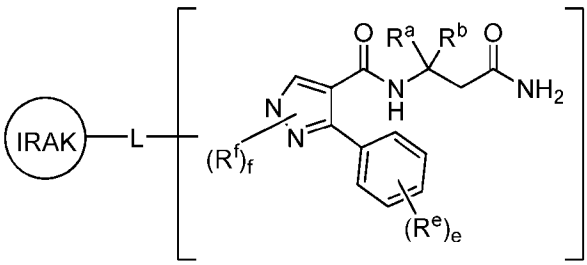
I-a-7



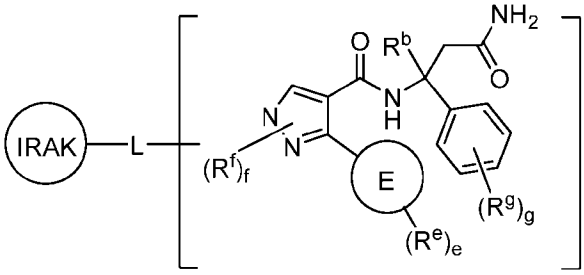
I-a-8



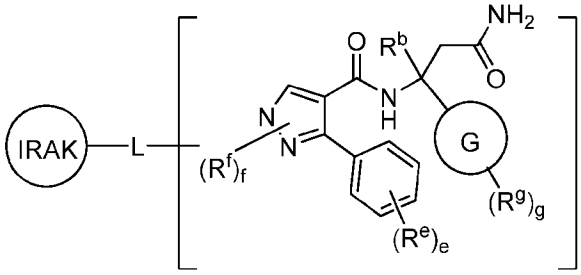
I-a-9



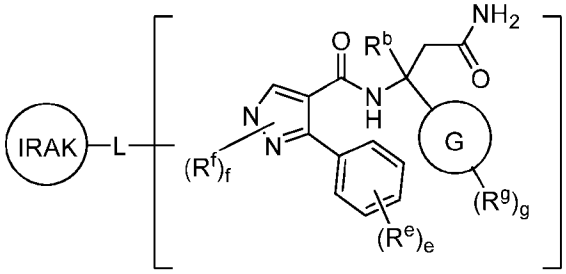
I-a-10

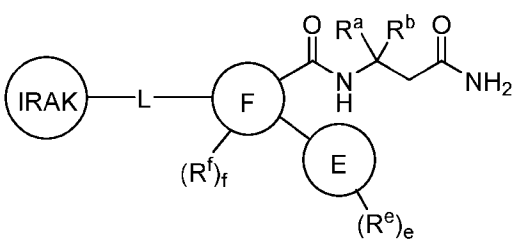


I-a-11

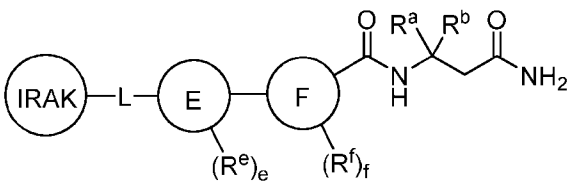


I-a-11

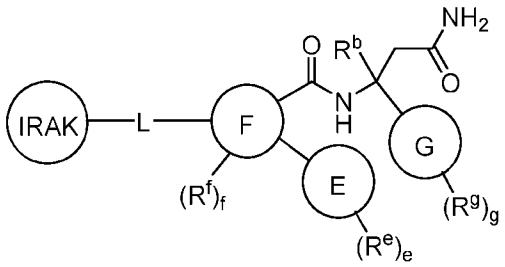




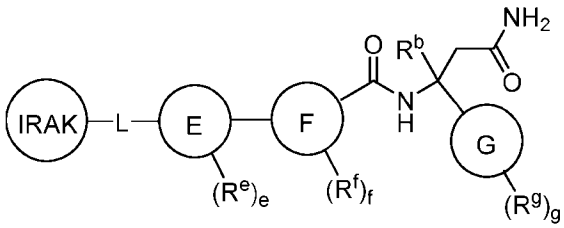
I-a-12



I-a-13

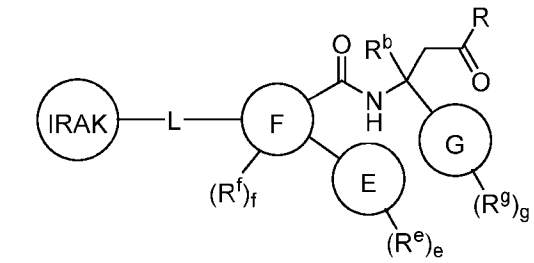


I-a-14



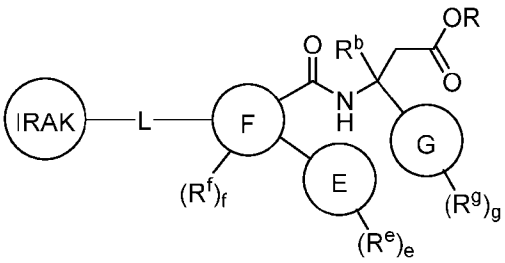
I-a-15

I-a-16

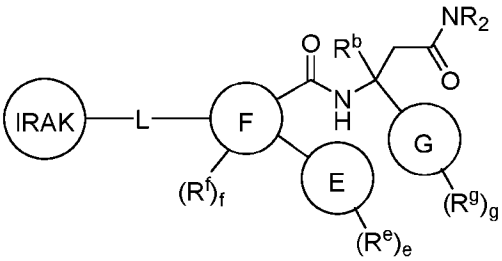


I-a-16'

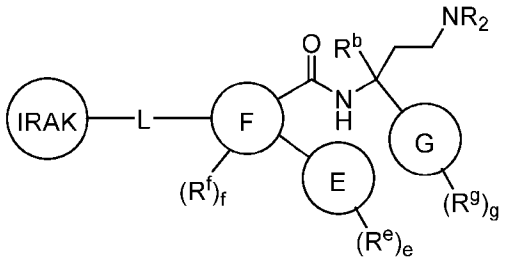
I-a-17



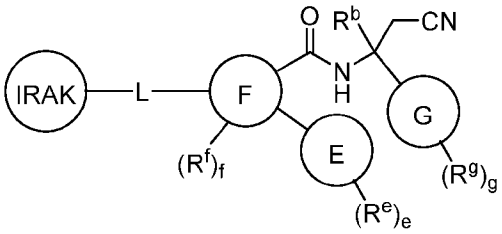
I-a-18



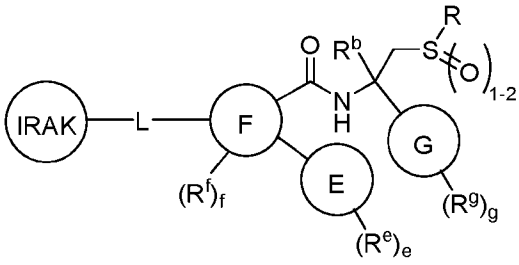
I-a-19

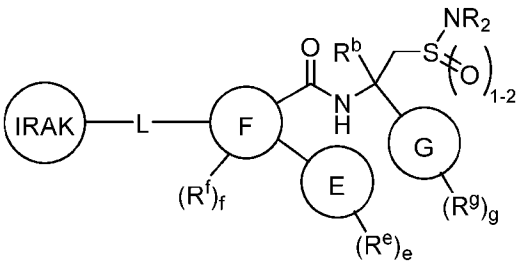


I-a-20

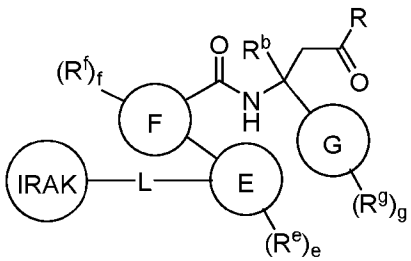


I-a-21

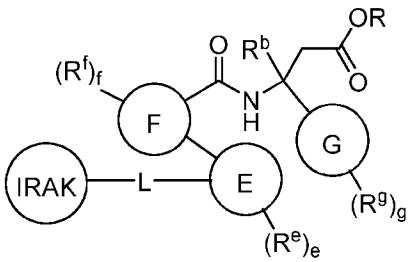




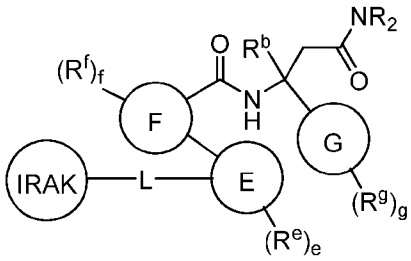
I-a-22



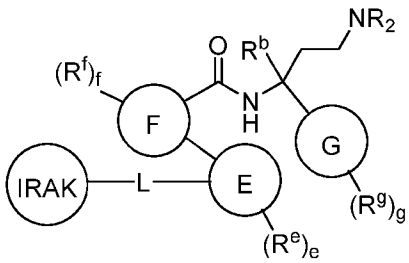
I-a-23



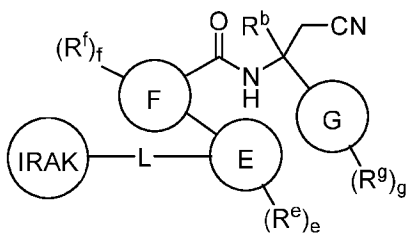
I-a-24



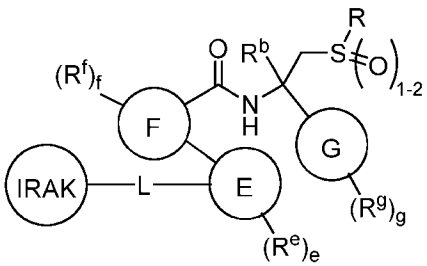
I-a-25



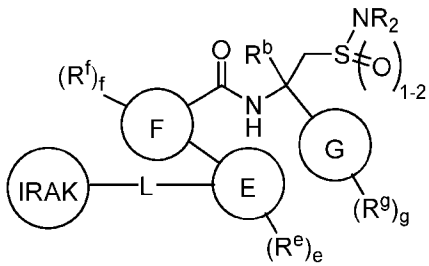
I-a-26



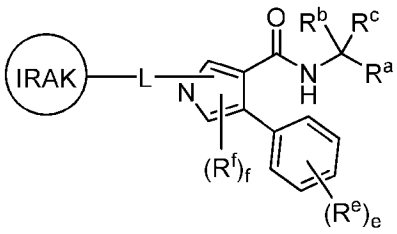
I-a-27



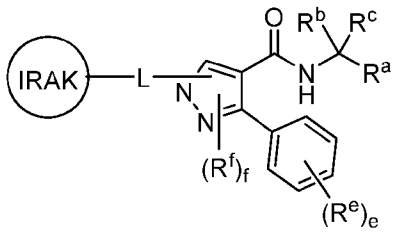
I-a-28



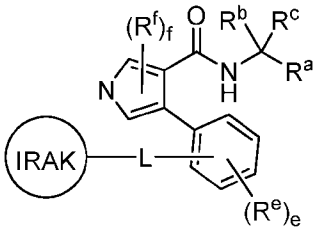
I-a-29



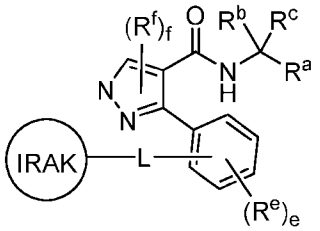
I-a-30



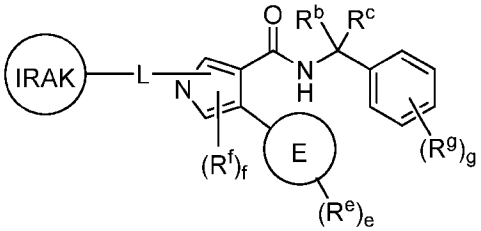
I-a-31



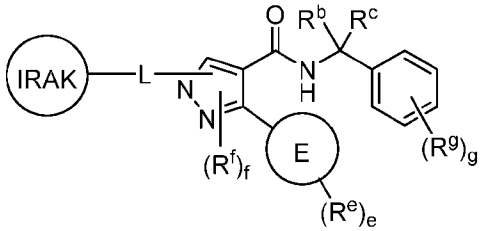
I-a-32



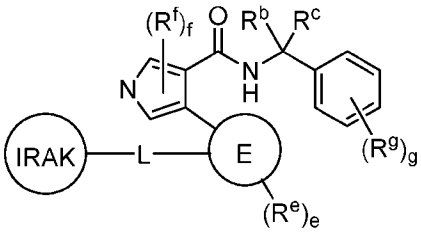
I-a-33



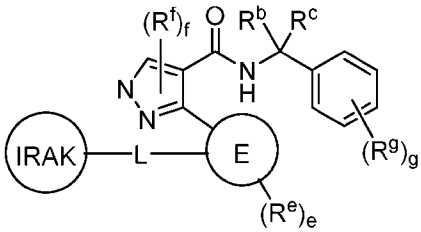
I-a-34



I-a-35



I-a-36



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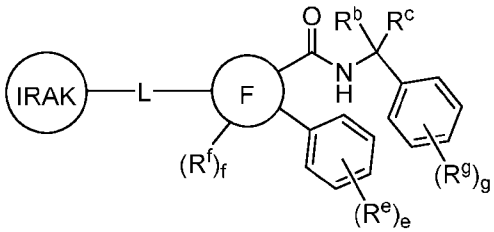

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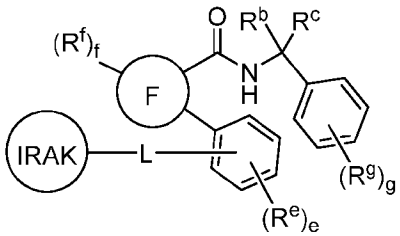

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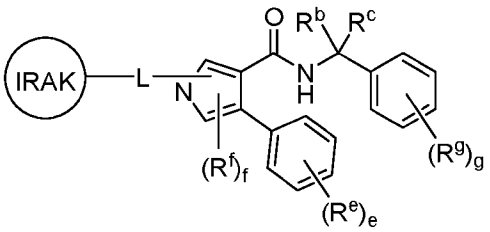

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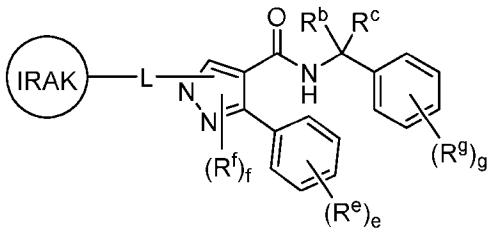

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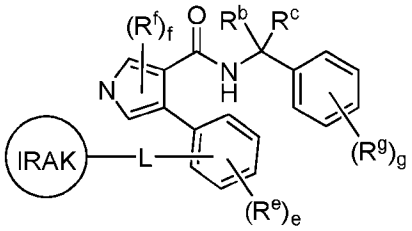

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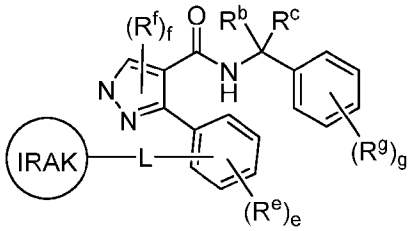

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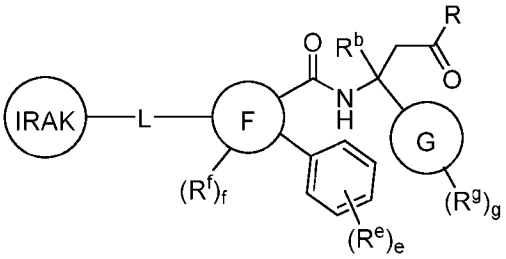

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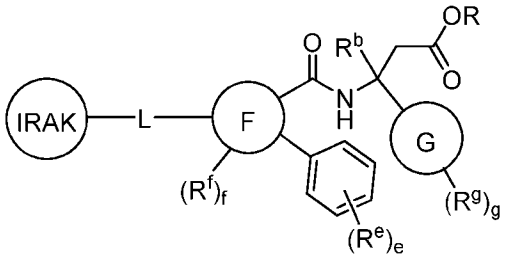

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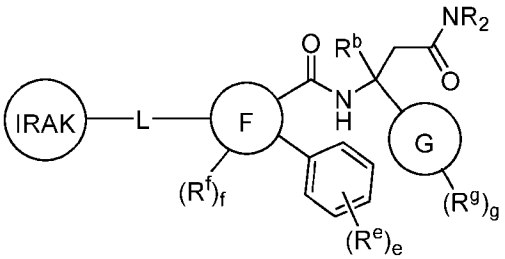

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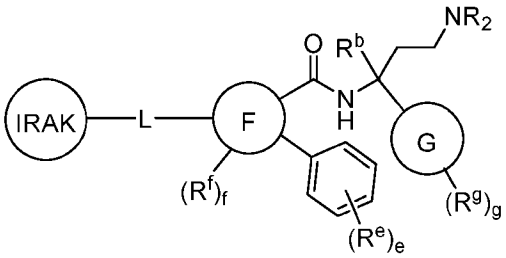

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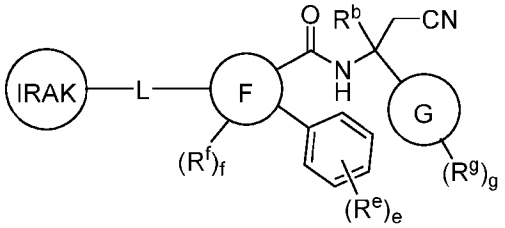

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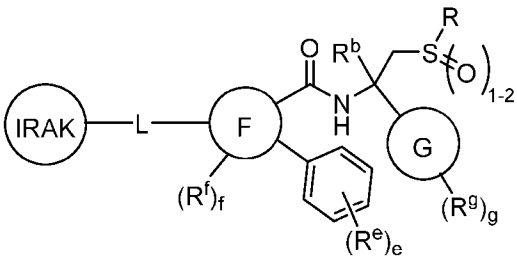

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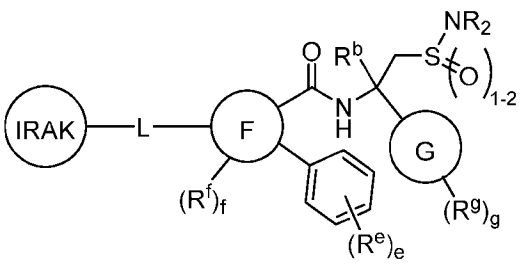

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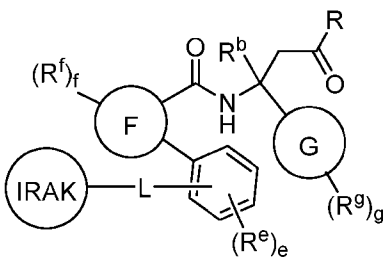

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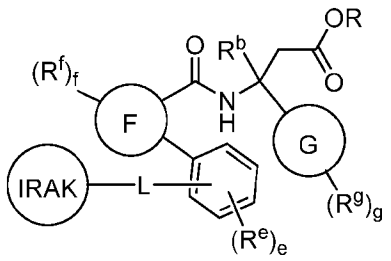

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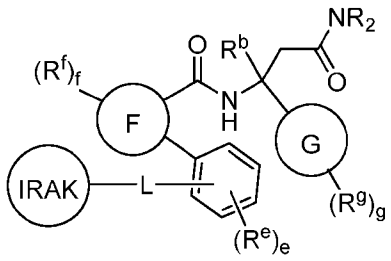

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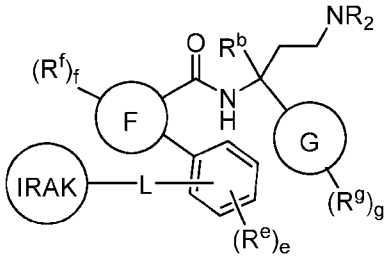

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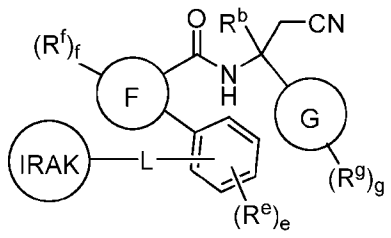

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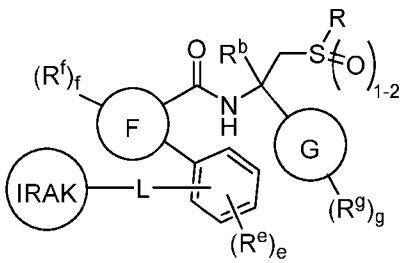

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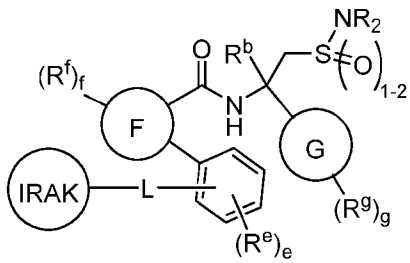

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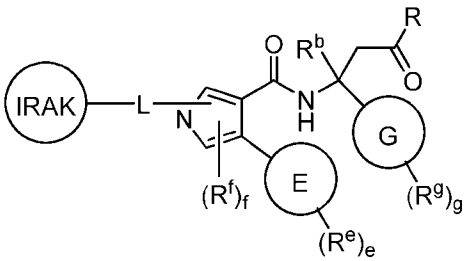

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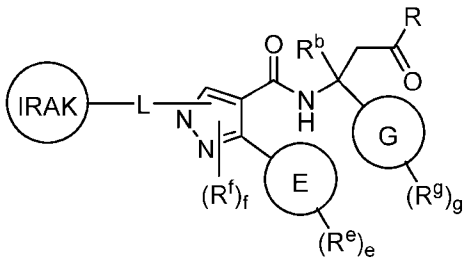

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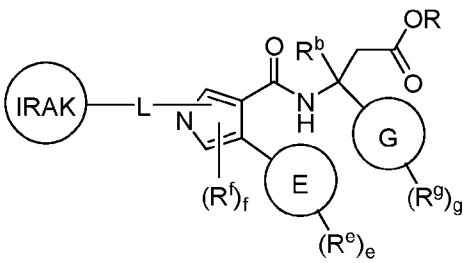

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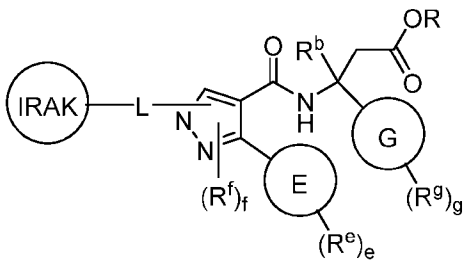

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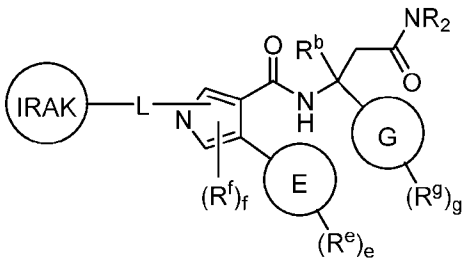

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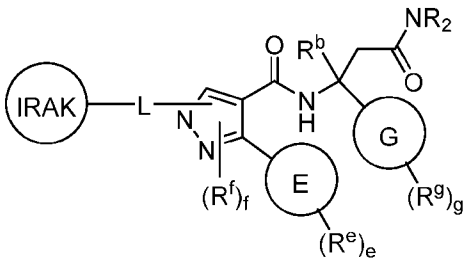

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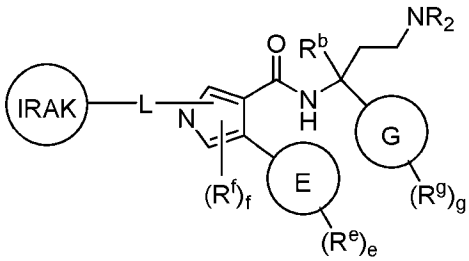

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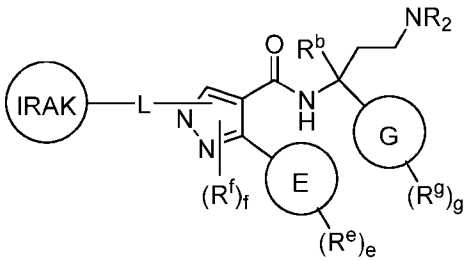

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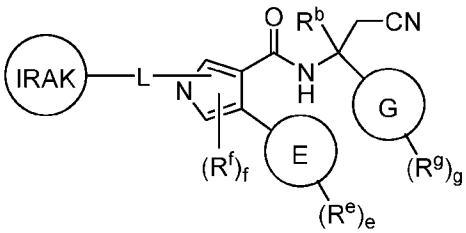

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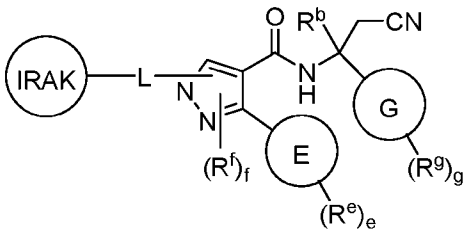

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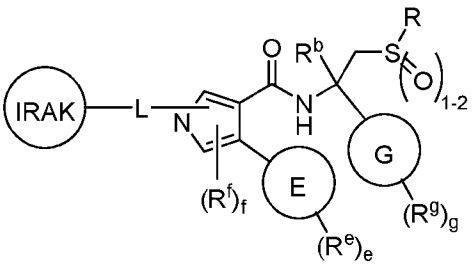

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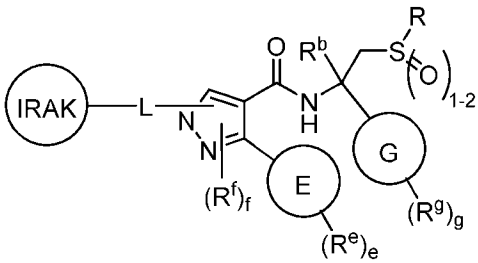

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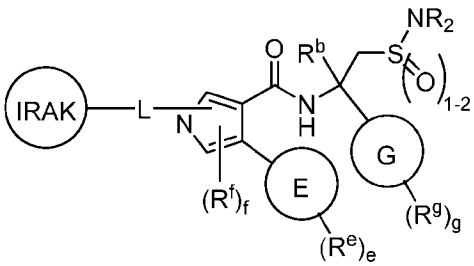

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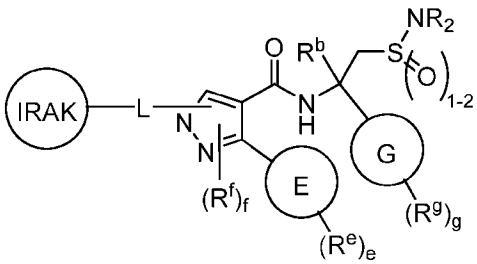

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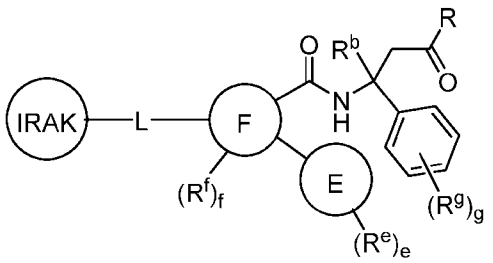

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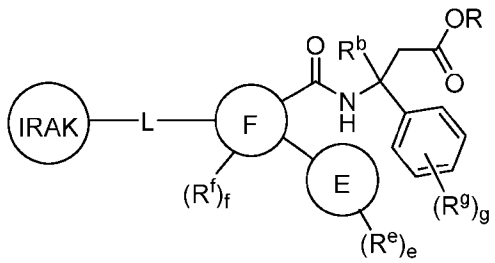

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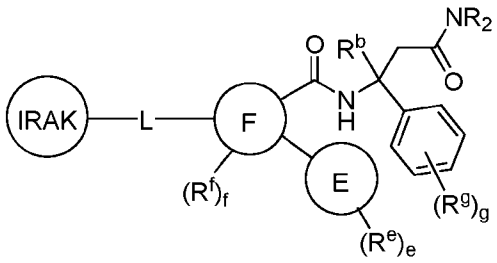

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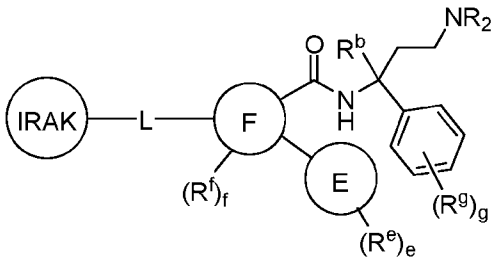

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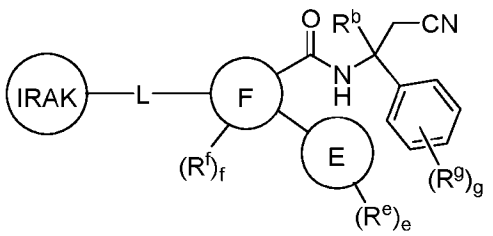

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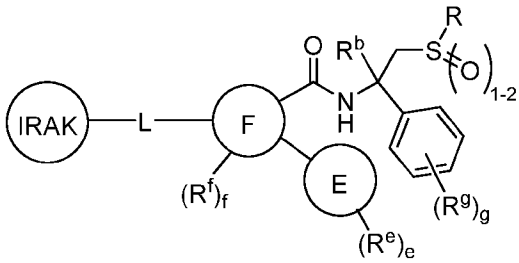

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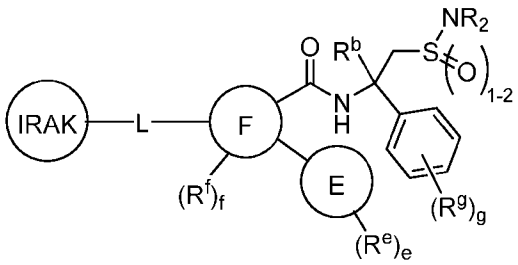

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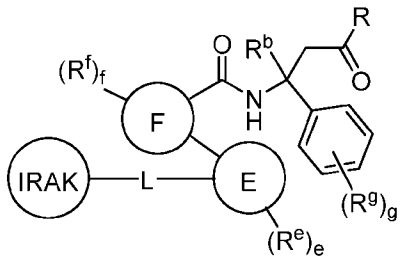

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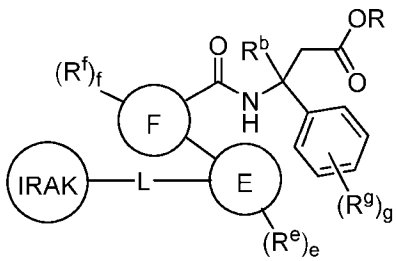

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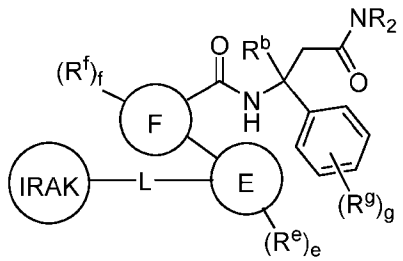

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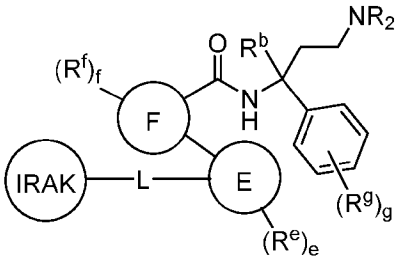

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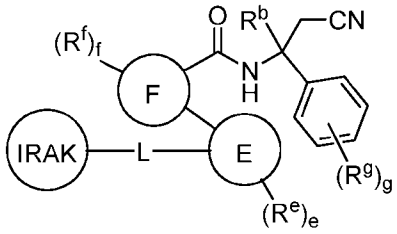

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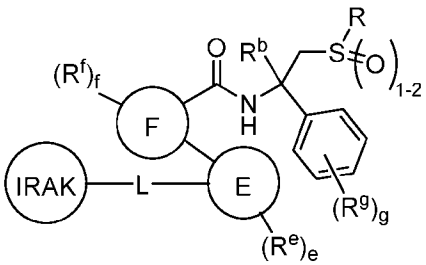

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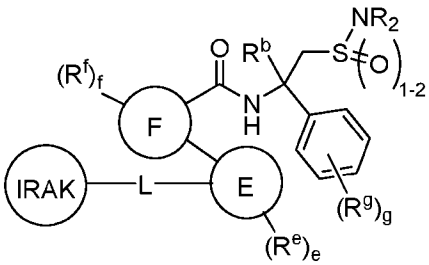

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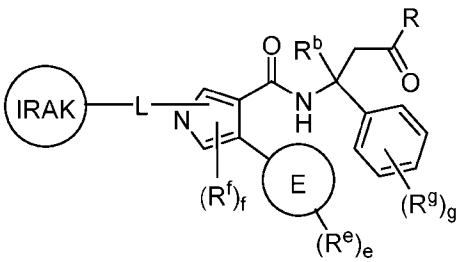
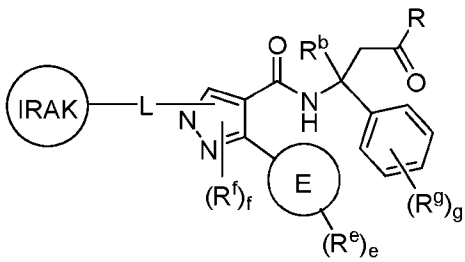


I-a-86



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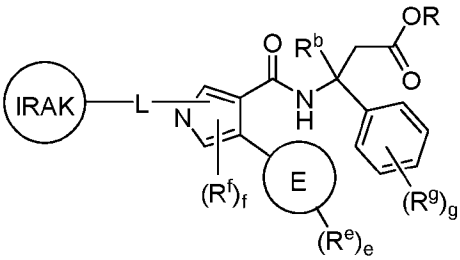

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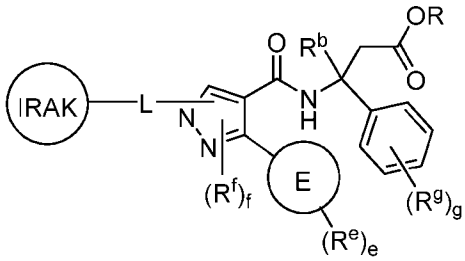

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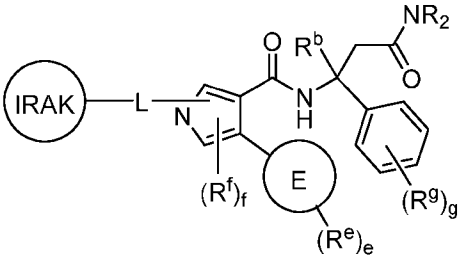

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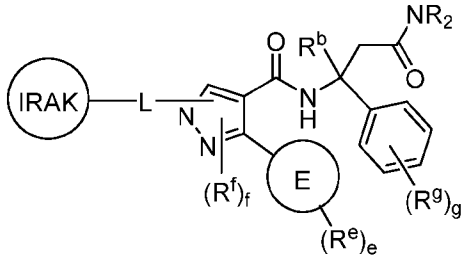
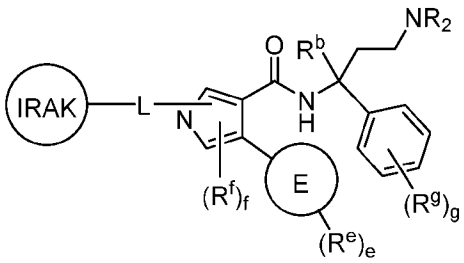
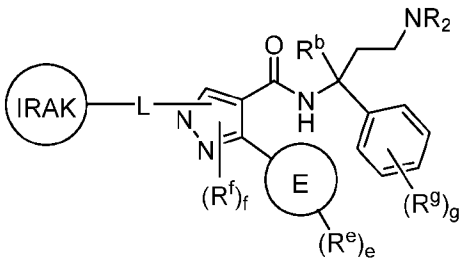


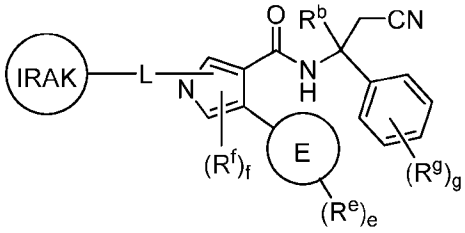
I-a-91



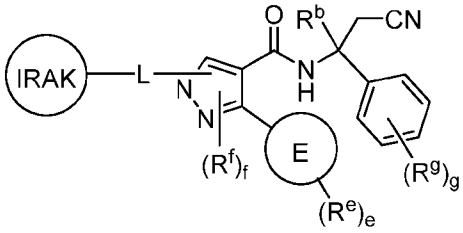
I-a-92



I-a-93



I-a-94



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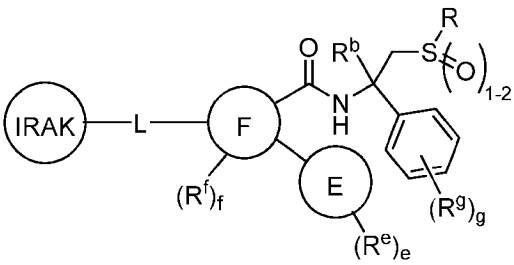
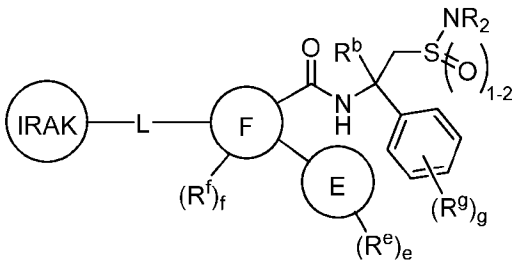


I-a-96



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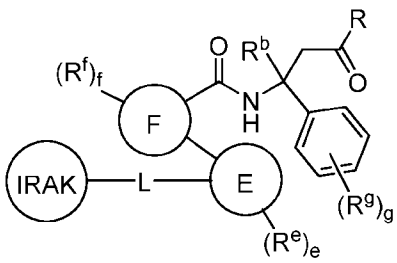

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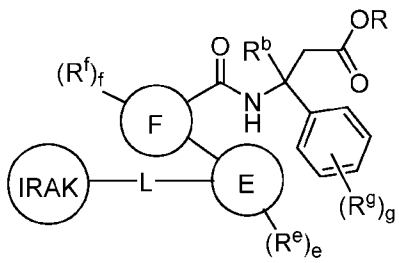

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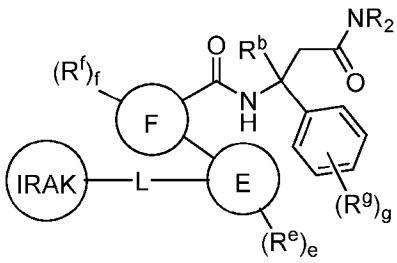

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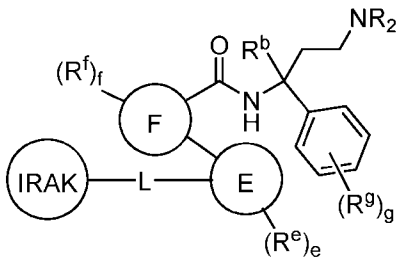

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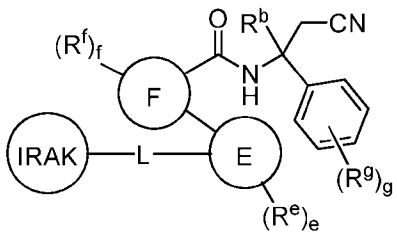

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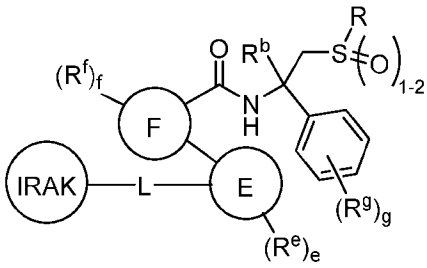

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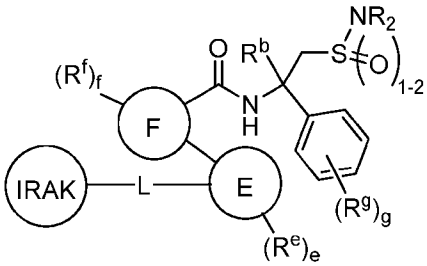

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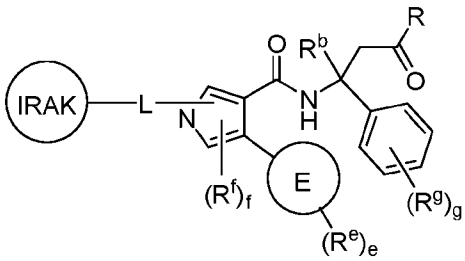

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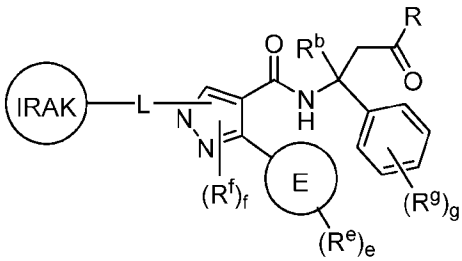

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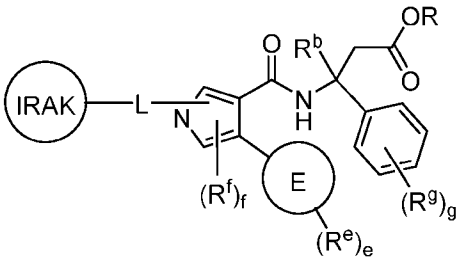

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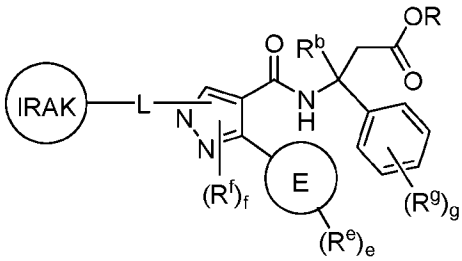

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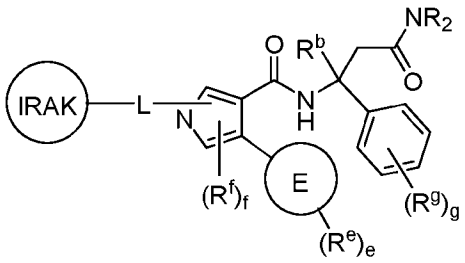

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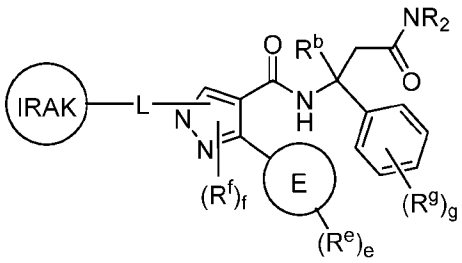

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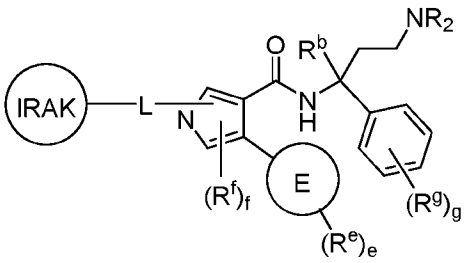

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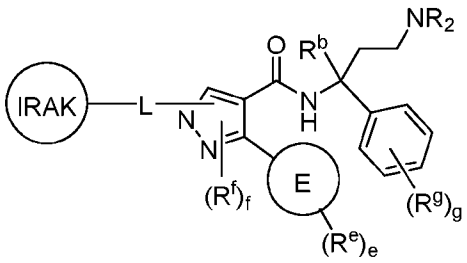

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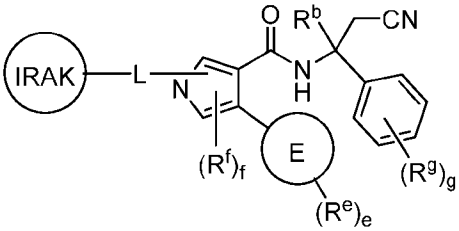

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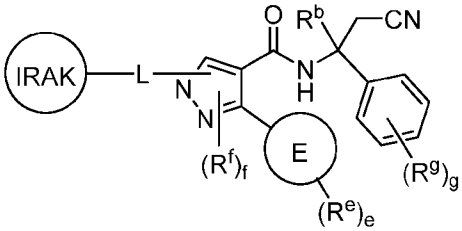

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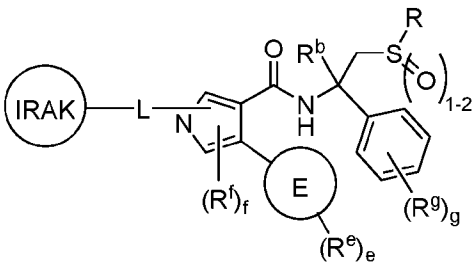

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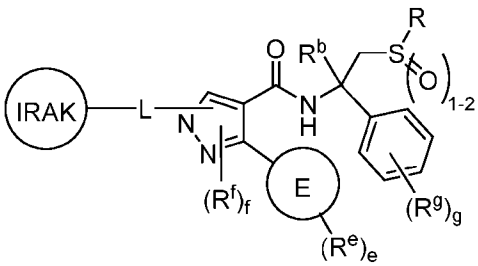

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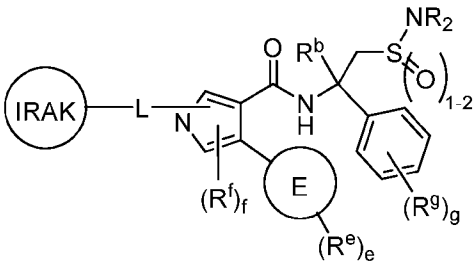

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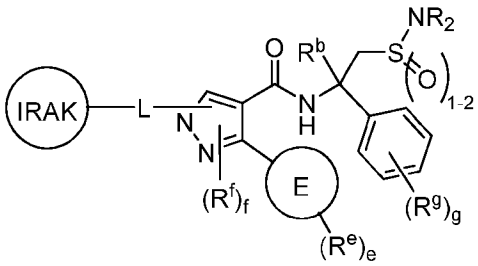

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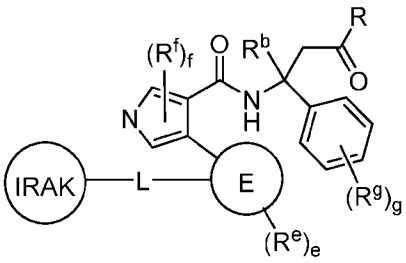

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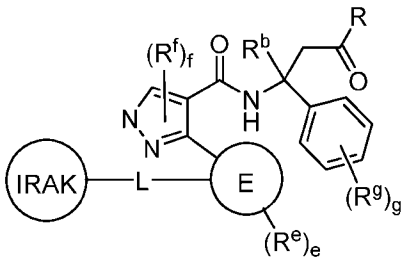

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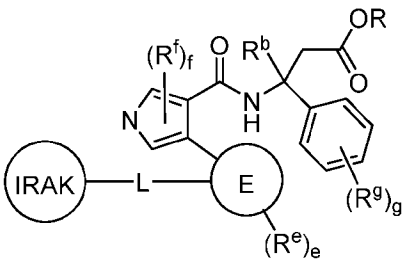

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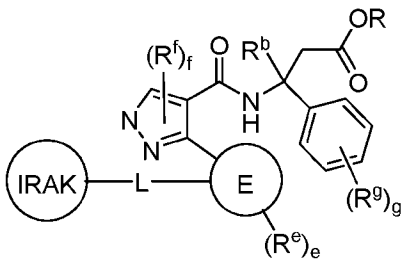

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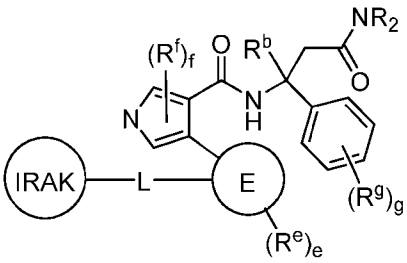

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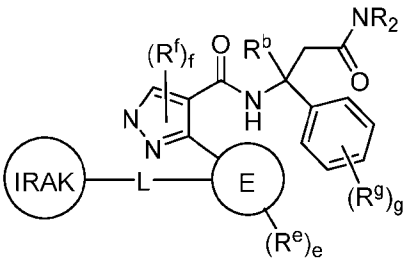

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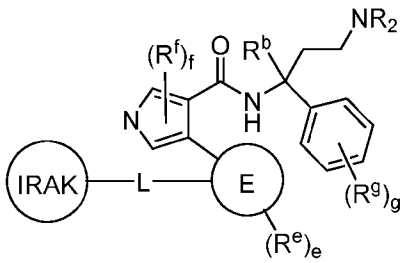

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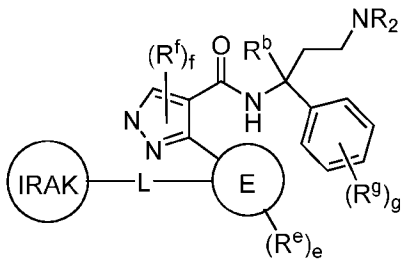

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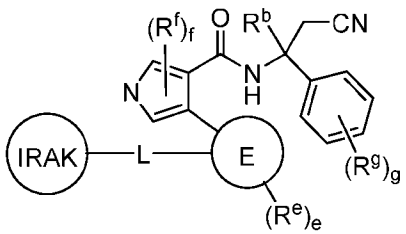

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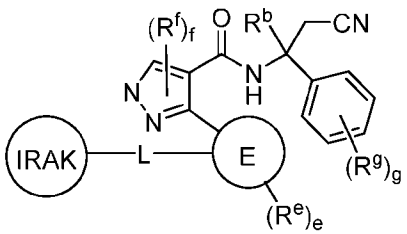

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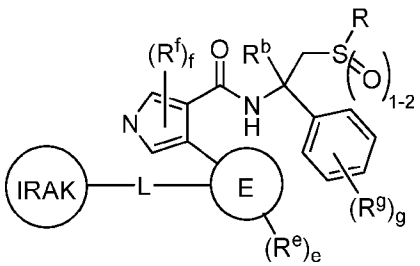

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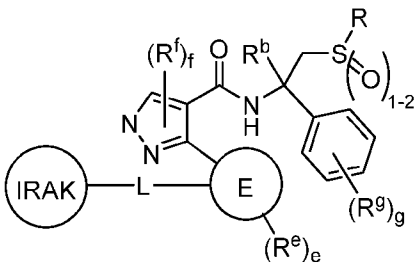

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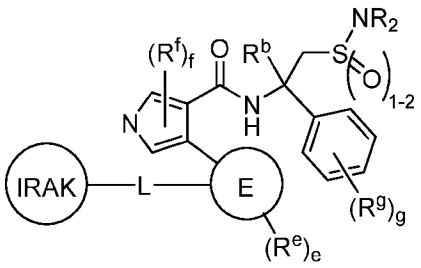

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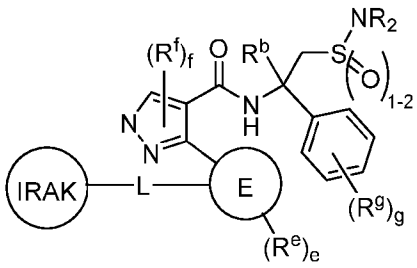

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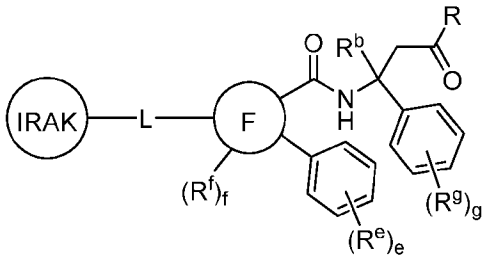

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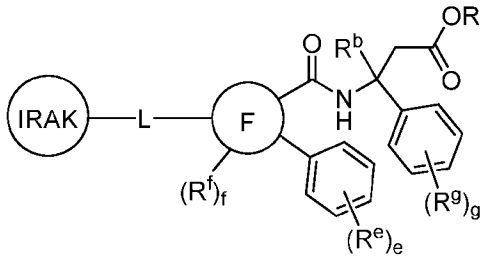

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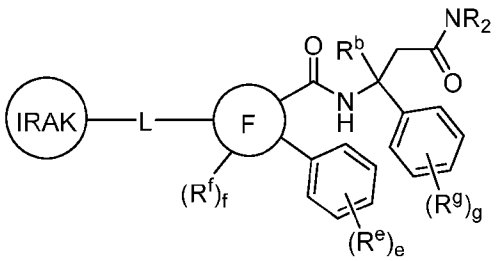

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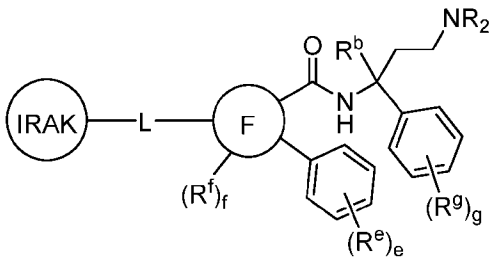

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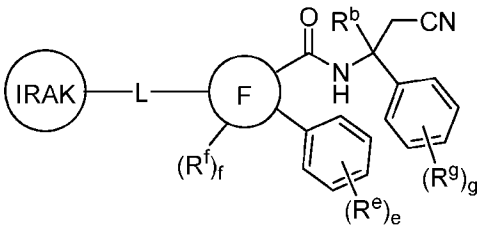

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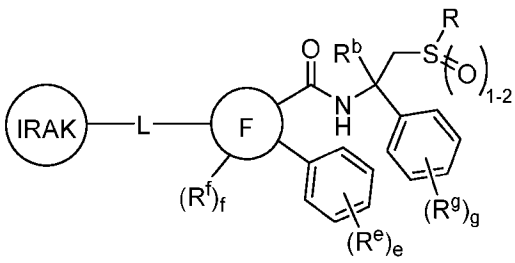

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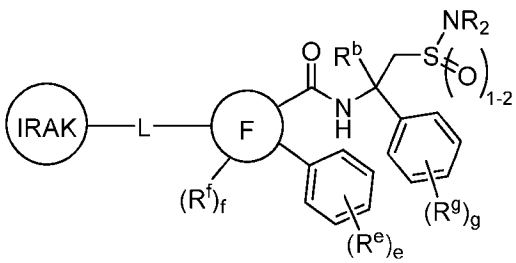

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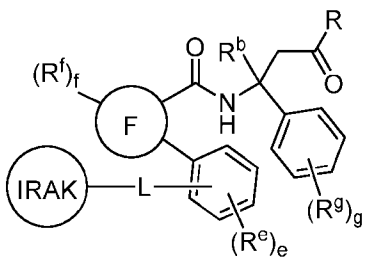

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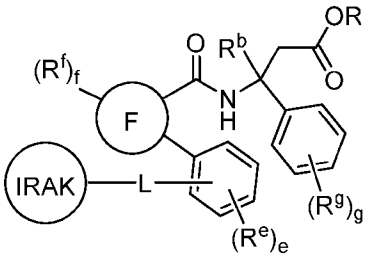

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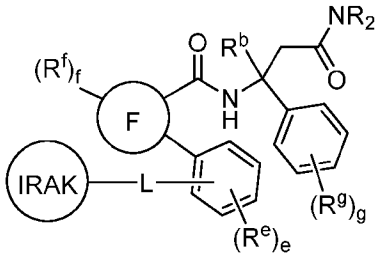

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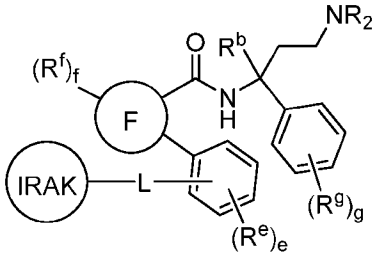

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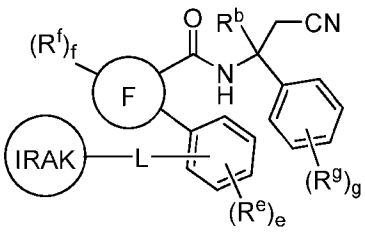

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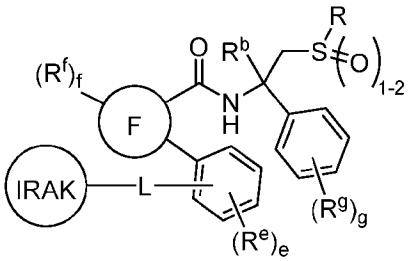

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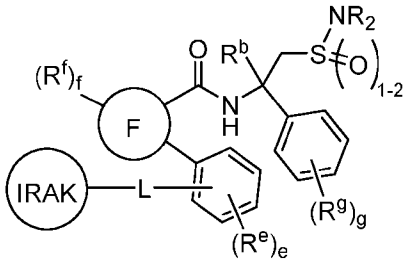

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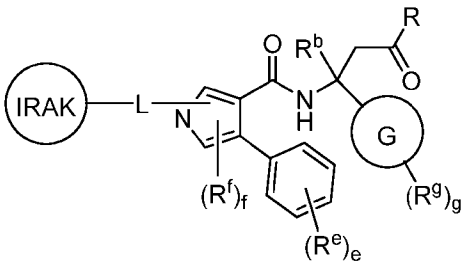

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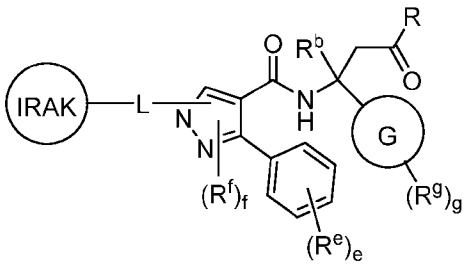

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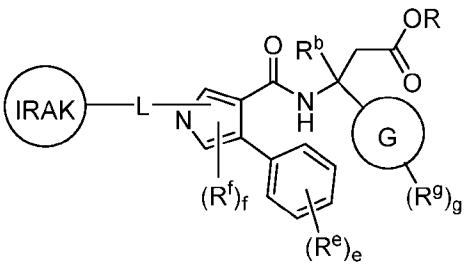
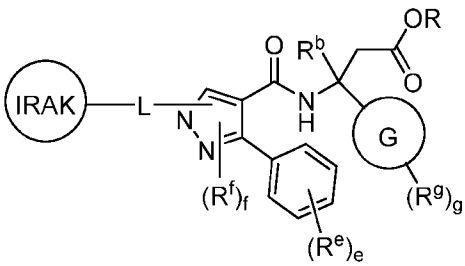
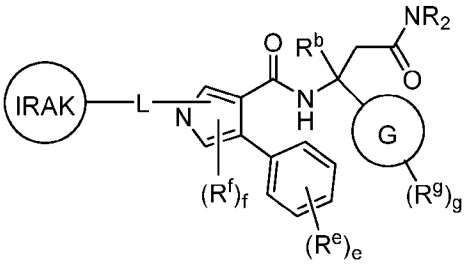


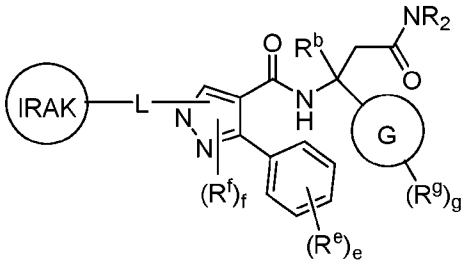
I-a-149



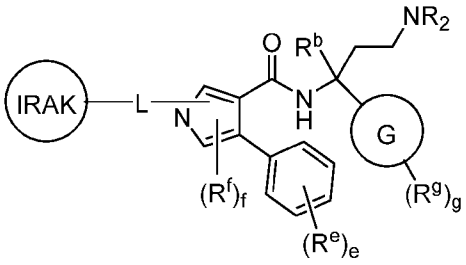
I-a-150



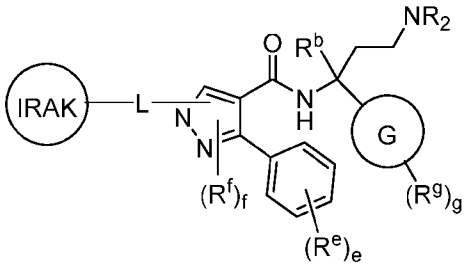
I-a-151



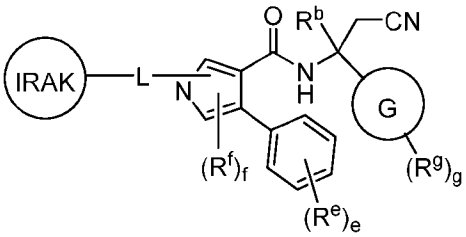
I-a-152



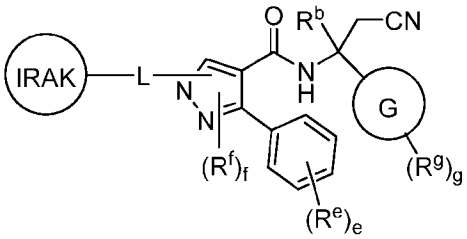
I-a-153



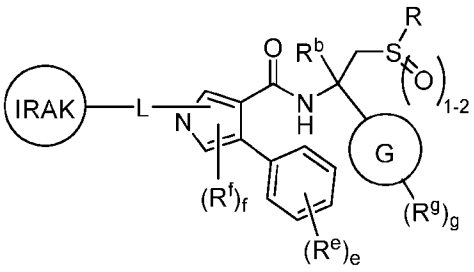
I-a-154



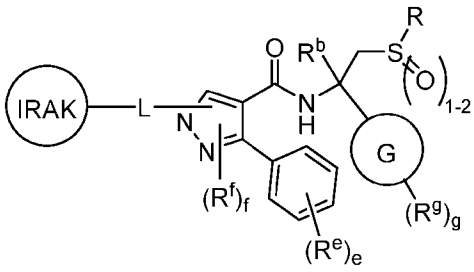
I-a-155



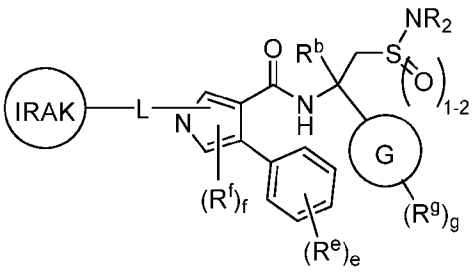
I-a-156



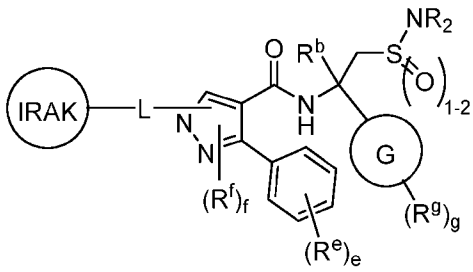
I-a-157



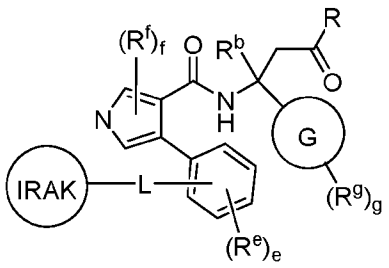
I-a-158



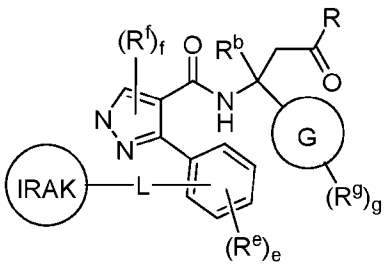
I-a-159



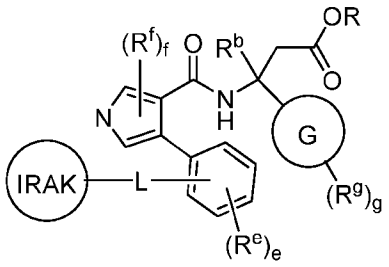
I-a-160



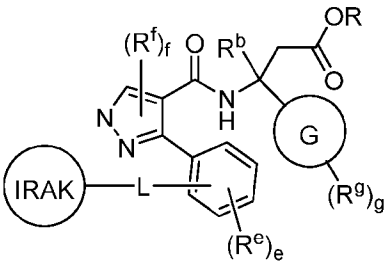
I-a-161



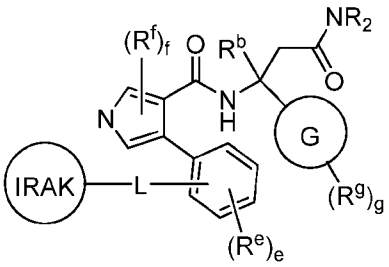
I-a-162



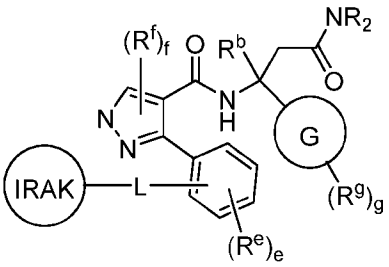
I-a-163



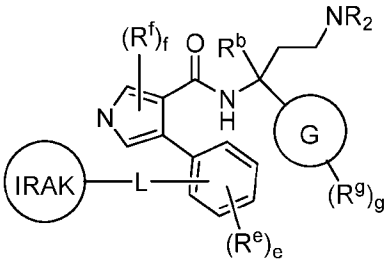
I-a-164



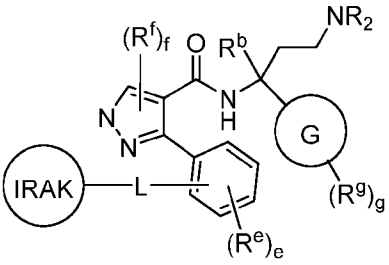
I-a-165



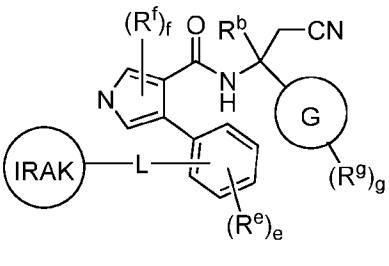
I-a-166



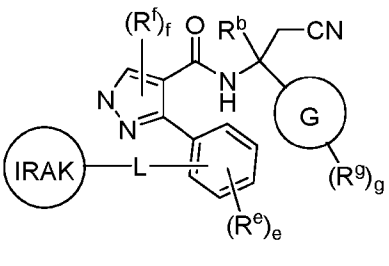
I-a-167



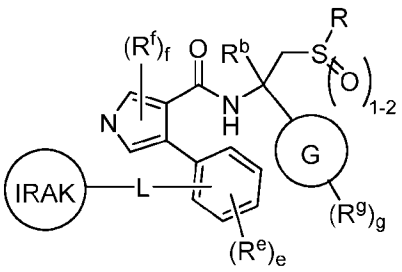
I-a-168



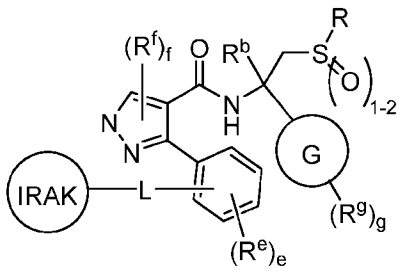
I-a-169



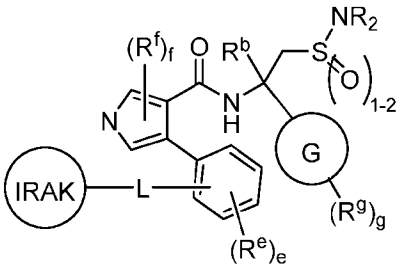
I-a-170



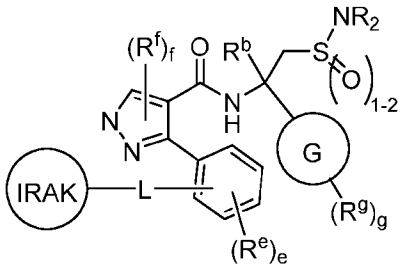
I-a-171



I-a-172



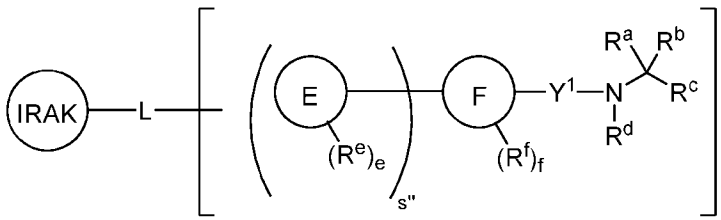
I-a-173



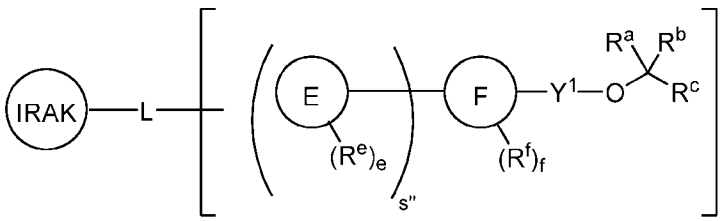
I-a-174

or a pharmaceutically acceptable salt thereof.

[00234] In certain embodiments, the present invention provides a compound of formula **I-a'** represented by any one of the following formulae:



I-a-1'



I-a-2'

or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, $-S(O)-$, $-S(O)_2-$, -C(OR)=; and wherein

when Y^1 is -C(OR)= in formula **I-a-1'**, R^c is optionally taken together with R of -C(OR)=, and with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-

1 heteroatoms, in addition to the 2 heteroatoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur.

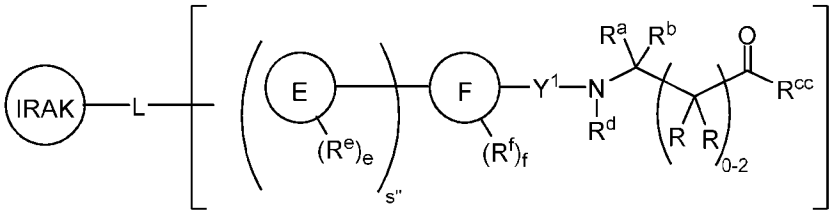
[00235] In some embodiments, Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, $-CR(OR)-$, $-C(O)-$, $-C(NR)-$, $-C(NOR)-$, $-S(O)-$, or $-S(O)_2-$.

[00236] In some embodiments, Y^1 is $-CR_2-$, $-CR(OR)-$, $-C(O)-$, $-C(NR)-$, $-C(NOR)-$, $-S(O)-$, or $-S(O)_2-$.

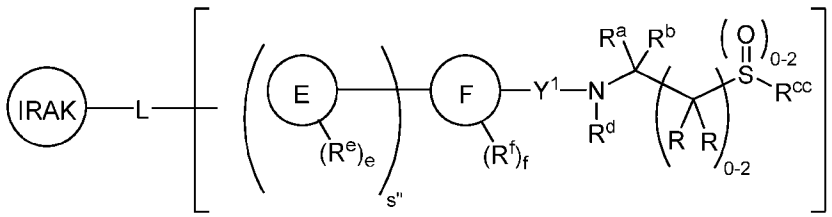
[00237] In some embodiments, Y^1 is $-C(O)-$.

[00238] In some embodiments, Y^1 is as depicted in the compounds of **Table 1**, below.

[00239] In certain embodiments, the present invention provides a compound of formula **I-a'** represented by any one of the following formulae:



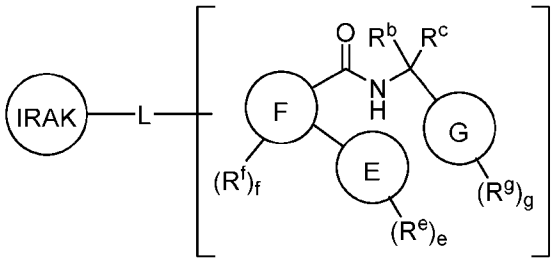
I-a-3'



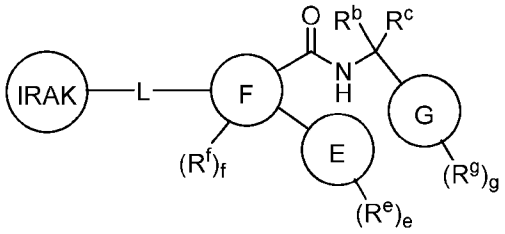
I-a-4'

or a pharmaceutically acceptable salt thereof.

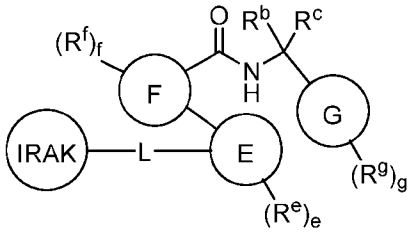
[00240] In certain embodiments, the present invention provides a compound of formula **I-a** or **I-a'** represented by any one of the following formulae:



I-a-5'



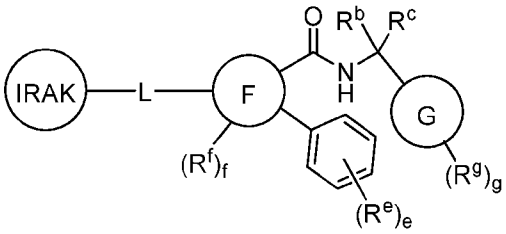
I-a-6'



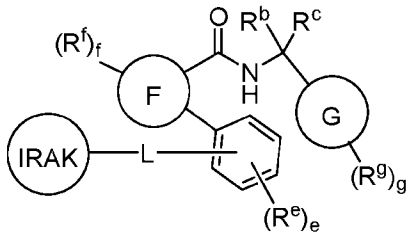
I-a-7'

or a pharmaceutically acceptable salt thereof.

[00241] In certain embodiments, the present invention provides a compound of formula **I-a** or **I-a'** represented by any one of the following formulae:



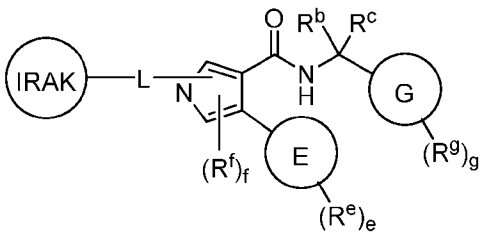
I-a-8'



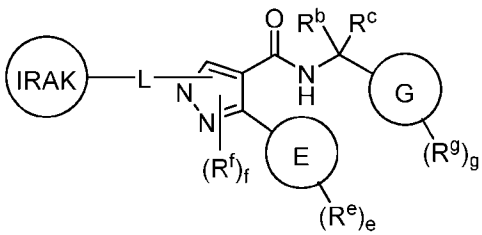
I-a-9'

or a pharmaceutically acceptable salt thereof.

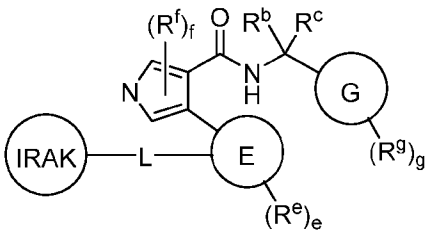
[00242] In certain embodiments, the present invention provides a compound of formula **I-a** or **I-a'** represented by any one of the following formulae:



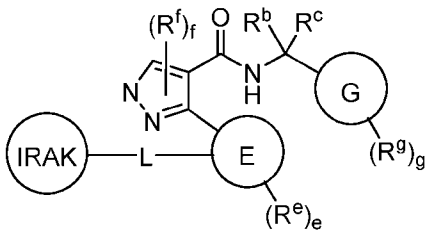
I-a-10'



I-a-11'



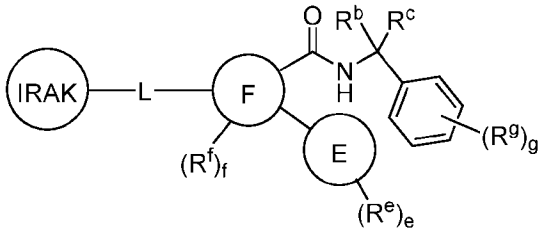
I-a-12'



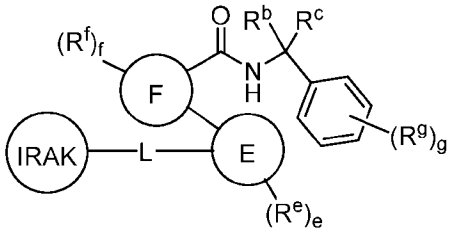
I-a-13'

or a pharmaceutically acceptable salt thereof.

[00243] In certain embodiments, the present invention provides a compound of formula **I-a** or **I-a'** represented by any one of the following formulae:



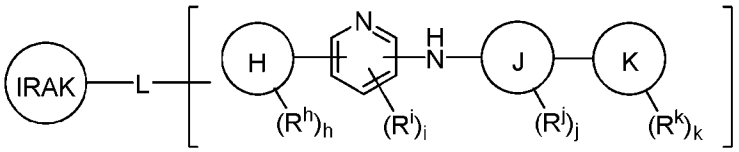
I-a-14'



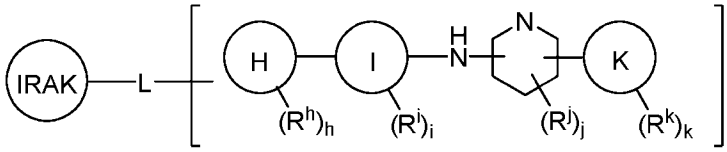
I-a-15'

or a pharmaceutically acceptable salt thereof.

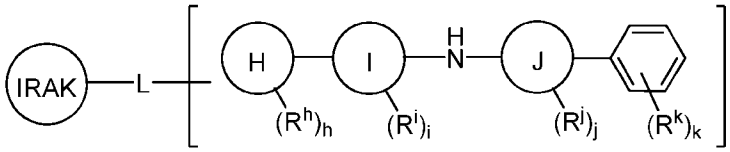
[00244] In certain embodiments, the present invention provides a compound of formula **I-b** or **I-b'** represented by any one of the following formulae:



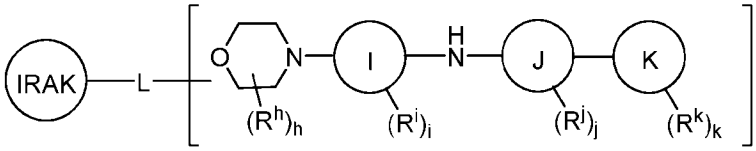
I-b-1



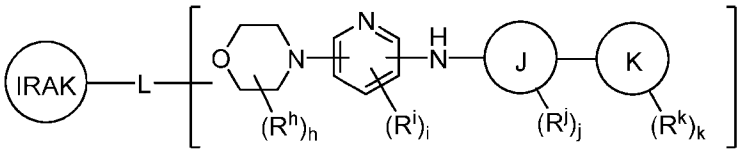
I-b-2



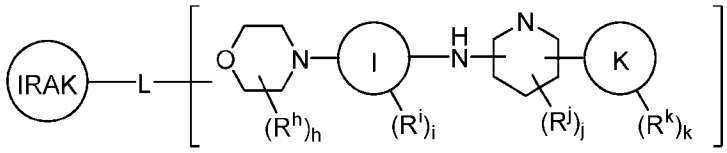
I-b-3



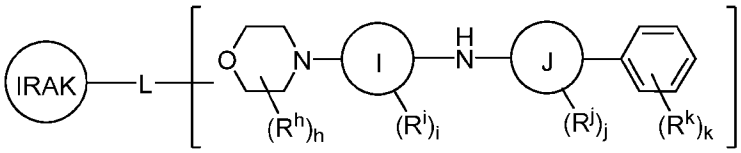
I-b-4



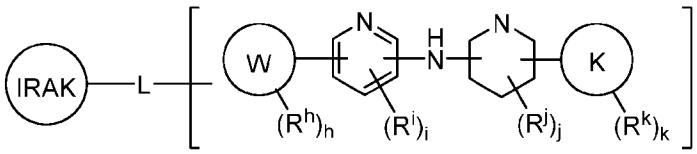
I-b-5



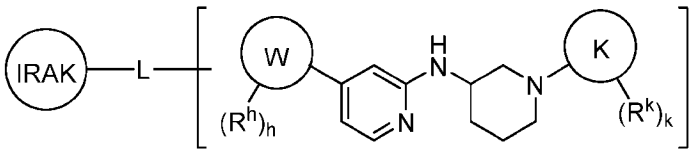
I-b-6



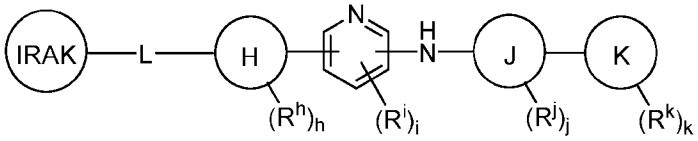
I-b-7



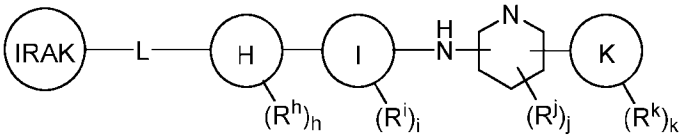
I-b-8



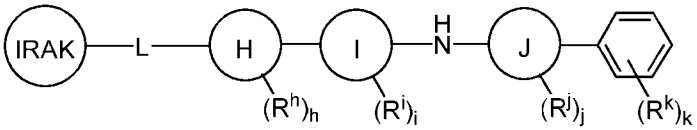
I-b-9



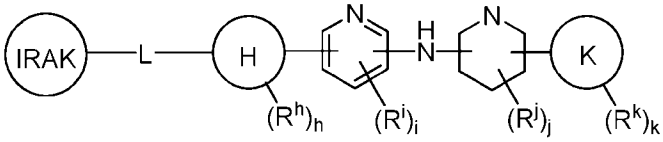
I-b-10



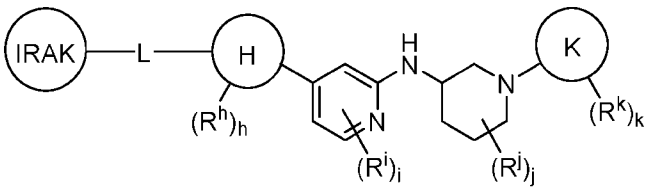
I-b-11



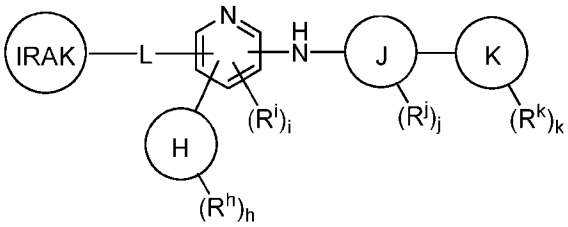
I-b-12



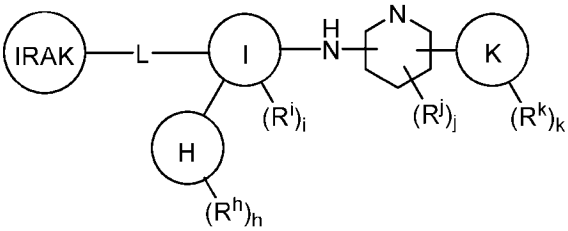
I-b-13



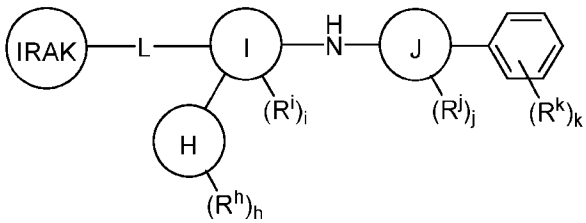
I-b-14



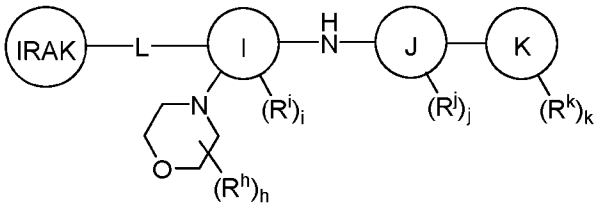
I-b-15



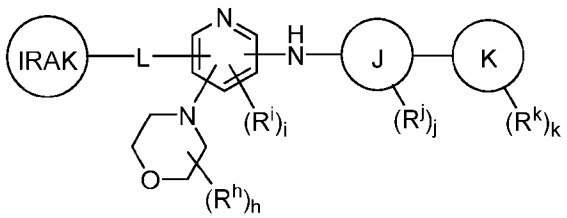
I-b-16



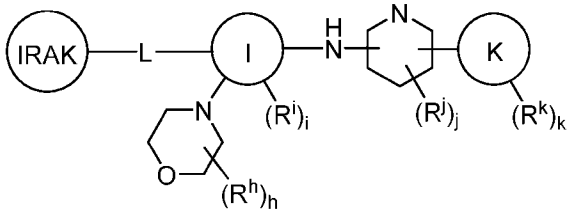
I-b-17



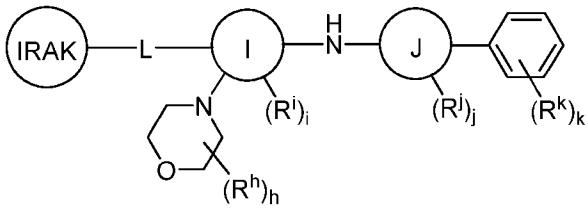
I-b-18



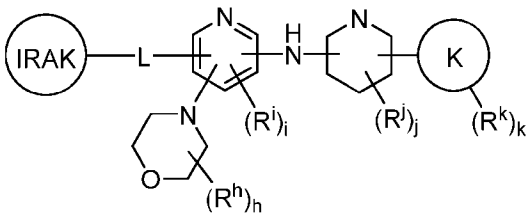
I-b-19



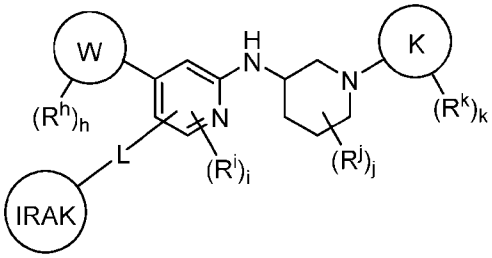
I-b-20



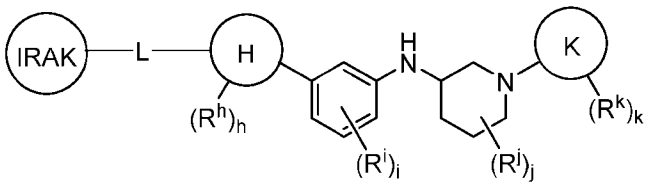
I-b-21



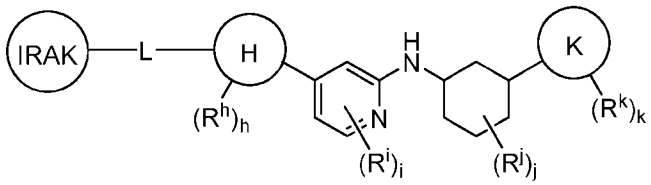
I-b-22



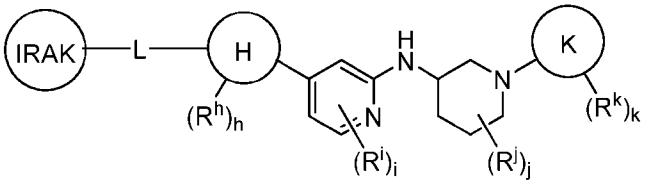
I-b-23



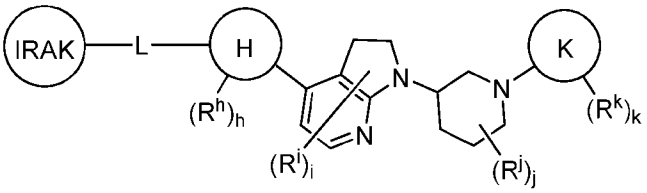
I-b-22'



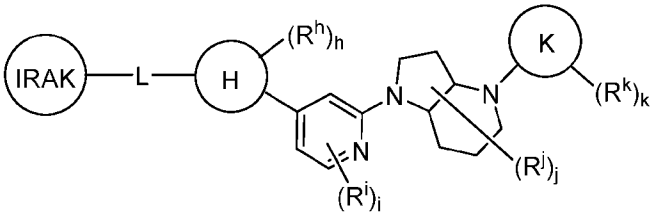
I-b-23'



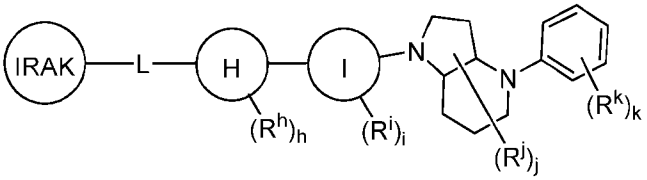
I-b-24



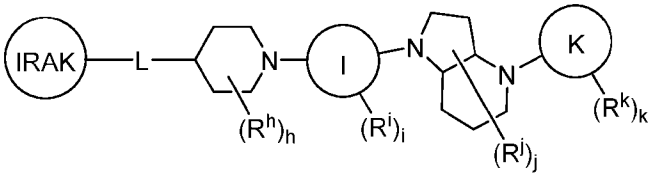
I-b-25



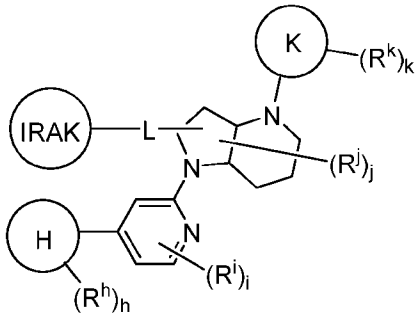
I-b-26



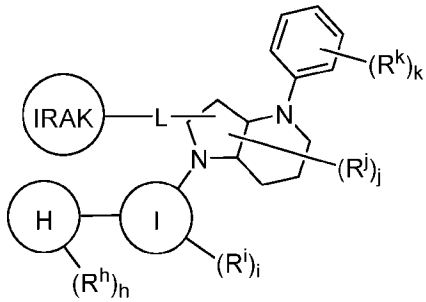
I-b-27



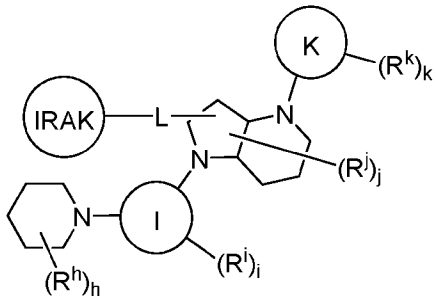
I-b-28



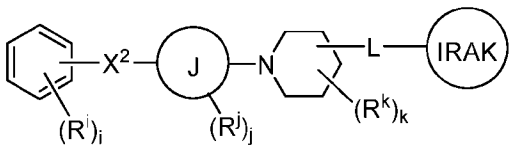
I-b-29



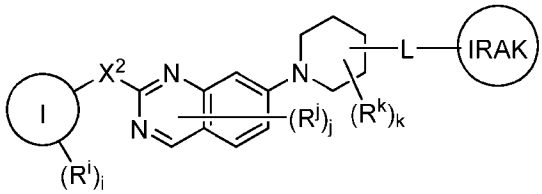
I-b-30



I-b-31



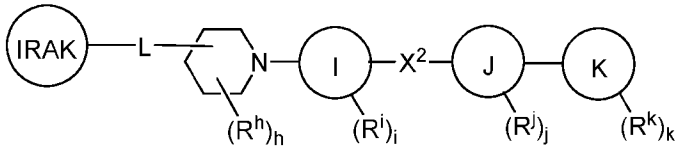
I-b-32



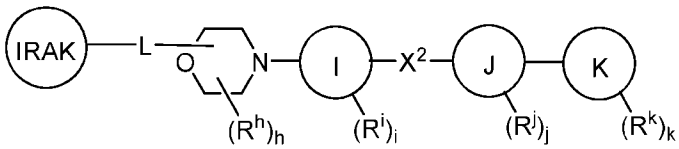
I-b-33

or a pharmaceutically acceptable salt thereof.

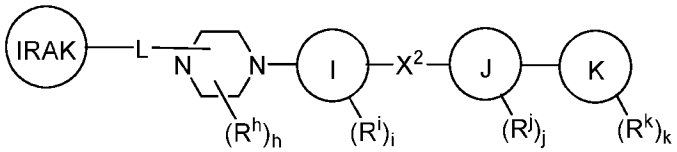
[00245] In certain embodiments, the present invention provides a compound of formula **I-b** or **I-b'** represented by any one of the following formulae:



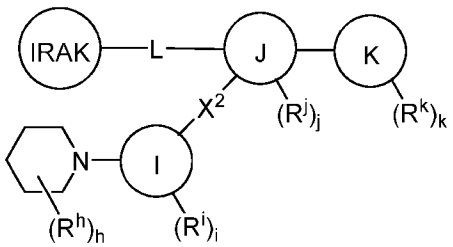
I-b-1'



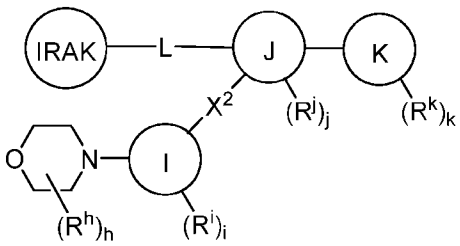
I-b-2'



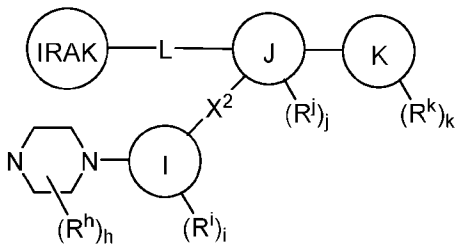
I-b-3'



I-b-4'



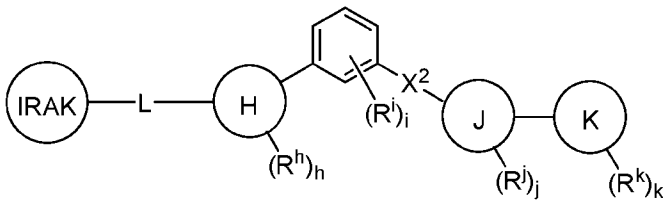
I-b-5'



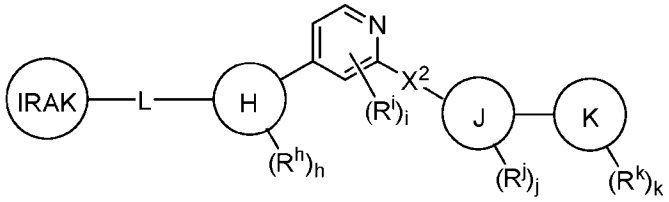
I-b-6'

or a pharmaceutically acceptable salt thereof.

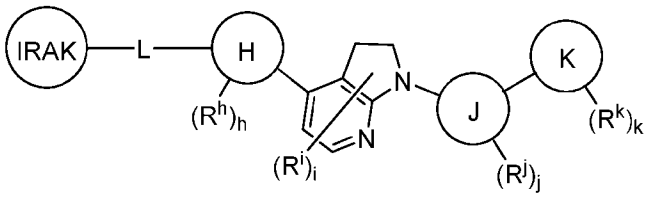
[00246] In certain embodiments, the present invention provides a compound of formula **I-b** or **I-b'** represented by any one of the following formulae:



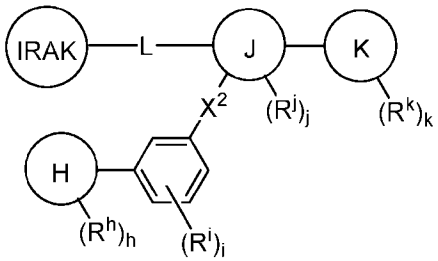
I-b-7'



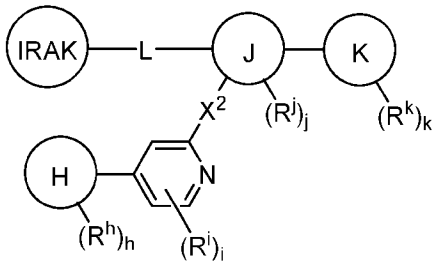
I-b-8'



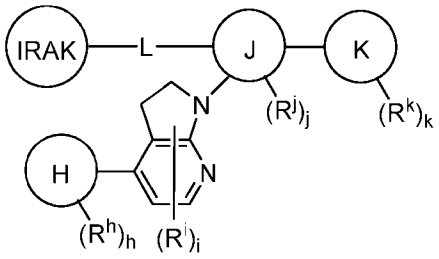
I-b-9'



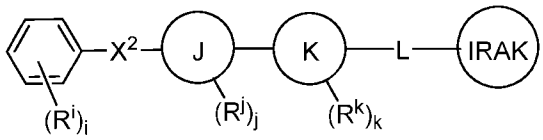
I-b-10'



I-b-11'



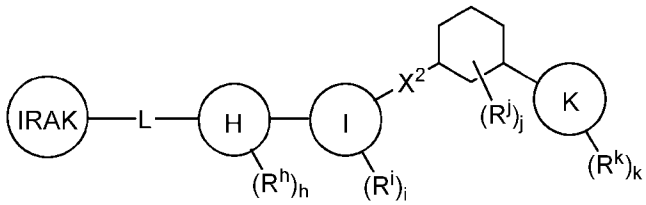
I-b-12'



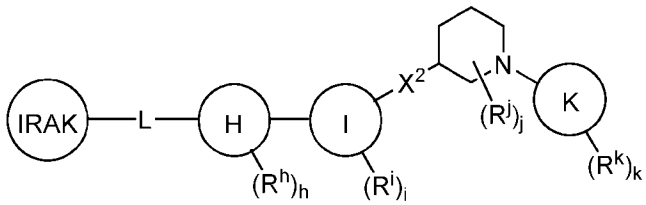
I-b-13'

or a pharmaceutically acceptable salt thereof.

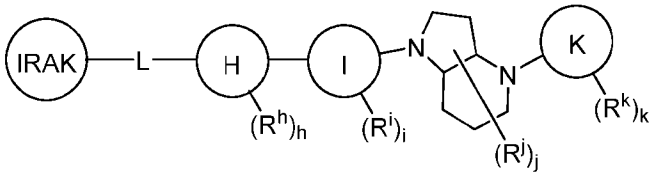
[00247] In certain embodiments, the present invention provides a compound of formula **I-b** or **I-b'** represented by any one of the following formulae:



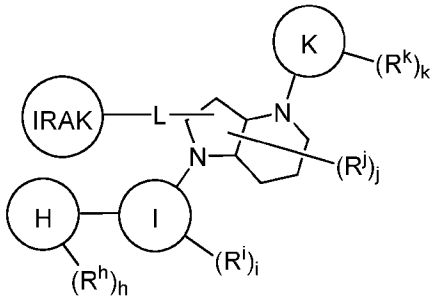
I-b-14'



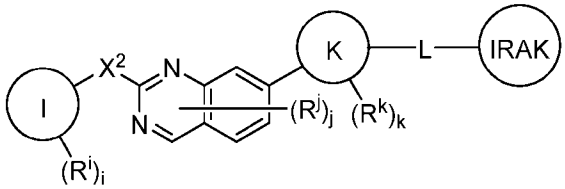
I-b-15'



I-b-16'



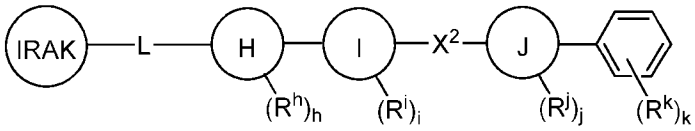
I-b-17'



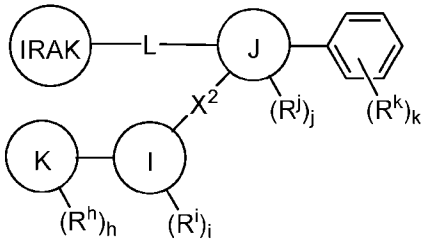
I-b-18'

or a pharmaceutically acceptable salt thereof.

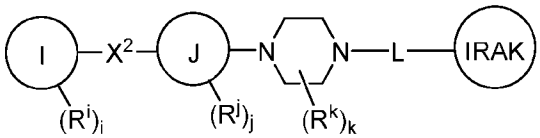
[00248] In certain embodiments, the present invention provides a compound of formula **I-b** or **I-b'** represented by any one of the following formulae:



I-b-19'

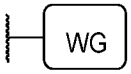


I-b-20'



I-b-21'

or a pharmaceutically acceptable salt thereof.

[00249] As defined above and described herein, said compound of formula **I-a**, **I-a'**, **I-b**, or **I-b'** is optionally substituted with 

, wherein

is a warhead group attached to a modifiable

carbon, oxygen, nitrogen or sulfur atom in formula **I-a**, **I-a'**, **I-b**, or **I-b'** or a substitution or replacement of any defined group in formula **I-a**, **I-a'**, **I-b**, or **I-b'** (e.g., replaced with one of R^e, R^f, R^g, R^h, R^i, R^j, or R^k).

[00250] In some embodiments, the warhead group is $-L^2$-Y, wherein:

L^2 is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L^2 are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, —SO_2N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR)—, —N=N—, or —C(=N_2)—;

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with 1-4 R^e groups; and

each R^e is independently selected from -Q-Z, oxo, NO_2, halogen, CN, a suitable leaving group, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein:

Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —N(R)—, —S—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —SO—, or —SO_2—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, or —SO_2N(R)—; and

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

[00251] In certain embodiments, L^2 is a covalent bond.

[00252] In certain embodiments, L^2 is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain. In certain embodiments, L^2 is —CH_2—.

[00253] In certain embodiments, L^2 is a covalent bond, —CH_2—, —NH—, —CH_2NH—, —NHCH_2—, —NHC(O)—, —NHC(O)CH_2OC(O)—, —CH_2NHC(O)—, —NHSO_2—, —NHSO_2CH_2—, —NHC(O)CH_2OC(O)—, or —SO_2NH—.

[00254] In some embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and one or two additional methylene units of L^2 are optionally and independently replaced by —NRC(O)—, —C(O)NR—, —N(R)SO_2—, —SO_2N(R)—, —S—, —S(O)—, —SO_2—, —OC(O)—, —C(O)O—, cyclopropylene, —O—, —N(R)—, or —C(O)—.

[00255] In certain embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —C(O)—, —NRC(O)—, —C(O)NR—, —N(R)SO_2—, —SO_2N(R)—, —S—, —S(O)—, —SO_2—, —OC(O)—, or —C(O)O—, and one or two additional methylene units of L^2 are optionally and independently replaced by cyclopropylene, —O—, —N(R)—, or —C(O)—.

[00256] In some embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —C(O)—, and one or two additional methylene units of L^2 are optionally and independently replaced by cyclopropylene, —O—, —N(R)—, or —C(O)—.

[00257] As described above, in certain embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond. One of ordinary skill in the art will recognize that such a double bond may exist within the hydrocarbon chain backbone or may be "exo" to the backbone chain and thus forming an alkylidene group. By way of example, such an L^2 group having an alkylidene branched chain includes —$CH_2C(=CH_2)CH_2$—. Thus, in some embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one alkylidenyl double bond. Exemplary L^2 groups include —$NHC(O)C(=CH_2)CH_2$—.

[00258] In certain embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —C(O)—. In certain embodiments, L^2 is —$C(O)CH=CH(CH_3)$—, —$C(O)CH=CHCH_2NH(CH_3)$—, —$C(O)CH=CH(CH_3)$—, —C(O)CH=CH—, —$CH_2C(O)CH=CH$—, —$CH_2C(O)CH=CH(CH_3)$—, —$CH_2CH_2C(O)CH=CH$—, —$CH_2CH_2C(O)CH=CHCH_2$—, —$CH_2CH_2C(O)CH=CHCH_2NH(CH_3)$—, or —$CH_2CH_2C(O)CH=CH(CH_3)$—, or —$CH(CH_3)OC(O)CH=CH$—.

[00259] In certain embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —OC(O)—.

[00260] In some embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —NRC(O)—, —C(O)NR—, —$N(R)SO_2$—, —$SO_2N(R)$—, —S—, —S(O)—, —SO_2—, —OC(O)—, or —C(O)O—, and one or two additional methylene units of L^2 are optionally and independently replaced by cyclopropylene, —O—, —N(R)—, or —C(O)—. In some embodiments, L^2 is —$CH_2OC(O)CH=CHCH_2$—, —CH_2—OC(O)CH=CH—, or —$CH(CH=CH_2)OC(O)CH=CH$—.

[00261] In certain embodiments, L^2 is —NRC(O)CH=CH—, —$NRC(O)CH=CHCH_2N(CH_3)$—, —$NRC(O)CH=CHCH_2O$—, —$CH_2NRC(O)CH=CH$—, —$NRSO_2CH=CH$—, —$NRSO_2CH=CHCH_2$—, —$NRC(O)(C=N_2)C(O)$—, —$NRC(O)CH=CHCH_2N(CH_3)$—, —$NRSO_2CH=CH$—, —$NRSO_2CH=CHCH_2$—, —$NRC(O)CH=CHCH_2O$—, —$NRC(O)C(=CH_2)CH_2$—, —$CH_2NRC(O)$—, —$CH_2NRC(O)CH=CH$—, —$CH_2CH_2NRC(O)$—, or —$CH_2NRC(O)$cyclopropylene-, wherein each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00262] In certain embodiments, L^2 is —NHC(O)CH=CH—, —$NHC(O)CH=CHCH_2N(CH_3)$—, —$NHC(O)CH=CHCH_2O$—, —$CH_2NHC(O)CH=CH$—, —$NHSO_2CH=CH$—, —$NHSO_2CH=CHCH_2$—, —$NHC(O)(C=N_2)C(O)$—, —$NHC(O)CH=CHCH_2N(CH_3)$—, —$NHSO_2CH=CH$—, —

$NHSO_2CH{=}CHCH_2$—, —NHC(O)CH=CHCH$_2$O—, —NHC(O)C(=CH$_2$)CH$_2$—, —CH$_2$NHC(O)—, —CH$_2$NHC(O)CH=CH—, —CH$_2$CH$_2$NHC(O)—, or —CH$_2$NHC(O)cyclopropylene-.

[00263] In some embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one triple bond. In certain embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one triple bond and one or two additional methylene units of L^2 are optionally and independently replaced by —NRC(O)—, —C(O)NR—, —S—, —S(O)—, —SO$_2$—, —C(=S)—, —C(=NR)—, —O—, —N(R)—, or —C(O)—. In some embodiments, L^2 has at least one triple bond and at least one methylene unit of L^2 is replaced by —N(R)—, —N(R)C(O)—, —C(O)—, —C(O)O—, or —OC(O)—, or —O—.

[00264] Exemplary L^2 groups include —C≡C—, —C≡CCH$_2$N(isopropyl)-, —NHC(O)C≡CCH$_2$CH$_2$—, —CH$_2$—C≡C≡CH$_2$—, —C≡CCH$_2$O—, —CH$_2$C(O)C≡C—, —C(O)C≡C—, or —CH$_2$OC(=O)C≡C—.

[00265] In certain embodiments, L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L^2 is replaced by cyclopropylene and one or two additional methylene units of L^2 are independently replaced by —C(O)—, —NRC(O)—, —C(O)NR—, —N(R)SO$_2$—, or —SO$_2$N(R)—. Exemplary L^2 groups include —NHC(O)-cyclopropylene-SO$_2$— and —NHC(O)-cyclopropylene-.

[00266] As defined generally above, Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 R^e groups, each R^e is independently selected from -Q-Z, oxo, NO_2, halogen, CN, a suitable leaving group, or C_{1-6} aliphatic, wherein Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —N(R)—, —S—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —SO—, or —SO$_2$—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO$_2$—, or —SO$_2$N(R)—; and, Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

[00267] In certain embodiments, Y is hydrogen.

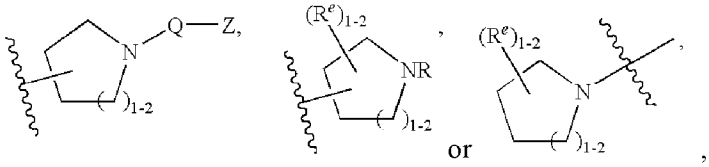
[00268] In certain embodiments, Y is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN. In some embodiments, Y is C_{2-6}alkenyl optionally substituted with oxo, halogen, NO_2, or CN. In other embodiments, Y is C_{2-6}alkynyl optionally substituted with oxo, halogen, NO_2, or CN. In some embodiments, Y is C_{2-6}alkenyl. In other embodiments, Y is C_{2-4} alkynyl.

[00269] In other embodiments, Y is C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN. Such Y groups include —CH$_2$F, —CH$_2$Cl, —CH$_2$CN, and —CH$_2$NO$_2$.

[00270] In certain embodiments, Y is a saturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Y is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

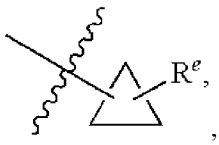
[00271] In some embodiments, Y is a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein. Exemplary such rings are epoxide and oxetane rings, wherein each ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein.

[00272] In other embodiments, Y is a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. Such rings include piperidine and pyrrolidine, wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is



wherein each R, Q, Z, and R^e is as defined above and described herein.

[00273] In some embodiments, Y is a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^egroups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is

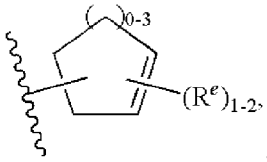


, wherein R^e is as defined above and described herein.

[00274] In certain embodiments, Y is cyclopropyl optionally substituted with halogen, CN or NO_2.

[00275] In certain embodiments, Y is a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

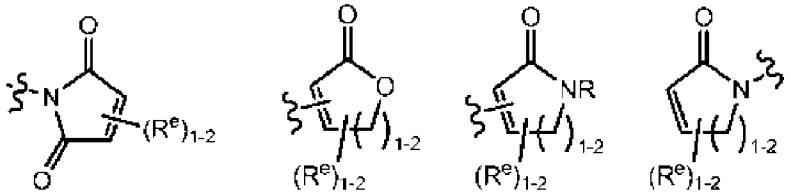
[00276] In some embodiments, Y is a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In some embodiments, Y is cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined 0-3 above and described herein. In certain embodiments, Y is



, wherein each R^e is as defined above and described herein.

[00277] In certain embodiments, Y is a partially unsaturated 4-6 membered heterocyclic ring having 1-

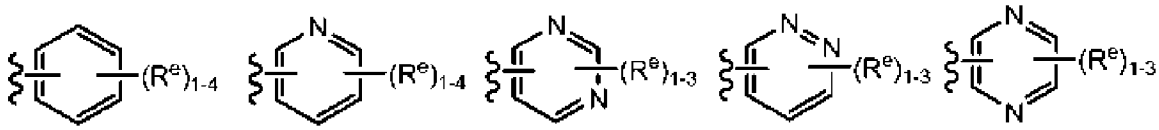
2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is selected from:



wherein each R and R^e is as defined above and described herein.

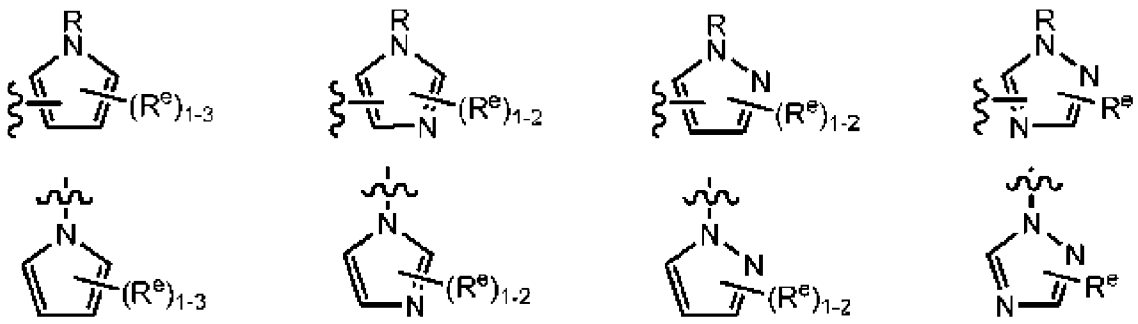
[00278] In certain embodiments, Y is a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein. In certain embodiments, Y is phenyl, pyridyl, or pyrimidinyl, wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

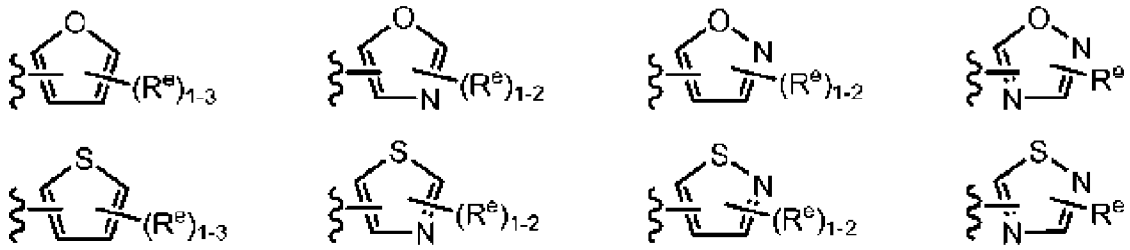
[00279] In some embodiments, Y is selected from:



wherein each R^e is as defined above and described herein.

[00280] In other embodiments, Y is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein. In some embodiments, Y is a 5 membered partially unsaturated or aryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein. Exemplary such rings are isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, thienyl, triazole, thiadiazole, and oxadiazole, wherein each ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein. In certain embodiments, Y is selected from:





wherein each R and R^e is as defined above and described herein.

[00281] In certain embodiments, Y is an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein. According to another aspect, Y is a 9-10 membered bicyclic, partially unsaturated, or aryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein $R^e$is as defined above and described herein. Exemplary such bicyclic rings include 2,3-dihydrobenzo[d]isothiazole, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein.

[00282] As defined generally above, each R^e group is independently selected from -Q-Z, oxo, NO_2, halogen, CN, a suitable leaving group, or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —N(R)—, —S—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —SO—, or —SO_2—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, or —SO_2N(R)—; and Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

[00283] In certain embodiments, R^e is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN. In other embodiments, R^e is oxo, NO_2, halogen, or CN.

[00284] In some embodiments, R^e is -Q-Z, wherein Q is a covalent bond and Z is hydrogen (i.e., R^e is hydrogen). In other embodiments, R^e is -Q-Z, wherein Q is a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —NRC(O)—, —C(O)NR—, —S—, —O—, —C(O)—, —SO—, or —SO_2—. In other embodiments, Q is a bivalent C_{2-6} straight or branched, hydrocarbon chain having at least one double bond, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —NRC(O)—, —C(O)NR—, —S—, —O—, —C(O)—, —SO—, or —SO_2—. In certain embodiments, the Z moiety of the R^e group is hydrogen. In some embodiments, -Q-Z is —NHC(O)CH=CH_2 or —C(O)CH=CH_2.

[00285] In certain embodiments, each R^e is independently selected from oxo, NO_2, CN, fluoro, chloro,

—NHC(O)CH=CH_2, —C(O)CH=CH_2, —CH_2CH=CH_2, —C≡CH, —C(O)OCH_2Cl, —C(O)OCH_2F, —C(O)OCH_2CN, —C(O)CH_2Cl, —C(O)CH_2F, —C(O)CH_2CN, or —CH_2C(O)CH_3.

[00286] In certain embodiments, R^e is a suitable leaving group, i.e., a group that is subject to nucleophilic displacement. A "suitable leaving" is a chemical group that is readily displaced by a desired incoming chemical moiety such as the thiol moiety of a cysteine of interest. Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 5th Ed., pp. 351-357, John Wiley and Sons, N.Y. Such leaving groups include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, and diazonium moieties. Examples of suitable leaving groups include chloro, iodo, bromo, fluoro, acetoxy, methanesulfonyloxy (mesyloxy), tosyloxy, triflyloxy, nitro-phenylsulfonyloxy (nosyloxy), and bromo-phenylsulfonyloxy (brosyloxy).

[00287] In certain embodiments, the following embodiments and combinations of - L^2-Y apply:

(a) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and one or two additional methylene units of L^2 are optionally and independently replaced by —NRC(O)—, —C(O)NR—, —N(R)SO_2—, —SO_2N(R)—, —S—, —S(O)—, —SO_2—, —OC(O)—, —C(O)O—, cyclopropylene, —O—, —N(R)—, or —C(O)—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(b) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —C(O)—, —NRC(O)—, —C(O)NR—, —N(R)SO_2—, —SO_2N(R)—, —S—, —S(O)—, —SO_2—, —OC(O)—, or —C(O)O—, and one or two additional methylene units of L^2 are optionally and independently replaced by cyclopropylene, —O—, —N(R)—, or —C(O)—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(c) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —C(O)—, and one or two additional methylene units of L^2 are optionally and independently replaced by cyclopropylene, —O—, —N(R)—, or —C(O)—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(d) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —C(O)—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(e) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one double bond and at least one methylene unit of L^2 is replaced by —OC(O)—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(f) L^2 is —NRC(O)CH=CH—, —NRC(O)CH=CHCH$_2$N(CH$_3$)—, —NRC(O)CH=CHCH$_2$O—, —CH$_2$NRC(O)CH=CH—, —NRSO$_2$CH=CH—, —NRSO$_2$CH=CHCH$_2$—, —NRC(O)(C=N$_2$)—, —NRC(O)(C=N$_2$)C(O)—, —NRC(O)CH=CHCH$_2$N(CH$_3$)—, —NRSO$_2$CH=CH—, —NRSO$_2$CH=CHCH$_2$—, —NRC(O)CH=CHCH$_2$O—, —NRC(O)C(=CH$_2$)CH$_2$—, —CH$_2$NRC(O)—, —CH$_2$NRC(O)CH=CH—, —CH$_2$CH$_2$NRC(O)—, or —CH$_2$NRC(O)cyclopropylene-; wherein R is H or optionally substituted C_{1-6} aliphatic; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(g) L^2 is —NHC(O)CH=CH—, —NHC(O)CH=CHCH$_2$N(CH$_3$)—, —NHC(O)CH=CHCH$_2$O—, —CH$_2$NHC(O)CH=CH—, —NHSO$_2$CH=CH—, —NHSO$_2$CH=CHCH$_2$—, —NHC(O)(C=N$_2$)—, —NHC(O)(C=N$_2$)C(O)—, —NHC(O)CH=CHCH$_2$N(CH$_3$)—, —NHSO$_2$CH=CH—, —NHSO$_2$CH=CHCH$_2$—, —NHC(O)CH=CHCH$_2$O—, —NHC(O)C(=CH$_2$)CH$_2$—, —CH$_2$NHC(O)—, —CH$_2$NHC(O)CH=CH—, —CH$_2$CH$_2$NHC(O)—, or —CH$_2$NHC(O)cyclopropylene-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(h) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one alkylidenyl double bond and at least one methylene unit of L^2 is replaced by —C(O)—, —NRC(O)—, —C(O)NR—, —N(R)SO$_2$—, —SO$_2$N(R)—, —S—, —S(O)—, —SO$_2$—, —OC(O)—, or —C(O)O—, and one or two additional methylene units of L^2 are optionally and independently replaced by cyclopropylene, —O—, —N(R)—, or —C(O)—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(i) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L^2 has at least one triple bond and one or two additional methylene units of L^2 are optionally and independently replaced by —NRC(O)—, —C(O)NR—, —N(R)SO$_2$—, —SO$_2$N(R)—, —S—, —S(O)—, —SO$_2$—, —OC(O)—, or —C(O)O—, and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(j) L^2 is —C≡C—, —C≡CCH$_2$N(isopropyl)-, —NHC(O)C≡CCH$_2$CH$_2$—, —CH$_2$—C≡C≡CH$_2$—, —C≡CCH$_2$O—, —CH$_2$C(O)C≡C—, —C(O)C≡C—, or —CH$_2$C(=O)C≡C—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(k) L^2 is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L^2 is replaced by cyclopropylene and one or two additional methylene units of L^2 are independently replaced by —NRC(O)—, —C(O)NR—, —N(R)SO$_2$—, —SO$_2$N(R)—, —S—, —S(O)—, —SO$_2$—, —OC(O)—, or —C(O)O—; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(l) L^2 is a covalent bond and Y is selected from:

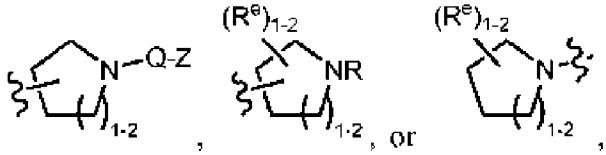
(i) C_{1-6} alkyl substituted with oxo, halogen, NO$_2$, or CN;

(ii) C_{2-6}alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iii) C_{2-6}alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iv) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

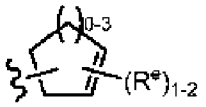
(v) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(vi)  , wherein each R, Q, Z, and R^e is as defined above and described herein; or

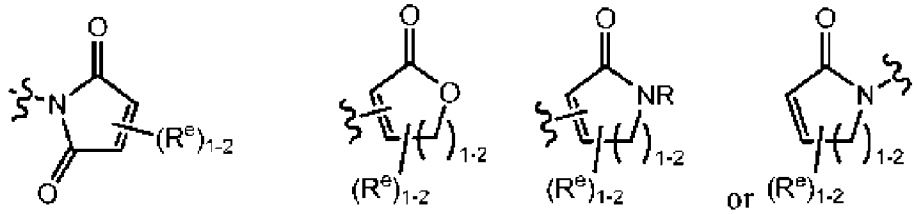
(vii) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(viii) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(ix) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^egroups, wherein each R^e is as defined above and described herein; or

(x)  , wherein each R^e is as defined above and described herein; or

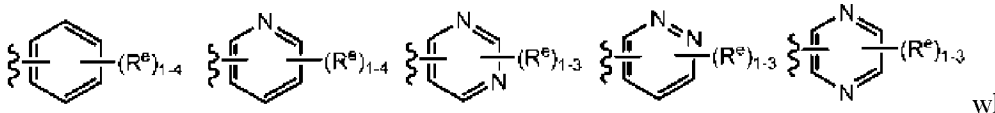
(xi) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(xii) 

wherein each R and R^e is as defined above and described herein; or

(xiii) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^egroups, wherein each R^e group is as defined above and described herein; or

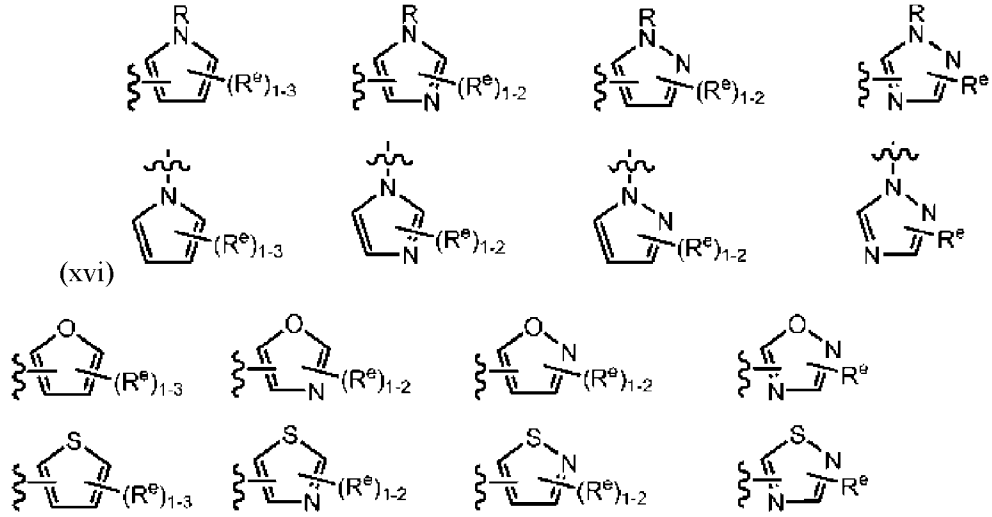
(xiv)



wherein each R^e is as defined above and described herein; or

(xv) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^egroups, wherein each R^e group is as defined above and described herein; or

(xvi)



wherein each R and R^e is as defined above and described herein; or

(xvii) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein;

(m) L^2 is —C(O)— and Y is selected from:

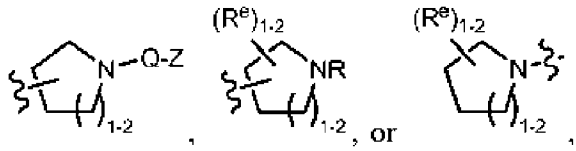
(i) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(ii) C_{2-6}alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iii) C_{2-6}alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iv) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

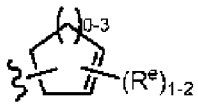
(v) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(vi)  , wherein each R, Q, Z, and R^e is as defined above and described herein; or

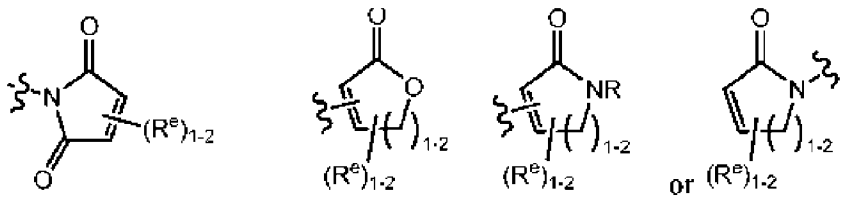
(vii) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(viii) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(ix) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^egroups, wherein each R^e is as defined above and described herein; or

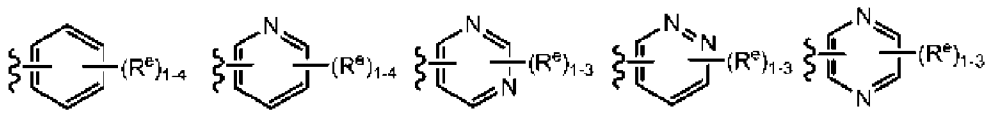
(x)  , wherein each R^e is as defined above and described herein; or

(xi) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(xii) 

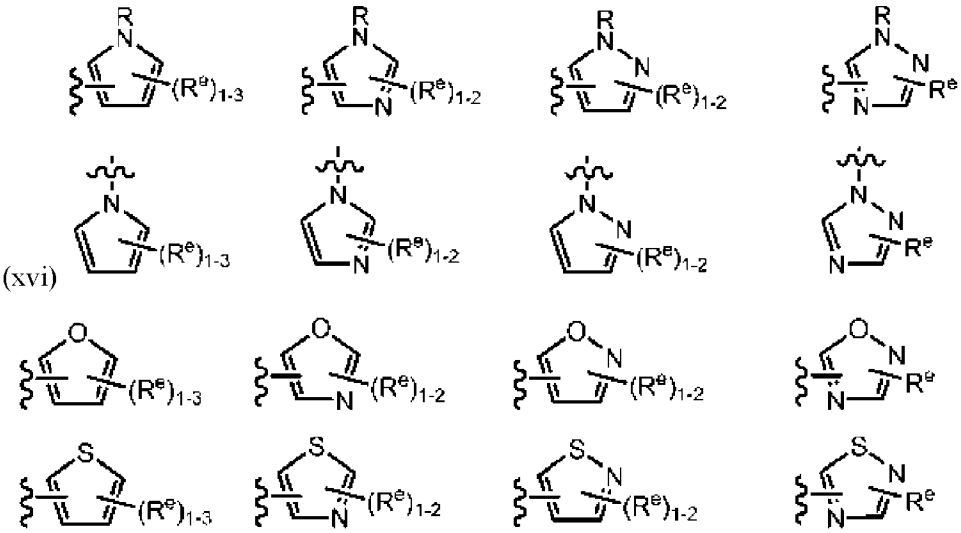
wherein each R and R^e is as defined above and described herein; or

(xiii) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^egroups, wherein each R^e group is as defined above and described herein; or

(xiv) 

wherein each R^e is as defined above and described herein; or

(xv) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^egroups, wherein each R^e group is as defined above and described herein; or

(xvi) 

wherein each R and R^e is as defined above and described herein; or

(xvii) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein;

(n) L^2 is —N(R)C(O)— and Y is selected from:

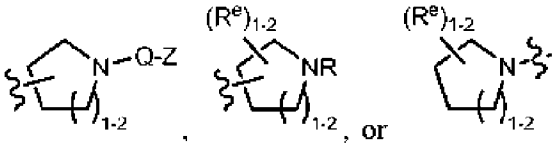
(i) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(ii) C_{2-6}alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iii) C_{2-6}alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iv) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

(v) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

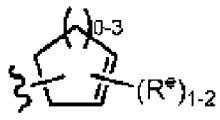
(vi)  , or , wherein each R, Q, Z, and R^e is as defined above and described herein; or

(vii) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

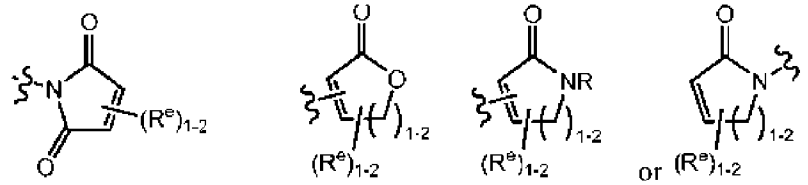
(viii) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups,

wherein each R^e is as defined above and described herein; or

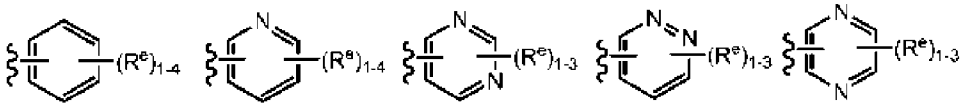
(ix) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^egroups, wherein each R^e is as defined above and described herein; or

(x)  , wherein each R^e is as defined above and described herein; or

(xi) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

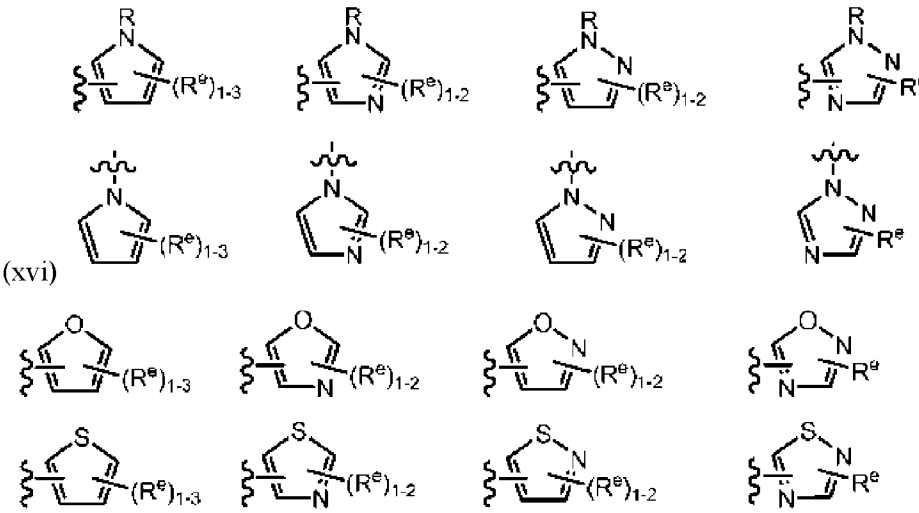
(xii)  , wherein each R and R^e is as defined above and described herein; or

(xiii) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^egroups, wherein each R^e group is as defined above and described herein; or

(xiv) 

wherein each R^e is as defined above and described herein; or

(xv) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^egroups, wherein each R^e group is as defined above and described herein; or

(xvi) 

wherein each R and R^e is as defined above and described herein; or

(xvii) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^egroups, wherein R^e is as defined above and described herein;

(o) L^2 is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and Y is selected from:

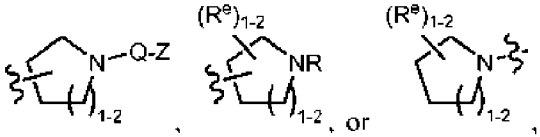
(i) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN;

(ii) C_{2-6}alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iii) C_{2-6}alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iv) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

(v) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

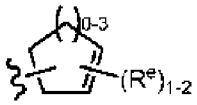
(vi) 

, wherein each R, Q, Z, and R^e is as defined above and described herein; or

(vii) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

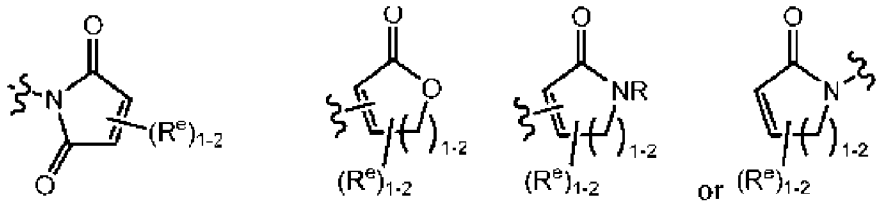
(viii) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(ix) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^egroups, wherein each R^e is as defined above and described herein; or

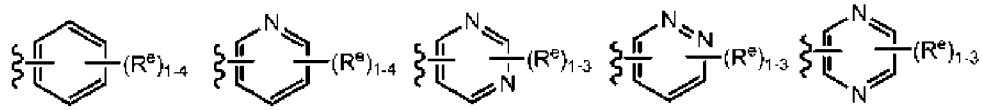
(x) 

, wherein each R^e is as defined above and described herein; or

(xi) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

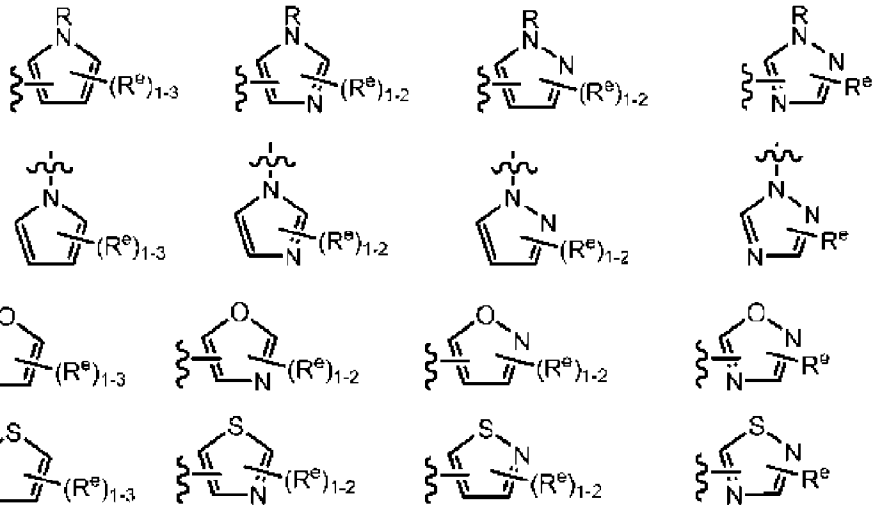
(xii)  , wherein each R and R^e is as defined above and described herein; or

(xiii) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^egroups, wherein each R^e group is as defined above and described herein; or

(xiv) 

wherein each R^e is as defined above and described herein; or

(xv) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^egroups, wherein each R^e group is as defined above and described herein; or

(xvi) 

wherein each R and R^e is as defined above and described herein; or

(xvii) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^egroups, wherein R^e is as defined above and described herein;

(p) L^2 is a covalent bond, —CH_2—, —NH—, —C(O)—, —CH_2NH—, —NHCH_2—, —NHC(O)—, —NHC(O)CH_2OC(O)—, —CH_2NHC(O)—, —NHSO_2—, —NHSO_2CH_2—, —NHC(O)CH_2OC(O)—, or —SO_2NH—; and Y is selected from:

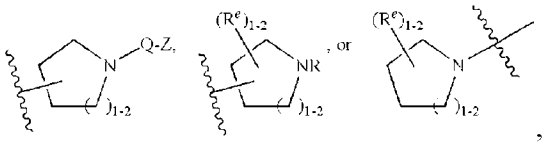
(i) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(ii) C_{2-6}alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iii) C_{2-6}alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(iv) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

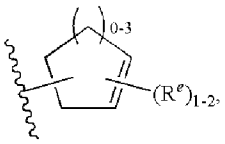
(v) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(vi)  , wherein each R, Q, Z, and R^e is as defined above and described herein; or

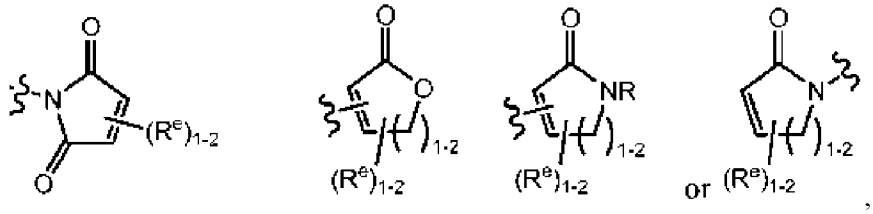
(vii) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(viii) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

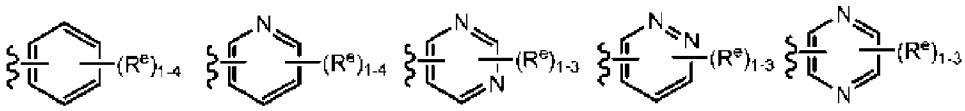
(ix) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^egroups, wherein each R^e is as defined above and described herein; or

(x)  wherein each R^e is as defined above and described herein; or

(xi) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

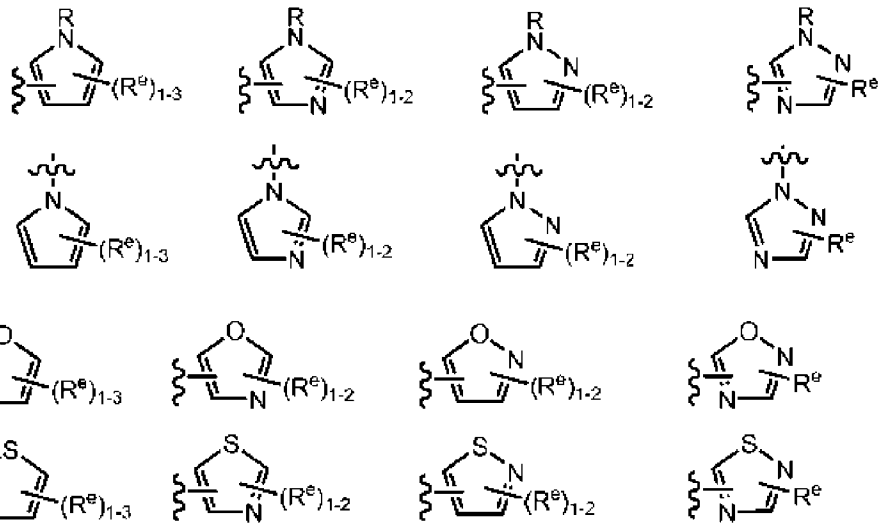
(xii)  , wherein each R and R^e is as defined above and described herein; or

(xiii) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^egroups, wherein each R^e group is as defined above and described herein; or

(xiv) 

wherein each R^e is as defined above and described herein; or

(xv) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^egroups, wherein each R^e group is as defined above and described herein; or

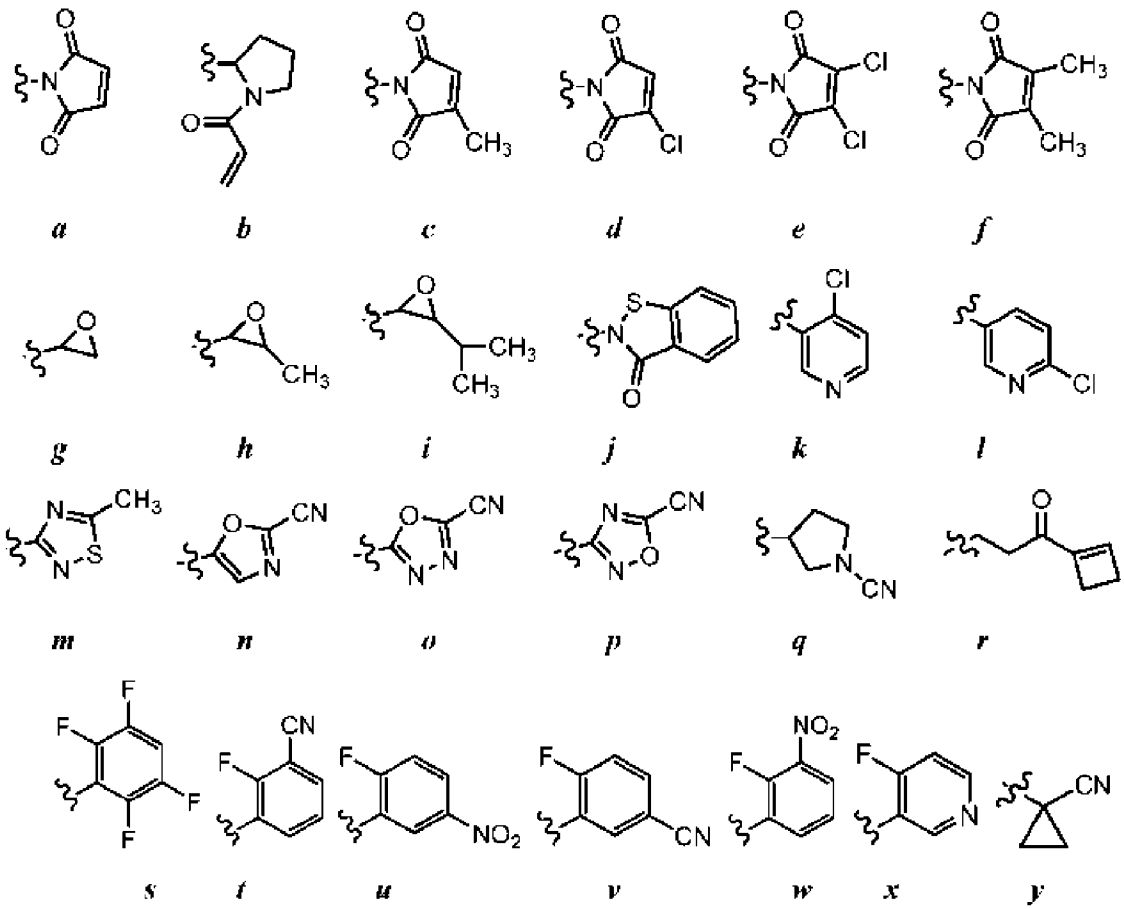
(xvi) 

wherein each R and R^e is as defined above and described herein; or

(xvii) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein.

[00288] In certain embodiments, the Y group is selected from those set forth in **Table 1A** below, wherein each wavy line indicates the point of attachment to the rest of the molecule.

Table 1A. Exemplary Y groups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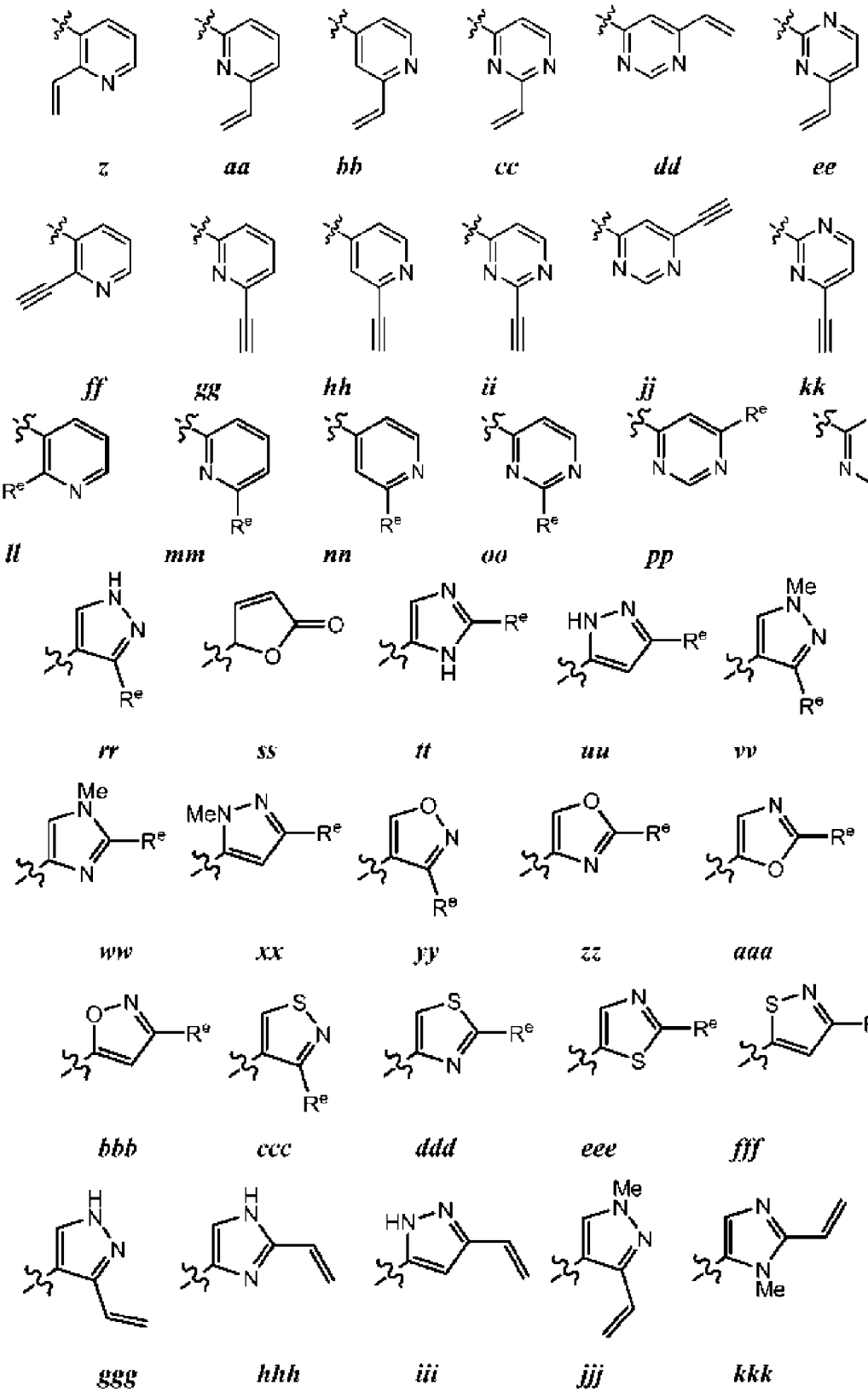
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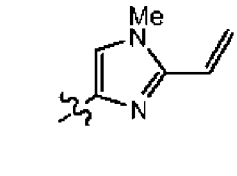

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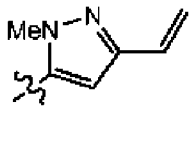

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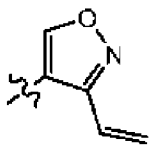

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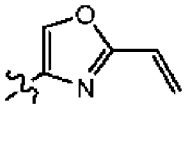

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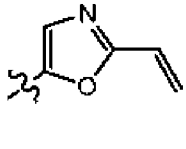

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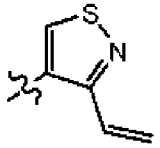

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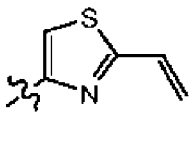

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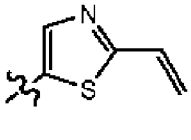

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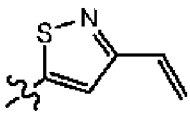

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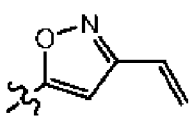

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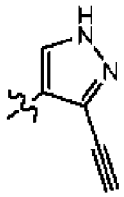

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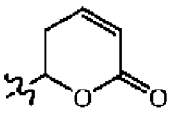

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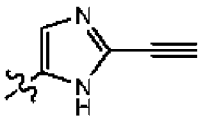

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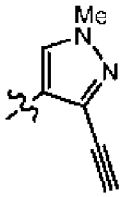

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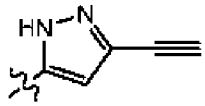

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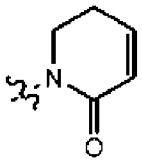

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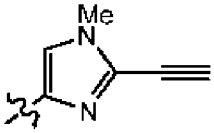

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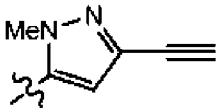

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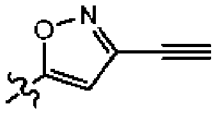

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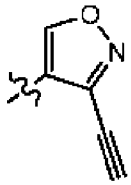

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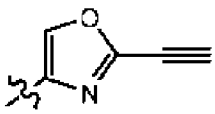

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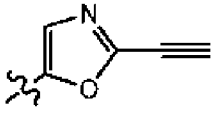

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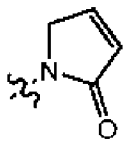

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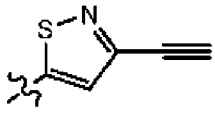

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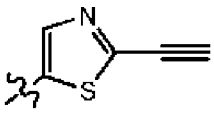

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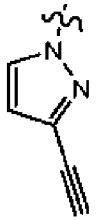

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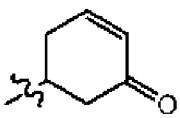

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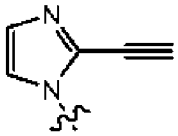

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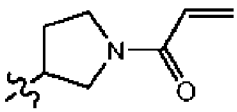

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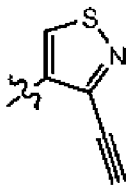

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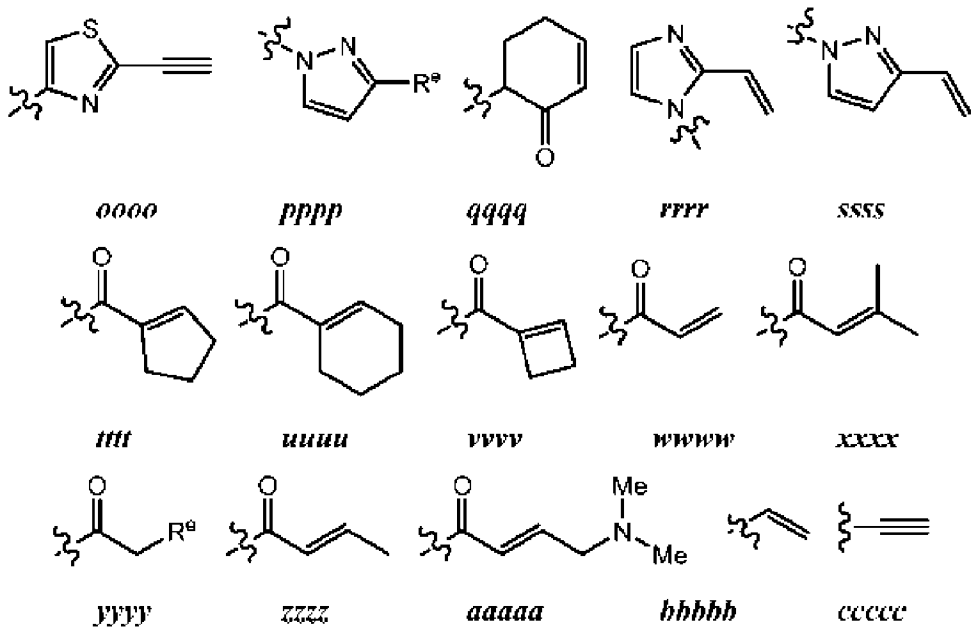
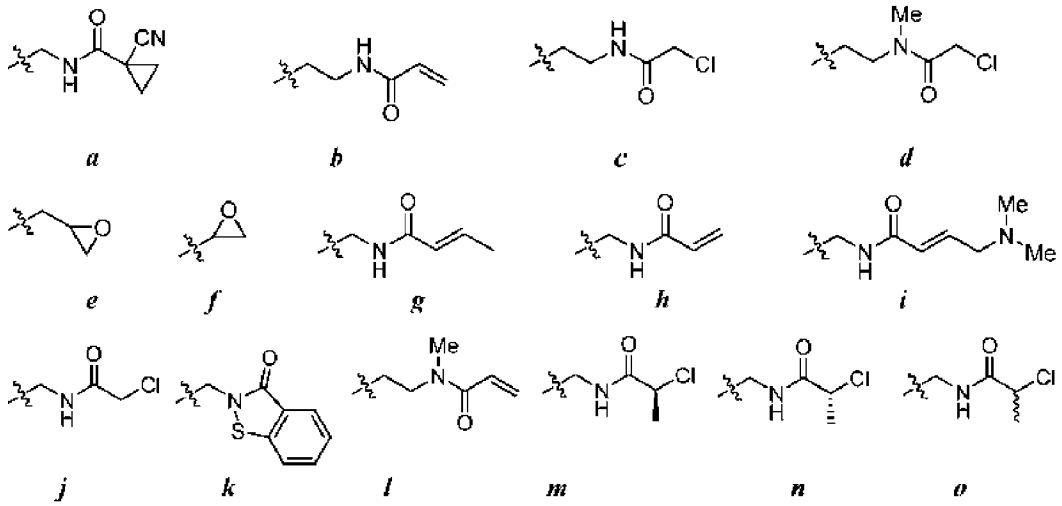


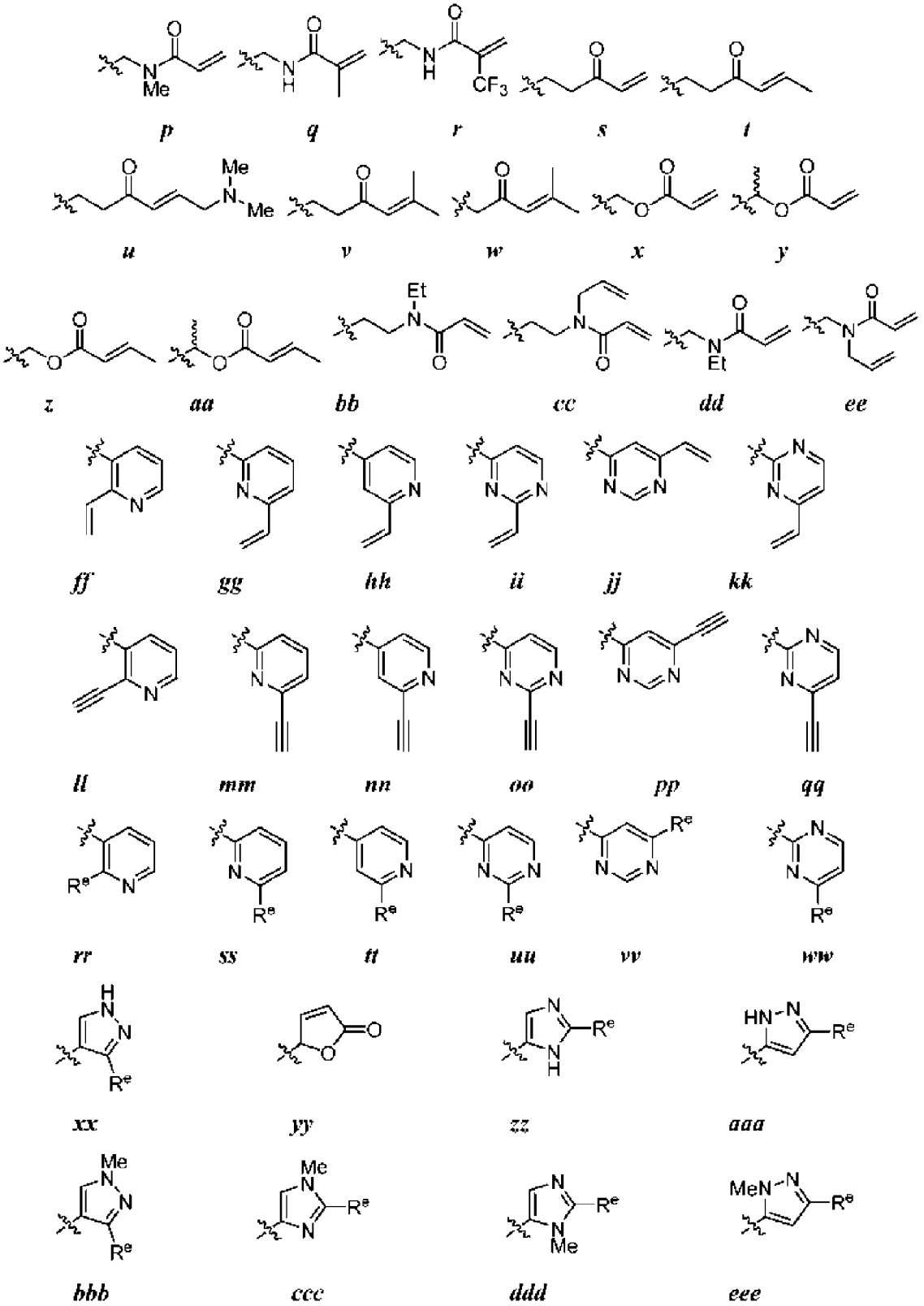
wherein each R^e is independently a suitable leaving group, NO_2, CN or oxo.

[00289] In certain embodiments, a warhead group is —C≡CH, —C≡CCH_2NH(isopropyl), —NHC(O)C≡CCH_2CH_3, —CH_2—C≡C≡CH_3, —C≡CCH_2OH, —CH_2C(O)C≡CH, —C(O)C≡CH, or —CH_2C(=O)C≡CH. In some embodiments, R^1 is selected from —NHC(O)CH=CH_2, —NHC(O)CH=C$HCH_2N(CH_3)_2$, or —CH_2NHC(O)CH=CH_2.

[00290] In certain embodiments, a warhead group is selected from those set forth in **Table 1B**, below, wherein each wavy line indicates the point of attachment to the rest of the molecule.

Table 1B. Exemplary Warhead Groups

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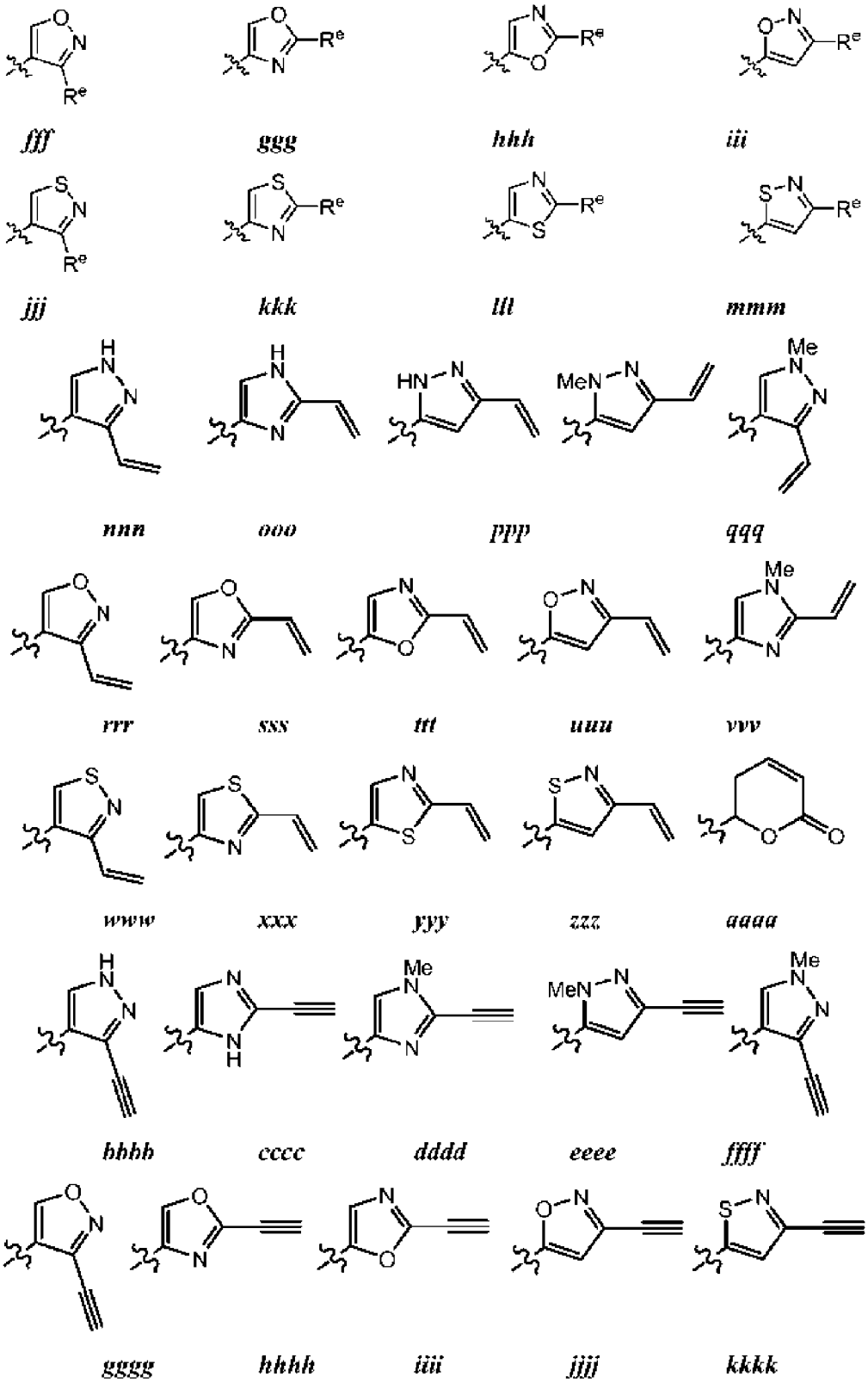
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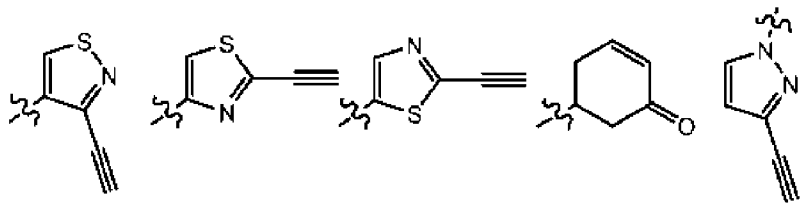

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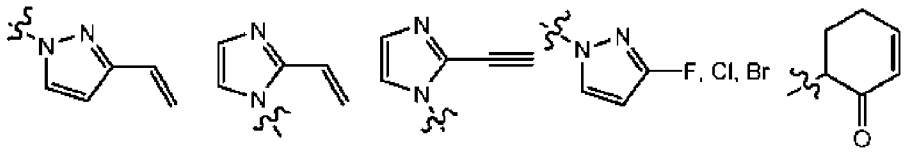

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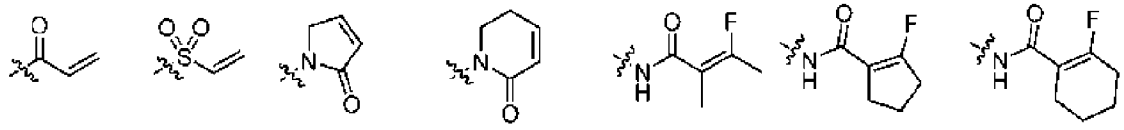

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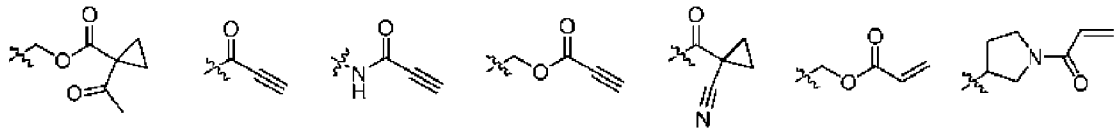

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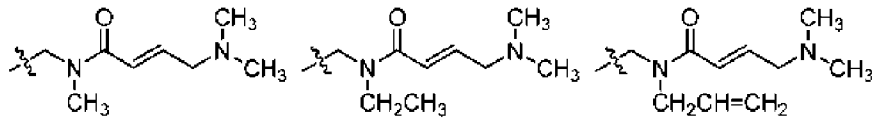

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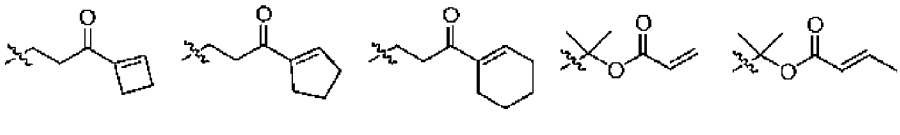

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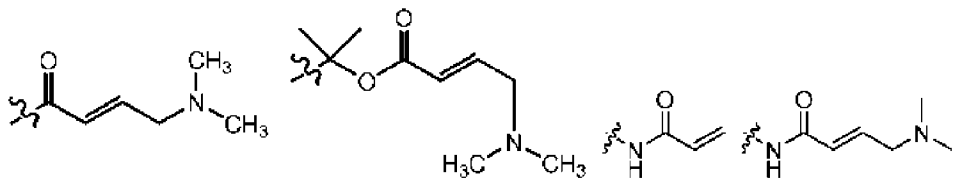

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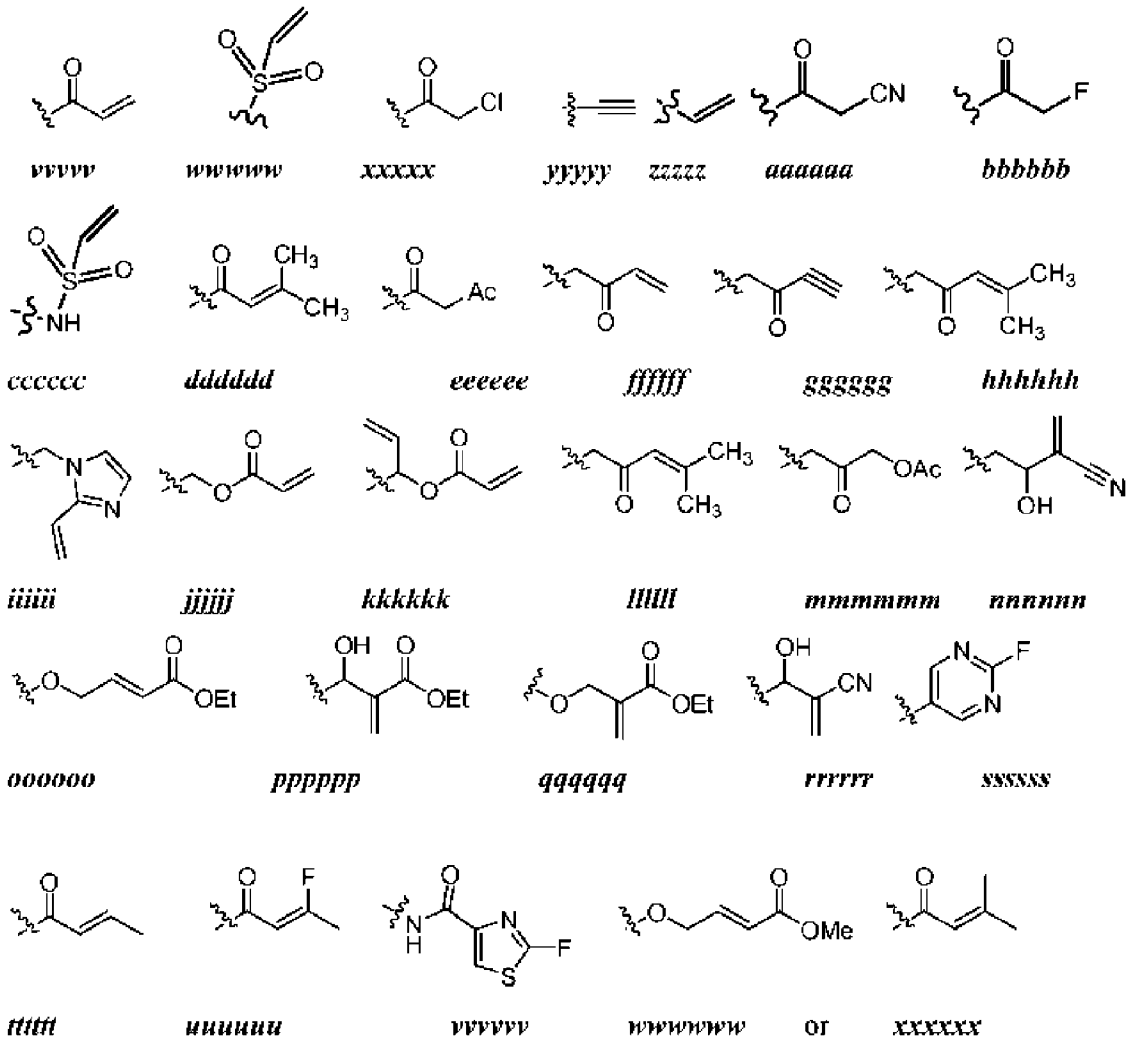
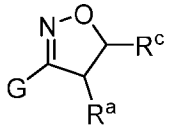
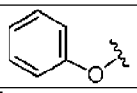
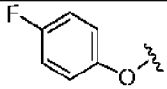
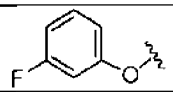
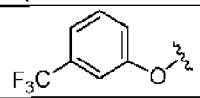
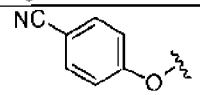
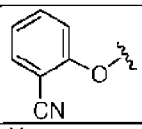
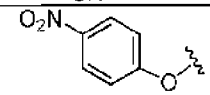
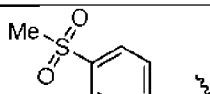
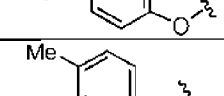
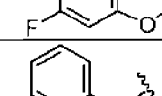
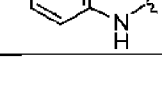


wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

[00291] In some embodiments, Y of a warhead group is an isoxazoline compound or derivative capable of covalently binding to serine. In some embodiments, Y of a warhead group is an isoxazoline compound or derivative described in WO 2010135360, the entire content of which is incorporated herein by reference. As understood by one skilled in the art, an isoxazoline compound or derivative described in WO 2010135360, as Y of a warhead group, can covalently connect to L^2 of the warhead group at any reasonable position of the isoxazoline compound or derivative. In some embodiments, Y of a warhead group is:



wherein G, R^a, and R^c are:

G	R^a	R^c
-Br	-H	-H
-Cl	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
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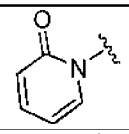
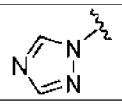
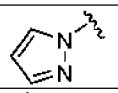
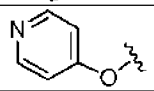
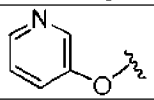
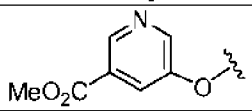
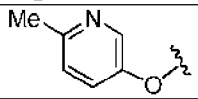
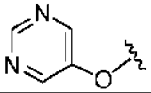
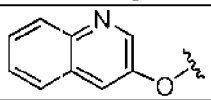
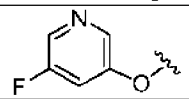
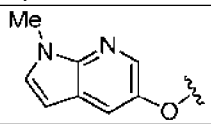
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
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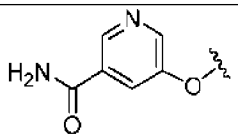
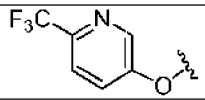
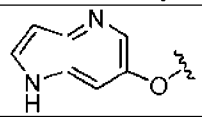
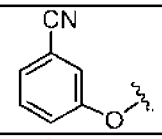
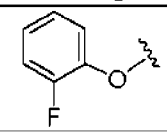
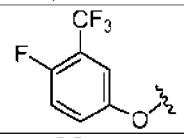
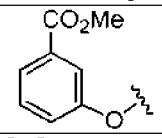
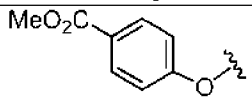
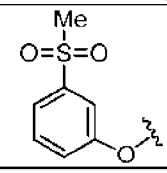
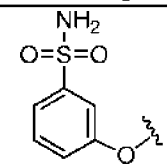
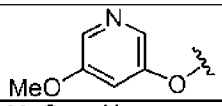
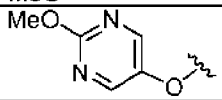
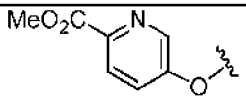
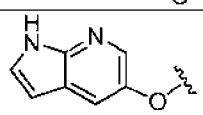
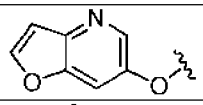
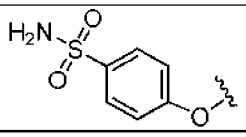
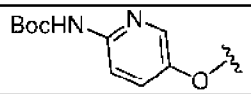
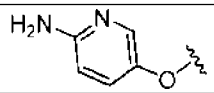
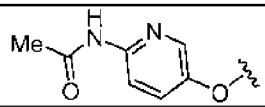
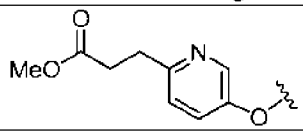
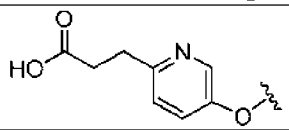
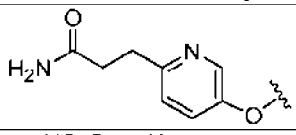
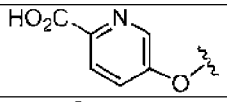
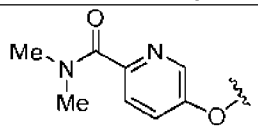
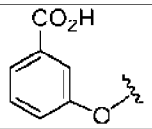
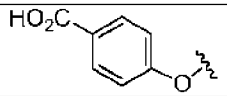
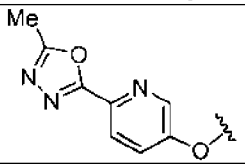
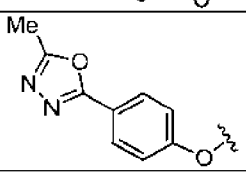
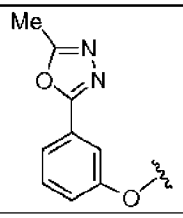
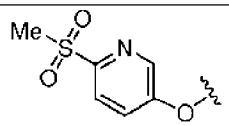
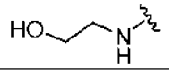
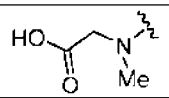
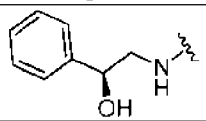
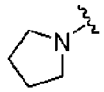
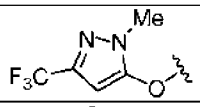
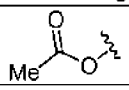
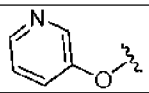
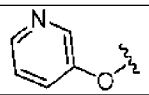
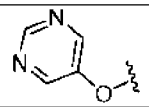
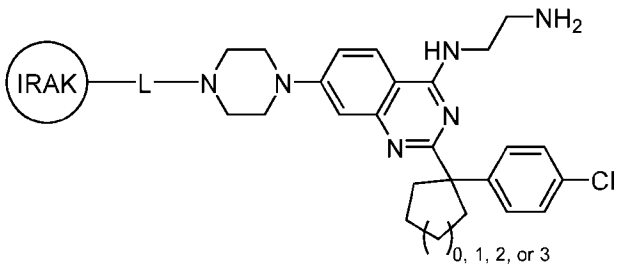
	-H	-H
	-H	-H
	-H	-H

	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H

	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H

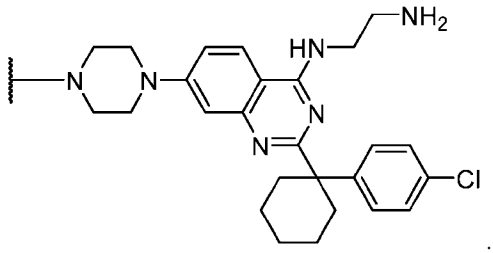
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
	-H	-H
-Br	$-CH_3$	-H
-Br	$-CH_3$	-H
	$-CH_3$	-H
-Br	-H	$-CH_3$
	-H	$-CH_3$
-Br	-H	$-CF_3$
	-H	$-CF_3$
-Br	-H	$-CH_2CH_3$

[00292] In certain embodiments, the present invention provides a compound of formula I as a compound of any one of the following formulae:



I-d-1

or a pharmaceutically acceptable salt thereof.

[00293] In some embodiments, DBM is 

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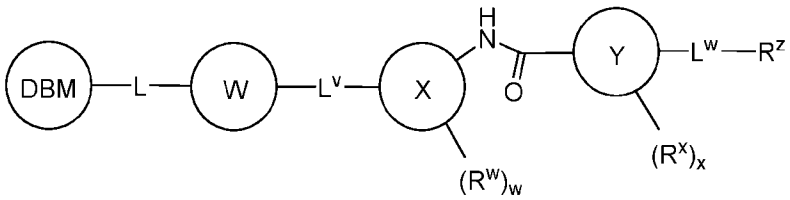
IRAK Binding Moiety (IRAK)

[00294] As defined above and described herein, IRAK is an IRAK binding moiety capable of binding to one or more of IRAK1, IRAK2, IRAK3, or IRAK4. In some embodiments, IRAK is an IRAK4 binding moiety.

[00295] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is a IRAK4 binding moiety of formula **I-aa**:



I-aa

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined and described herein, and wherein:

Ring W is a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring X is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Y is phenyl or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

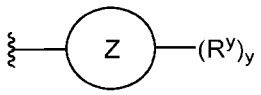
each of L^v and L^w is independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-;

each R^w is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, or $-C(O)NR_2$;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^x is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^z is selected from 

, hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Z is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, -

$CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

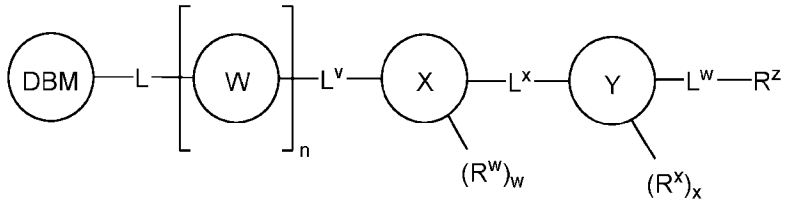
each R^A is independently an optionally substituted group selected from C_{1-10} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

w is 0, 1, or 2;

x is 0, 1, 2, 3 or 4; and

y is 0, 1, 2, 3 or 4.

[00296] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is a IRAK4 binding moiety of formula **I-aa'**:



I-aa'

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined and described herein, and wherein:

Ring W is phenyl, naphthyl, a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring X is phenyl, naphthyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Y is phenyl, naphthyl, a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of L^v, L^w , and L^x is independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -

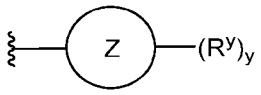
CR=CR-;

each R^w is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, or $-C(O)NR_2$;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom, or different atoms, are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^x is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, $-OC(O)R$, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^z is selected from 

, hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Z is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, $-OC(O)R$, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-10} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;
n is 0 or 1;
w is 0, 1, or 2;
x is 0, 1, 2, 3 or 4; and
y is 0, 1, 2, 3 or 4.

[00297] The below embodiments are to compounds of formula **I-aa** and **I-aa'**.

[00298] As defined generally above, Ring W is a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or hetereocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00299] As generally defined above, Ring W is phenyl, naphthyl, a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

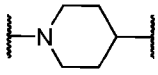
[00300] In some embodiments, Ring W is phenyl. In some embodiments, Ring W is naphthyl. In some embodiments, Ring W is a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring W is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

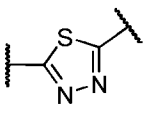
[00301] In some embodiments, Ring W is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00302] In some embodiments, Ring W is a 5-membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00303] In some embodiments, Ring W is a 4-6 membered saturated monocyclic carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00304] In some embodiments, Ring W is a 6-membered saturated monocyclic carbocyclic or heterocyclic ring having 1 heteroatom.

[00305] In some embodiments, Ring W is cyclohexyl. In some embodiments, Ring W is 

. In some embodiments, Ring W is 

.

[00306] In some embodiments, Ring W is selected from those depicted in **Table 1**, below.

[00307] As generally defined above, Ring X is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently

selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

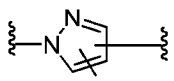
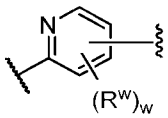
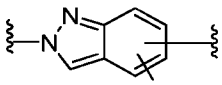
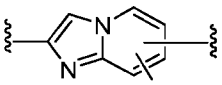
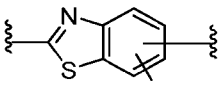
[00308] As generally defined above, Ring X is phenyl, naphthyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00309] In some embodiments, Ring X is phenyl. In some embodiments, Ring X is naphthyl. In some embodiments, Ring X is a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring X is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00310] In some embodiments, Ring X is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00311] In some embodiments, Ring X is a 5-membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00312] In some embodiments, Ring X is a 9-membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00313] In some embodiments, Ring X is  . In some embodiments, Ring X is  . In some embodiments, Ring X is  . In some embodiments, Ring X is  . In some embodiments, Ring X is  .

[00314] As defined generally above, Ring Y is phenyl or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00315] As generally defined above, Ring Y is phenyl, naphthyl, a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

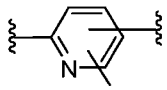
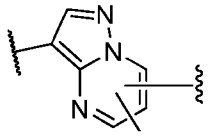
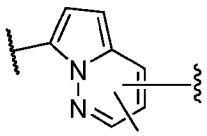
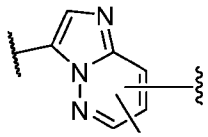
[00316] In some embodiments, Ring Y is phenyl or a 6-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00317] In some embodiments, Ring Y is phenyl. In some embodiments, Ring Y is naphthyl. In some embodiments, Ring Y is a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring Y is a 5-10 membered mono- or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00318] In some embodiments, Ring Y is phenyl, a 5-membered monocyclic, or a 9-membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00319] In some embodiments, Ring Y is a 5-membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00320] In some embodiments, Ring Y is a 9-membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00321] In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  .

[00322] In some embodiments, Ring Y is selected from those depicted in **Table 1**, below.

[00323] As generally defined above, L^v is a bivalent moiety selected from a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-.

[00324] In some embodiments, L^v is a covalent bond. In some embodiments, L^v is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-.

[00325] In some embodiments, L^v is a covalent bond or -C(O)NH-.

[00326] As generally defined above, L^w is a bivalent moiety selected from a covalent bond or a C_{1-3}

bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -CR=CR-.

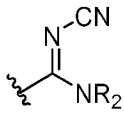
[00327] In some embodiments, L^w is a covalent bond. In some embodiments, L^w is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -CR=CR-.

[00328] As generally defined above, L^x is a bivalent moiety selected from a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -CR=CR-.

[00329] In some embodiments, L^x is a covalent bond. In some embodiments, L^x is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -CR=CR-.

[00330] In some embodiments, L^v is a covalent bond or -C(O)NH-. In some embodiments, L^x is a -C(O)NH-.

[00331] In some embodiments, L^v, L^w , and L^x are selected from those depicted in **Table 1**, below.

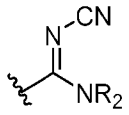
[00332] As defined generally above, each R^w is independently hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, -$P(O)(OR)_2$, -$P(O)(NR_2)_2$, -$CF_2(R)$, -CFR_2, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, –$N(R)S(O)_2R$, -$N^+(O^-)R_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -$P(O)R_2$, -SiR_3, -$Si(OR)R_2$, -SF_5, or  .

[00333] In some embodiments, R^w is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

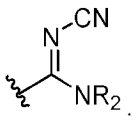
[00334] In some embodiments, R^w is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

[00335] In some embodiments, R^w is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -$CR_2(OR)$, -OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

[00336] In some embodiments, R^w is hydrogen. In some embodiments, R^w is R^A. In some

embodiments, R^w is halogen. In some embodiments, R^w is –CN. In some embodiments, R^w is -NO_2. In some embodiments, R^w is –OR. In some embodiments, R^w is –SR. In some embodiments, R^w is -NR_2. In some embodiments, R^w is -$S(O)_2R$. In some embodiments, R^w is -$S(O)_2NR_2$. In some embodiments, R^w is -S(O)R. In some embodiments, R^w is -S(O)(NR)R. In some embodiments, R^w is -$P(O)(OR)_2$. In some embodiments, R^w is -$P(O)(NR_2)_2$. In some embodiments, R^w is -$CF_2(R)$. In some embodiments, R^w is -CFR_2. In some embodiments, R^w is -CF_3. In some embodiments, R^w is -$CR_2(OR)$. In some embodiments, R^w is -$CR_2(NR_2)$. In some embodiments, R^w is -C(O)R. In some embodiments R^w is -C(O)OR. In some embodiments, R^w is -$C(O)NR_2$. In some embodiments, R^w is -C(O)N(R)OR. In some embodiments, R^w is -OC(O)R. In some embodiments, R^w is -$OC(O)NR_2$. In some embodiments, R^w is -N(R)C(O)OR. In some embodiments, R^w is -N(R)C(O)R. In some embodiments, R^w is -$N(R)C(O)NR_2$. In some embodiments, R^w is -$N(R)S(O)_2R$. In some embodiments, R^w is -$N^+(O^-)R_2$. In some embodiments, R^w is -$OP(O)R_2$. In some embodiments, R^w is -$OP(O)(OR)_2$. In some embodiments, R^w is -$OP(O)(OR)NR_2$. In some embodiments, R^w is -$OP(O)(NR_2)_2$. In some embodiments, R^w is -$P(O)R_2$. In some embodiments, R^w is -SiR_3. In some embodiments, R^w is -$Si(OR)R_2$. In some embodiments, R^w is -SF_5. In some embodiments, R^w is  .

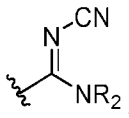
[00337] In some embodiments, R^w is -CHF_2. In some embodiments, R^w is -$C(OH)(CH_3)_2$. In some embodiments, R^w is -OMe.

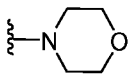
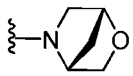
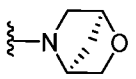
[00338] As defined generally above, each R^x and R^y are independently hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, -$P(O)(OR)_2$, -$P(O)(NR_2)_2$, -$CF_2(R)$, -CFR_2, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)S(O)_2R$, -$N^+(O^-)R_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -$P(O)R_2$, -SiR_3, -$Si(OR)R_2$, -SF_5, or  .

[00339] In some embodiments, R^x is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

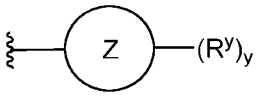
[00340] In some embodiments, R^x is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

[00341] In some embodiments, R^x is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -$CR_2(OR)$, -OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

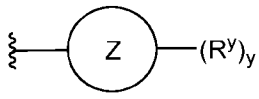
[00342] In some embodiments, one or more of R^x and R^y is hydrogen. In some embodiments, each R^x and R^y are independently R^A. In some embodiments, each R^x and R^y are independently halogen. In some embodiments, one or more of R^x and R^y is –CN. In some embodiments, one or more of R^x and R^y is $-NO_2$. In some embodiments, one or more of R^x and R^y is –OR. In some embodiments, one or more of R^x and R^y is –SR. In some embodiments, one or more of R^x and R^y is $-NR_2$. In some embodiments, one or more of R^x and R^y is $-S(O)_2R$. In some embodiments, one or more of R^x and R^y is $-S(O)_2NR_2$. In some embodiments, one or more of R^x and R^y is -S(O)R. In some embodiments, one or more of R^x and R^y is -S(O)(NR)R. In some embodiments, one or more of R^x and R^y is $-P(O)(OR)_2$. In some embodiments, one or more of R^x and R^y is $-P(O)(NR_2)_2$. In some embodiments, one or more of R^x and R^y is $-CF_2(R)$. In some embodiments, one or more of R^x and R^y is $-CFR_2$. In some embodiments, one or more of R^x and R^y is $-CF_3$. In some embodiments, one or more of R^x and R^y is $-CR_2(OR)$. In some embodiments, one or more of R^x and R^y is $-CR_2(NR_2)$. In some embodiments, one or more of R^x and R^y is -C(O)R. In some embodiments, one or more of R^x and R^y is -C(O)OR. In some embodiments, one or more of R^x and R^y is $-C(O)NR_2$. In some embodiments, one or more of R^x and R^y is -C(O)N(R)OR. In some embodiments, one or more of R^x and R^y is -OC(O)R. In some embodiments, one or more of R^x and R^y is $-OC(O)NR_2$. In some embodiments, one or more of R^x and R^y is -N(R)C(O)OR. In some embodiments, one or more of R^x and R^y is -N(R)C(O)R. In some embodiments, one or more of R^x and R^y is $-N(R)C(O)NR_2$. In some embodiments, one or more of R^x and R^y is $-N(R)S(O)_2R$. In some embodiments, one or more of R^x and R^y is $-N^+(O^-)R_2$. In some embodiments, one or more of R^x and R^y is $-OP(O)R_2$. In some embodiments, one or more of R^x and R^y is $-OP(O)(OR)_2$. In some embodiments, one or more of R^x and R^y is $-OP(O)(OR)NR_2$. In some embodiments, one or more of R^x and R^y is $-OP(O)(NR_2)_2$. In some embodiments, one or more of R^x and R^y is $-P(O)R_2$. In some embodiments, one or more of R^x and R^y is $-SiR_3$. In some embodiments, one or more of R^x and R^y is $-Si(OR)R_2$. In some embodiments, one or more of R^x and R^y is $-SF_5$. In some embodiments, one or more of R^x and R^y is  .

[00343] In some embodiments, R^x is  . In some embodiments, R^x is  . In some embodiments, R^x is  .

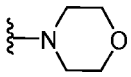
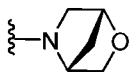
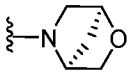
[00344] In some embodiments, each R^w, R^x, and R^y are independently selected from those depicted in **Table 1**, below.

[00345] As generally defined above, R^z is selected from  , hydrogen, or an

optionally substituted group selected from C_{1-6} aliphatic or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spiro ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00346] In some embodiments, R^z is  . In some embodiments, R^z is hydrogen. In some embodiments, R^z is an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, R^z is an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00347] In some embodiments, R^z is hydrogen or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00348] In some embodiments, R^z is  . In some embodiments, R^z is  . In some embodiments, R^z is  .

[00349] As defined generally above, Ring Z is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00350] In some embodiments, Ring Z is phenyl. In some embodiments, Ring Z is a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring Z is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00351] In some embodiments, Ring D is selected from those depicted in **Table 1**, below.

[00352] As generally defined above, each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to

which they are attached, independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same atom, or different atoms, are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur.

[00353] In some embodiments, each R is independently hydrogen. In some embodiments, each R is an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, each R is an optionally substituted phenyl. In some embodiments, each R is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spiro, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same atom, or different atoms, are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur.

[00354] In some embodiments, each R is selected from those depicted in **Table 1**, below.

[00355] As generally defined above, each R^A is independently an optionally substituted group selected from C_{1-10} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00356] In some embodiments, each R^A is independently an optionally substituted group selected from C_{1-10} aliphatic. In some embodiments, each R^A is independently an optionally substituted phenyl. In some embodiments, each R^A is independently an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^A is independently an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00357] In some embodiments, each R^A is selected from those depicted in **Table 1**, below.

[00358] As generally defined above, n is 0 or 1.

[00359] In some embodiments, n is 0. In some embodiments, n is 1.

[00360] In some embodiments, n is selected from those depicted in **Table 1**, below.

[00361] As generally defined above, w is independently 0, 1, or 2.

[00362] In some embodiments, w is 0. In some embodiments, w is 1. In some embodiments, w is 2. In some embodiments, w is 0 or 1. In some embodiments, w is 1 or 2.

[00363] As generally defined above, x is independently 0, 1, 2, 3 or 4.

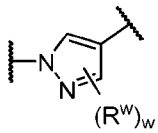
[00364] In some embodiments, x is 0. In some embodiments, x is 1. In some embodiments, x is 2. In some embodiments, x is 3. In some embodiments, x is 4. In some embodiments, x is 0 or 1. In some embodiments, x is 1 or 2.

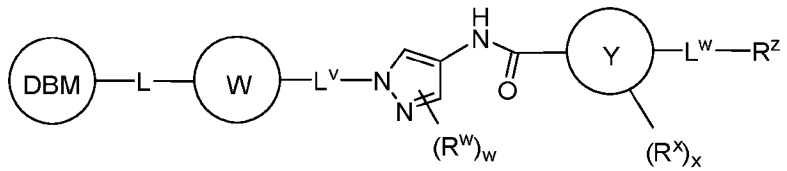
[00365] As generally defined above, y is independently 0, 1, 2, 3 or 4.

[00366] In some embodiments, y is 0. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4. In some embodiments, y is 0 or 1. In some embodiments, y is 1 or 2.

[00367] In some embodiments, w, x, and y are selected from those depicted in **Table 1**, below.

[00368] In certain embodiments, the present invention provides the compound of formula **I-aa**, wherein

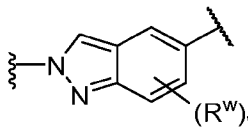
Ring X is  , thereby forming a compound of formula **I-aa-1**:

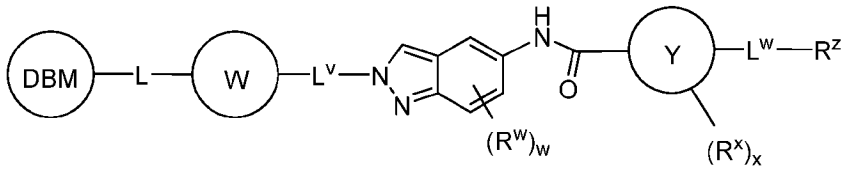


I-aa-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of Ring W, Ring Y, R^w, R^x, R^z, L^v, L^w, w, and x is as defined above and described in embodiments herein, both singly and in combination.

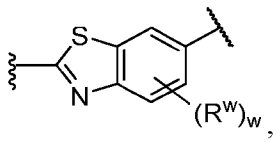
[00369] In certain embodiments, the present invention provides the compound of formula **I-aa**, wherein

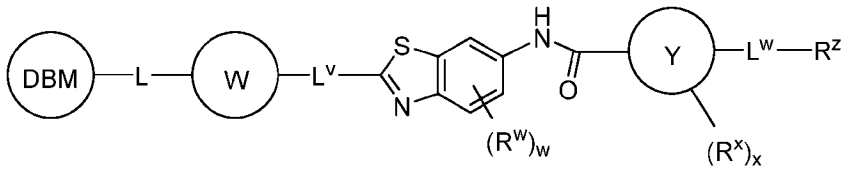
Ring X is  , thereby forming a compound of formula **I-aa-2**:



I-aa-2

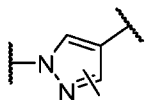
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of Ring W, Ring Y, R^w, R^x, R^z, L^v, L^w, w, and x is as defined above and described in embodiments herein, both singly and in combination.

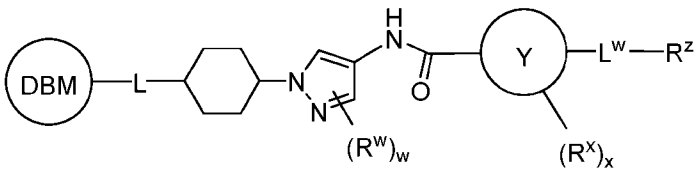
[00370] In certain embodiments, the present invention provides the compound of formula **I-aa**, wherein Ring X is  , thereby forming a compound of formula **I-aa-3**:



I-aa-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of Ring W, Ring Y, R^w, R^x, R^z, L^v, L^w, w, and x is as defined above and described in embodiments herein, both singly and in combination.

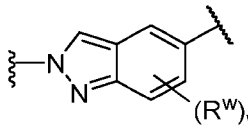
[00371] In certain embodiments, the present invention provides the compound of formula **I-aa**, wherein Ring W is cyclohexyl, L^v is a covalent bond, and Ring X is  , thereby forming a compound of formula **I-aa-4**:

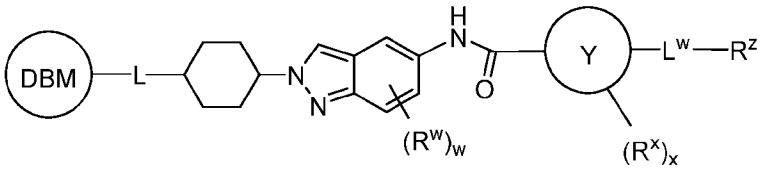


I-aa-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of Ring Y, R^w, R^x, R^z, L^w, w, and x is as defined above and described in embodiments herein, both singly and in combination.

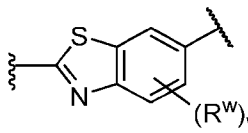
[00372] In certain embodiments, the present invention provides the compound of formula **I-aa**, wherein

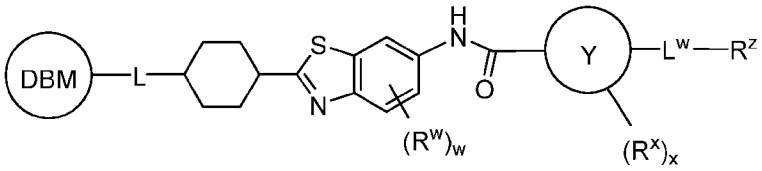
Ring W is cyclohexyl, L^y is a covalent bond, and Ring X is  , thereby forming a compound of formula **I-aa-5**:



I-aa-5

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of Ring Y, R^w, R^x, R^z, L^w, w, and x is as defined above and described in embodiments herein, both singly and in combination.

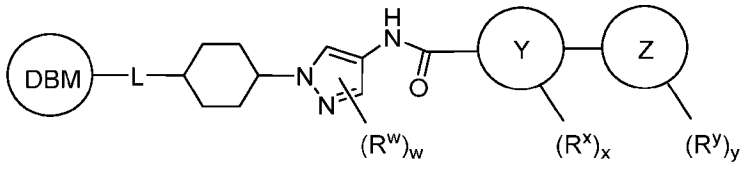
[00373] In certain embodiments, the present invention provides the compound of formula **I-aa**, wherein Ring W is cyclohexyl, L^y is a covalent bond, and Ring X is  , thereby forming a compound of formula **I-aa-6**:



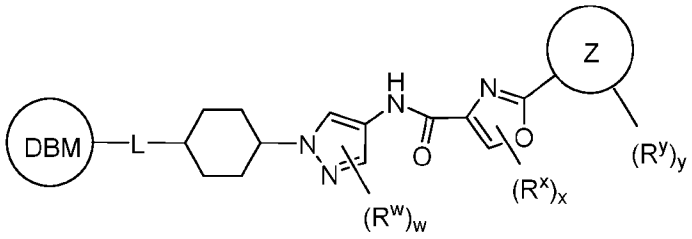
I-aa-6

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of Ring Y, R^w, R^x, R^z, L^w, w, and x is as defined above and described in embodiments herein, both singly and in combination.

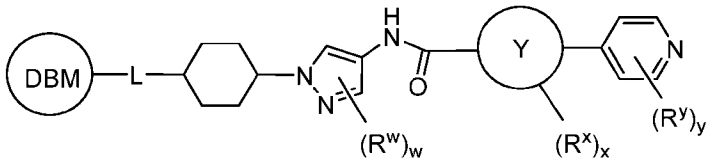
[00374] In certain embodiments, the present invention provides the compound of formula **I-aa** as a compound of any one of the following formulae:



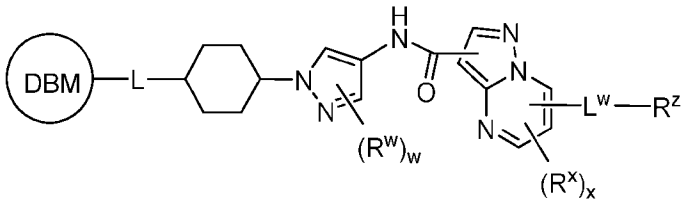
I-aa-7



I-aa-8



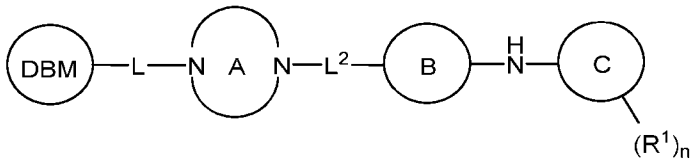
I-aa-9



I-aa-10

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

[00375] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is a IRAK4 binding moiety of formula **I-aa-11**:



I-aa-11

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 4-7 membered saturated monocyclic ring having two ring nitrogen atoms;

Ring B is a 4-10 membered saturated mono- or bicyclic carbocyclic or hetereocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is phenyl, a 4-10 membered saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently

selected from nitrogen, oxygen, and sulfur;

L^2 is a bivalent moiety selected from a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-;

each R^1 is independently hydrogen, R^4, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

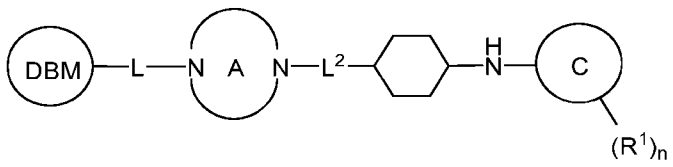
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

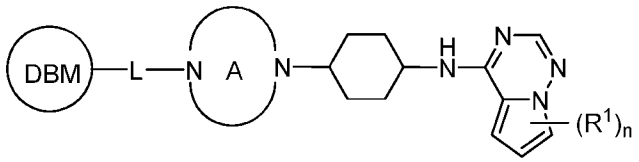
each R^4 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each n is 0, 1, 2, 3 or 4.

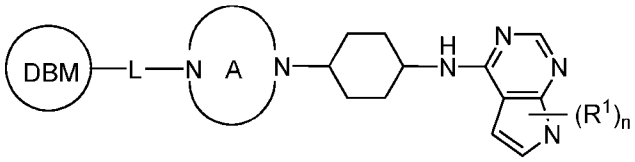
[00376] In certain embodiments, the present invention provides the compound of formula **I-aa-11** as a compound of any one of the following formulae:



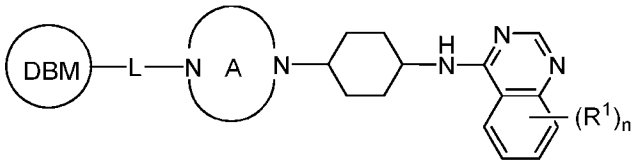
I-aa-11-1



I-aa-11-2



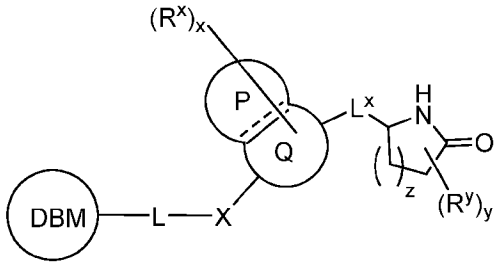
I-aa-11-3



I-aa-11-4

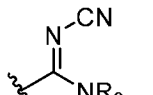
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

[00377] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is a IRAK4 binding moiety of formula **I-aa-12**:



I-aa-12

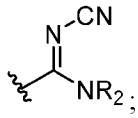
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

each R^x is independently hydrogen, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, or  ; or two R^x groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, or  ;

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring P and Ring Q are fused rings independently selected from benzo or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring Q is optionally substituted with 1-2 oxo groups;

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$, wherein R of $-CR_2-$, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

$-Cy^x-$ is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein $-Cy^x-$ is optionally substituted with 1-2 oxo groups;

X is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein one methylene unit of the chain is optionally replaced with 4-6 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

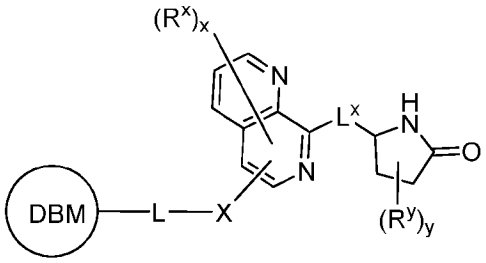
is a single or double bond;

each x is 0, 1, 2, 3 or 4;

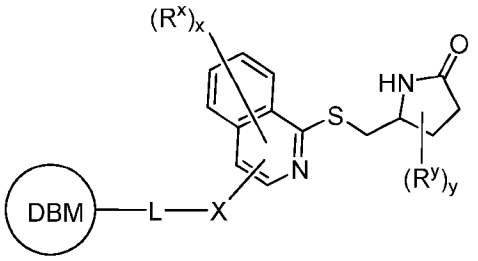
each y is 0, 1, 2, 3 or 4; and

z is 0, 1, or 2.

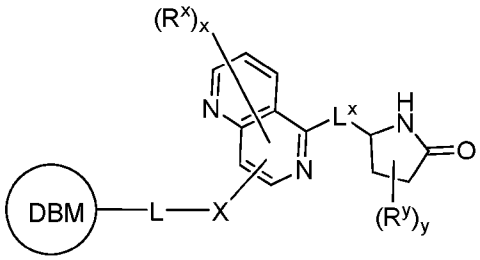
[00378] In certain embodiments, the present invention provides the compound of formula **I-aa-12** as a compound of any one of the following formulae:



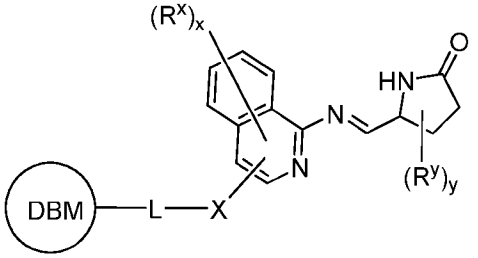
I-aa-12-1



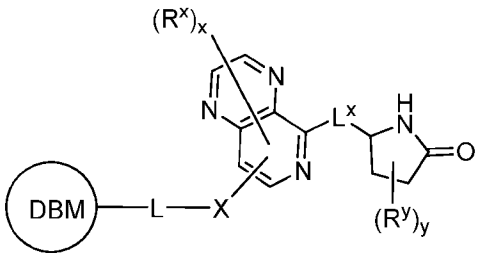
I-aa-12-5



I-aa-12-2



I-aa-12-6



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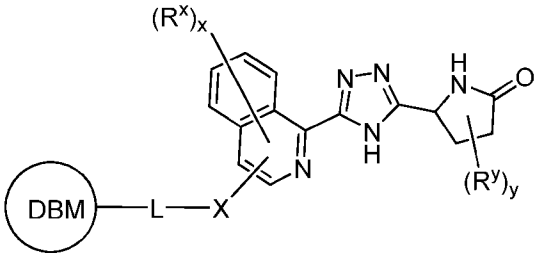

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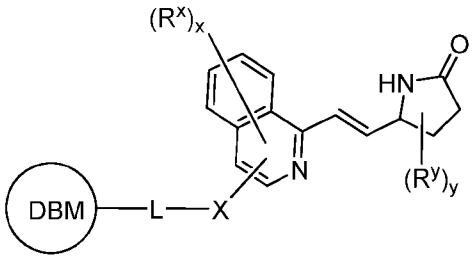

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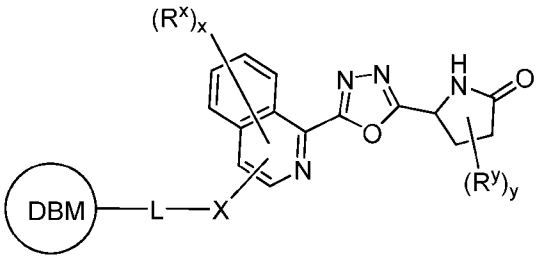
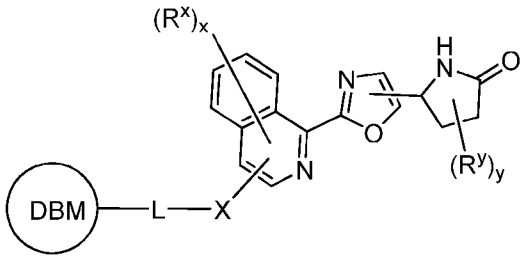
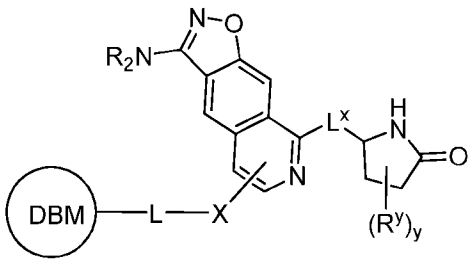


I-aa-12-8



I-aa-12-9



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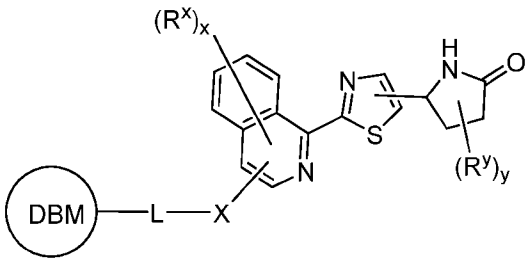
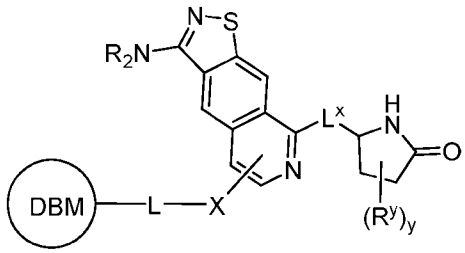


I-aa-12-10



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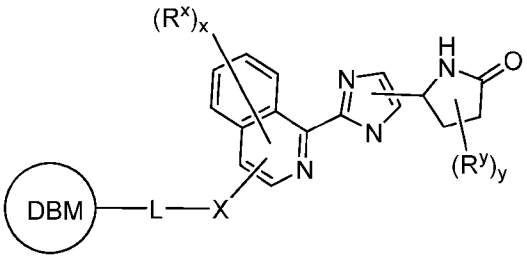
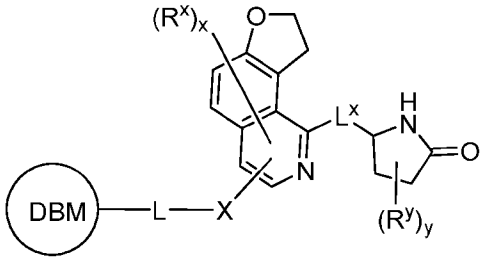
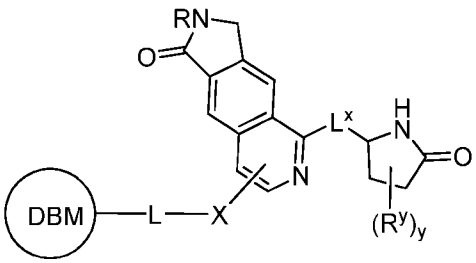


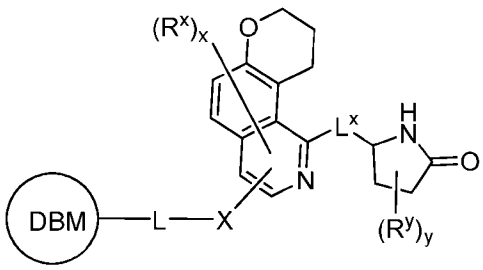
I-aa-12-11



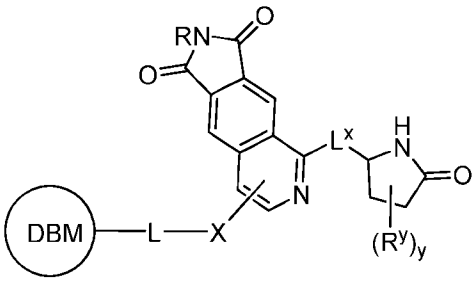
I-aa-12-16



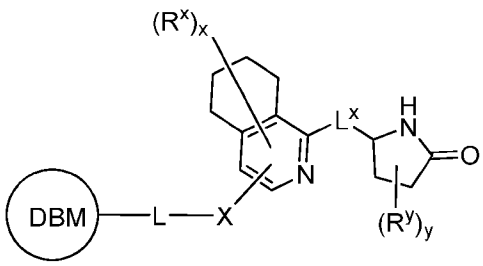
I-aa-12-12



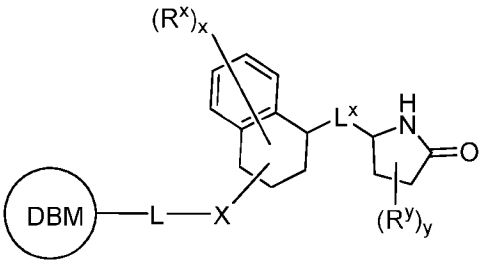
I-aa-12-17



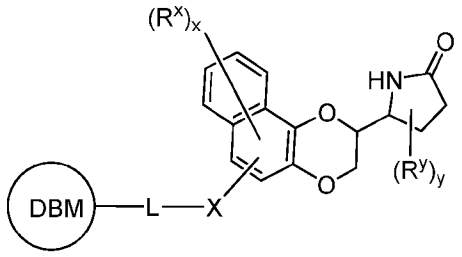
I-aa-12-13



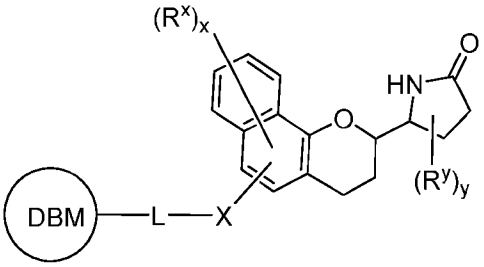
I-aa-12-18



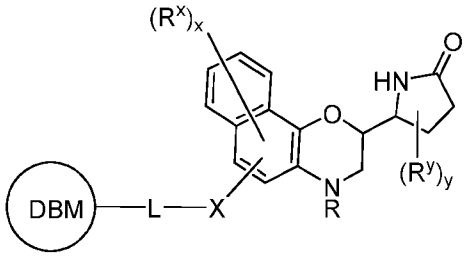
I-aa-12-19



I-aa-12-21



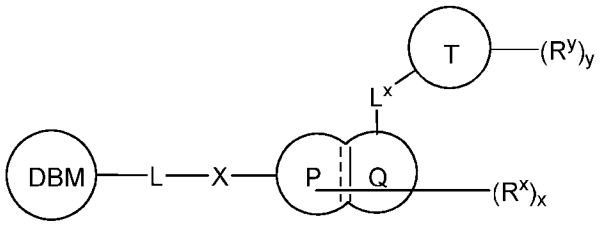
I-aa-12-20



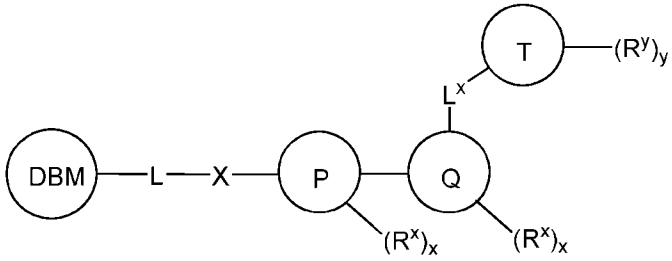
I-aa-12-22

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

[00379] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is a IRAK4 binding moiety of either of the following formulae:



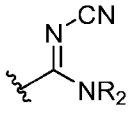
I-aa-13a



I-aa-13b

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

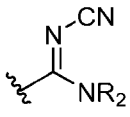
each R^x is independently hydrogen, R^z, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R,

$-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(S)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or  ; or

two R^x groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic spiro fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spiro, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^z, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(S)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, $-SF_5$, or  ; or

a single R^y and a single R^x are optionally taken together with their intervening atoms to form a 8-20 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic or bicyclic ring having 1-10 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-9 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-2 heteroatoms independently selected from nitrogen,

oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring P and Ring Q are optionally fused rings independently selected from phenyl or benzo, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring P and Ring Q are independently and optionally substituted with 1-2 oxo groups;

Ring T is selected from phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$, wherein R of $-CR_2-$, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

$-Cy^x-$ is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein $-Cy^x-$ is optionally substituted with 1-2 oxo groups;

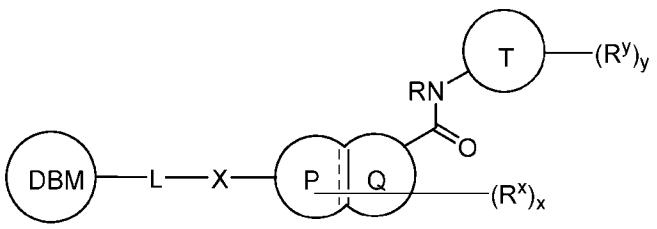
X is a covalent bond or a 4-6 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

==== is a single or double bond;

each x is 0, 1, 2, 3 or 4; and

each y is 0, 1, 2, 3 or 4.

[00380] In certain embodiments, the present invention provides the compound of formula **I-aa-13a** or **I-aa-13b** as a compound of any one of the following formulae:



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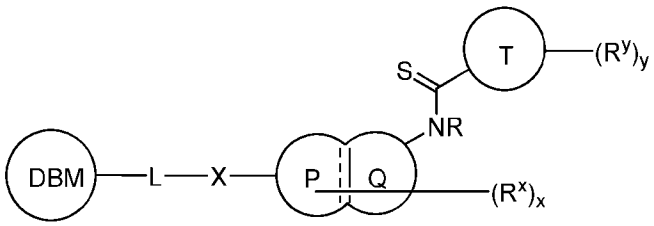

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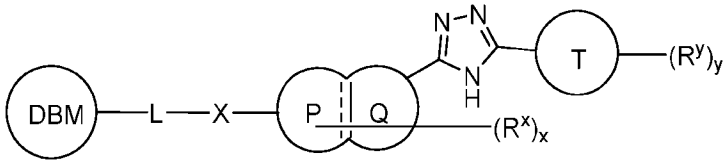

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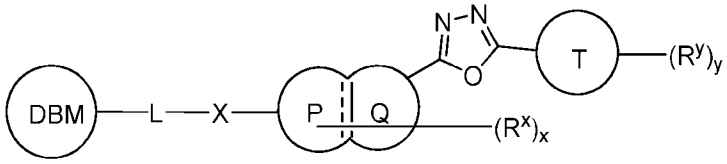

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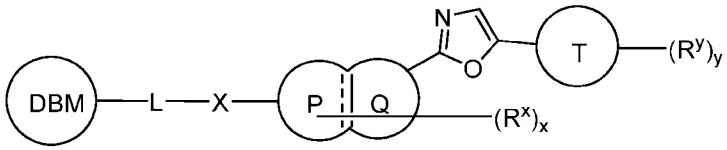

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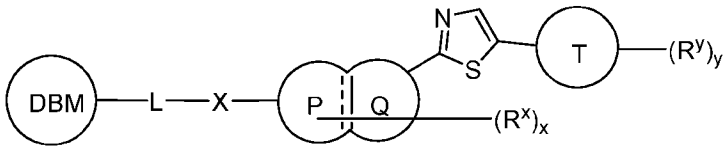

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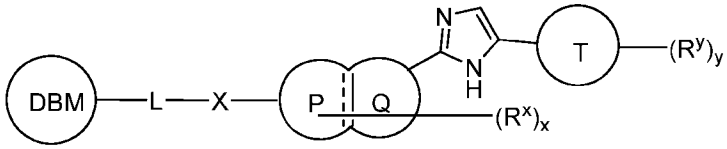

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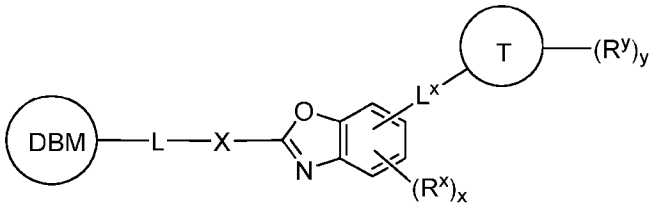

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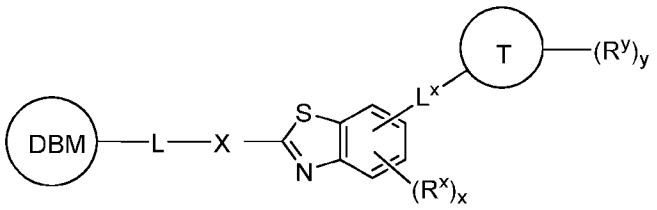

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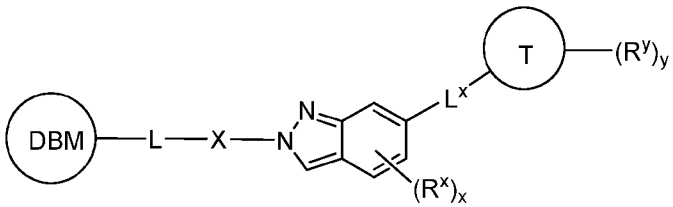

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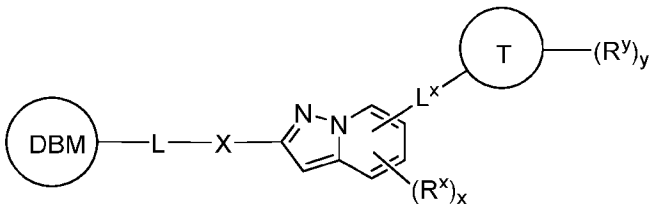

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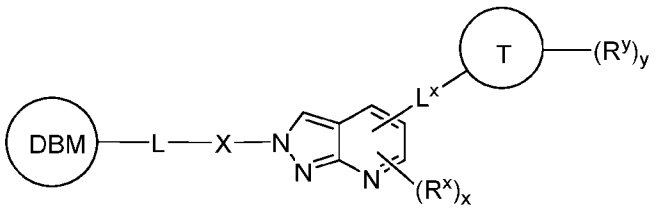

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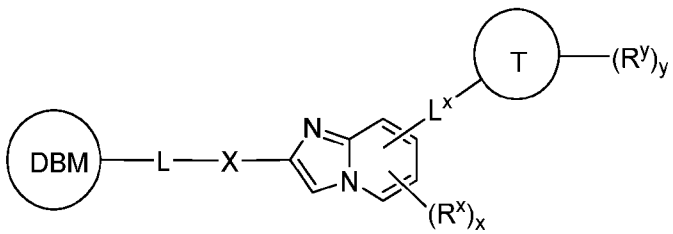

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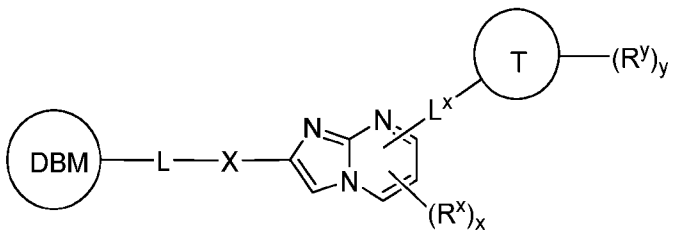

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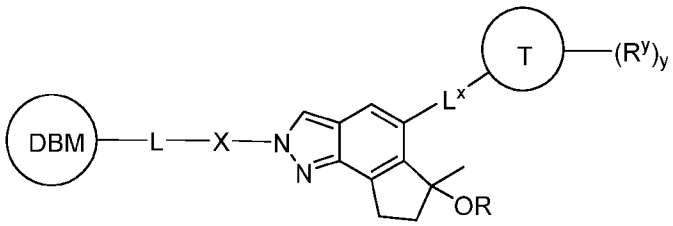

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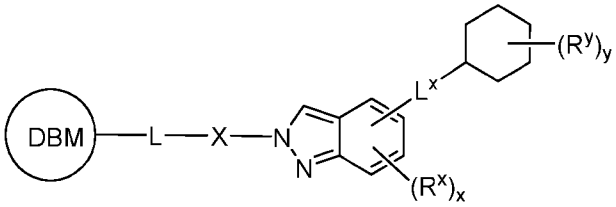

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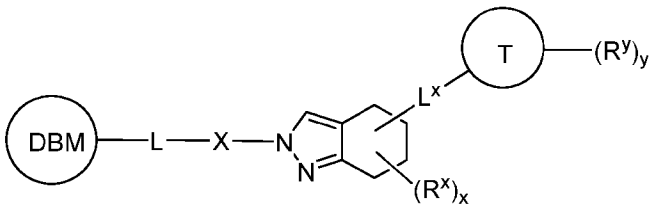

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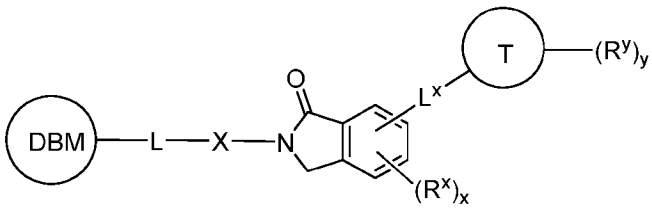

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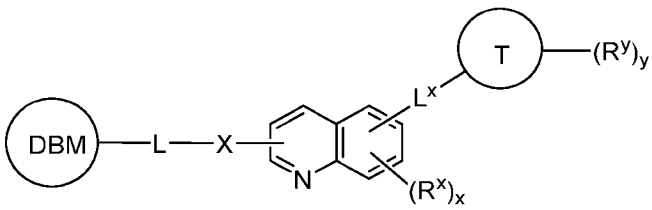

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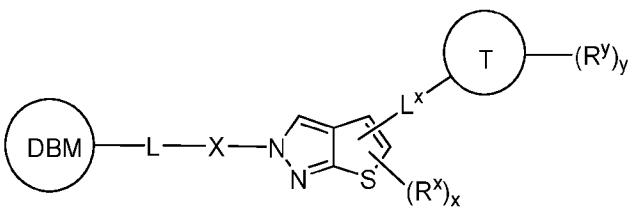

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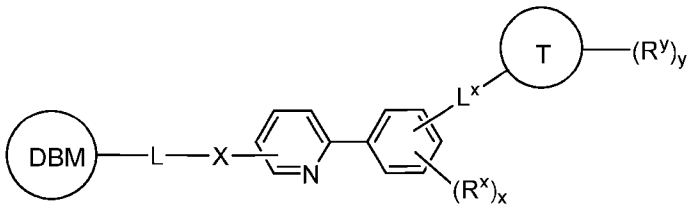

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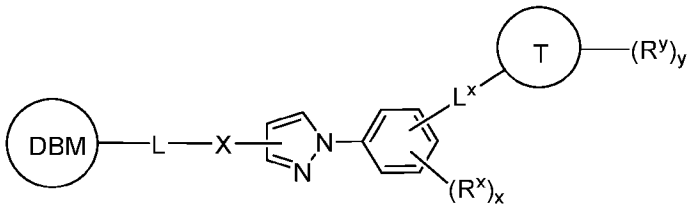

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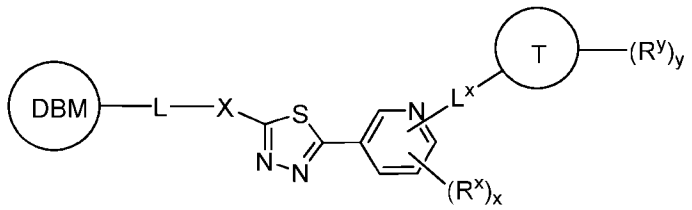
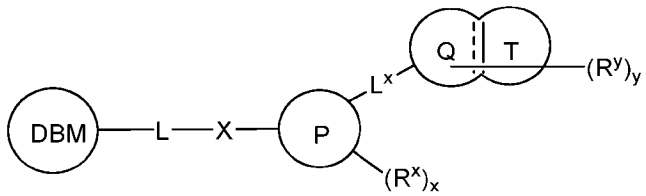


I-aa-13-23

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

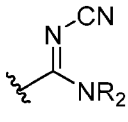
[00381] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is a IRAK4 binding moiety of formula **I-aa-14**:



I-aa-14

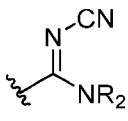
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

each R^x is independently hydrogen, deuterium, R^z, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -CF_2R, -CF_3, -CR_2F, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)S(O)_2R$, -$N^+(O^-)R_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -

$OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or  ;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, deuterium, R^z, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-CF_2R$, $-CF_3$, $-CR_2F$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(S)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or  ; or

two R^y groups are optionally taken together to form an optionally substituted 5-10 membered mono- or bicyclic partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring P is selected from phenyl, a 4-9 membered monocyclic or bicyclic saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is optionally substituted with 1-2 oxo groups;

Ring Q and Ring T are fused rings independently selected from benzo, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring Q and Ring T are independently and optionally substituted with 1-2 oxo groups;

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -Cy^x-, -O-, -S-, -C(O)-, -C(S)-, -CR_2-, -CRF-, -CF_2-, -NR-, -N=CR-, -CR=CR-, or -$S(O)_2$-, wherein R of -CR_2-, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

-Cy^x- is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein -Cy^x- is optionally substituted with 1-2 oxo groups;

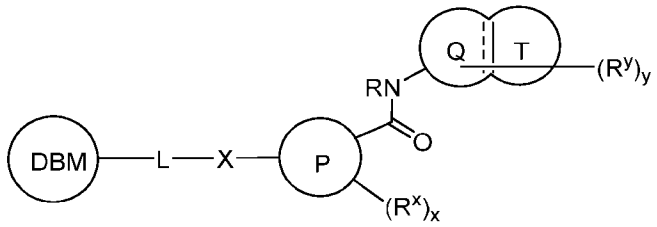
X is a covalent bond or an optionally substituted bivalent ring selected from phenylenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

==== is a single or double bond;

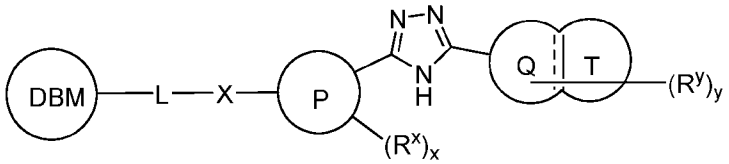
each x is 0, 1, 2, 3 or 4; and

each y is 0, 1, 2, 3 or 4.

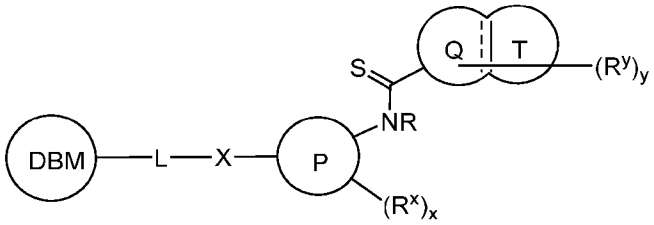
[00382] In certain embodiments, the present invention provides the compound of formula **I-aa-14** as a compound of any one of the following formulae:



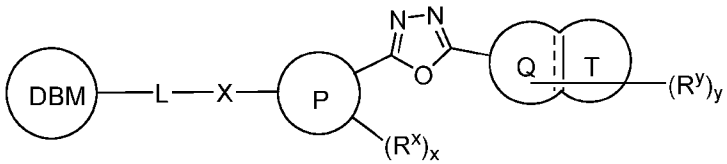
I-aa-14-1



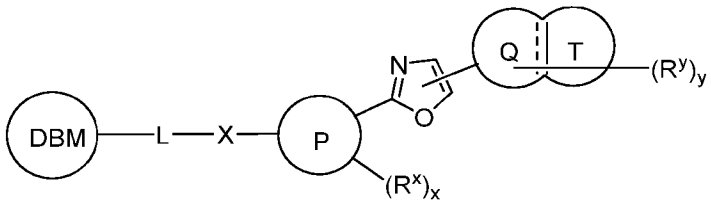
I-aa-14-2



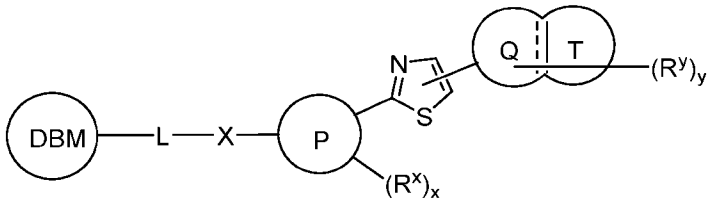
I-aa-14-3



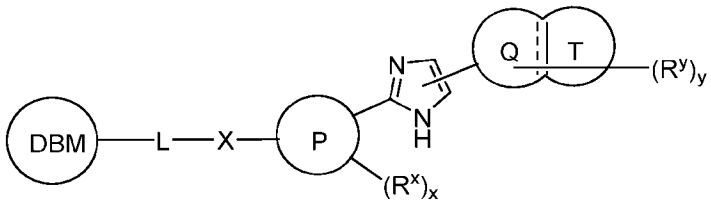
I-aa-14-4



I-aa-14-5



I-aa-14-6



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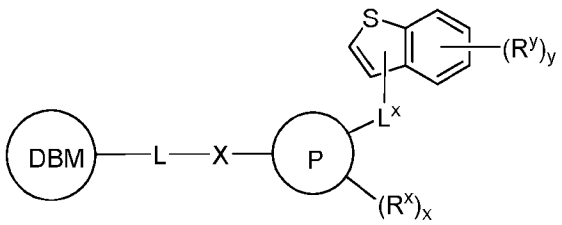

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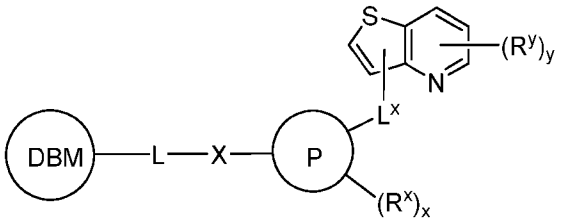

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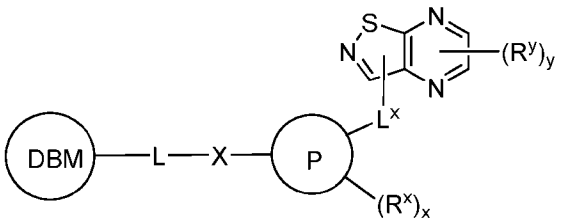

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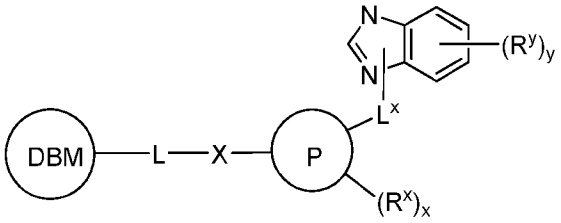
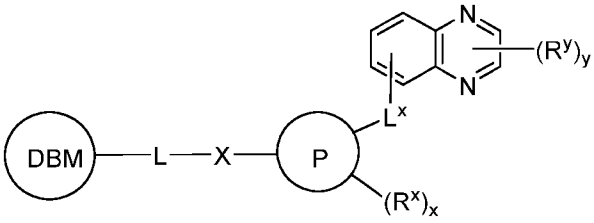
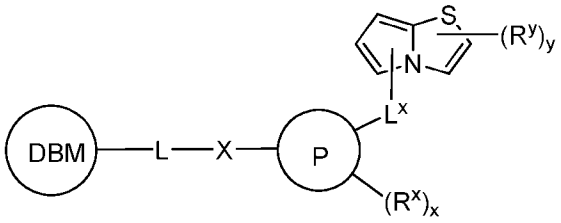


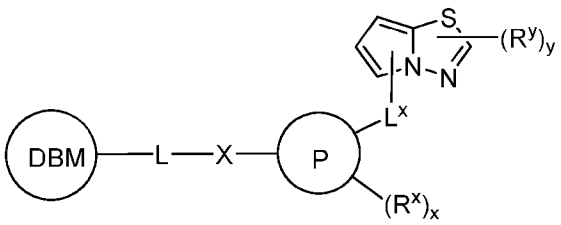
I-aa-14-11



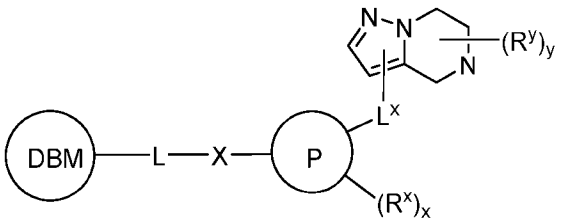
I-aa-14-12



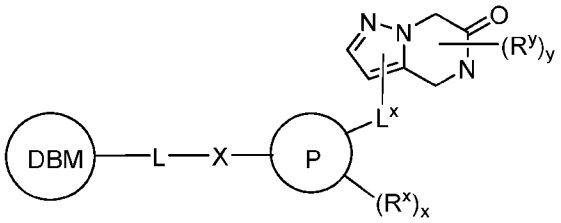
I-aa-14-13



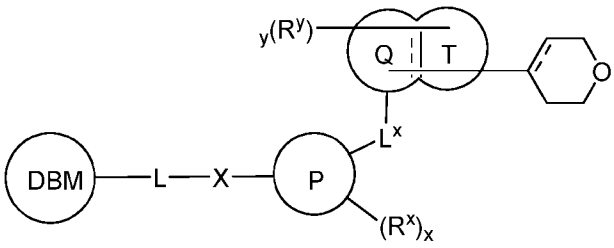
I-aa-14-14



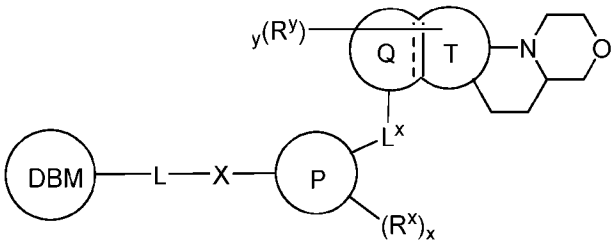
I-aa-14-15



I-aa-14-16



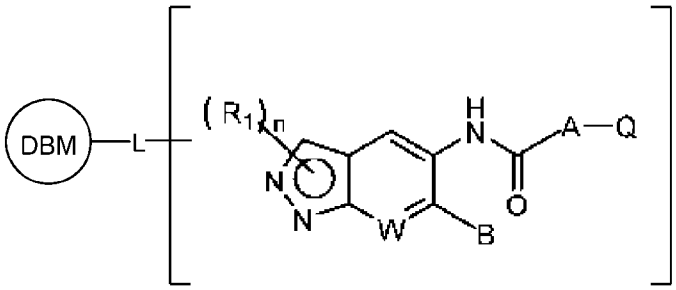
I-aa-14-17



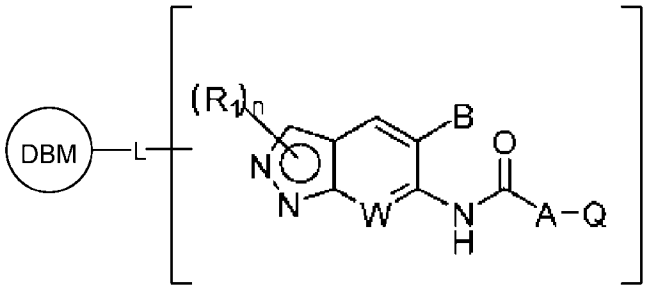
I-aa-14-18

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

[00383] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bb-1** or **I-bb-2**:



I-bb-1



I-bb-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, wherein:

A is optionally substituted heteroaryl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkyl-NR_x—, optionally substituted heterocycloalkyl-NR_x—, optionally substituted aryl-NR_x—, optionally substituted heteroaryl-NR_x—, optionally substituted cycloalkyl-O—, optionally substituted heterocycloalkyl-O—, optionally substituted aryl-O— or optionally substituted heteroaryl-O—; e.g., wherein each optional substituent independently represents an occurrence of R_z;

B is hydrogen, halogen, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, —NR_aR_b, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkyl-NR_x—, optionally substituted heterocycloalkyl-NR_x—, optionally substituted aryl-NR_x—, optionally substituted heteroaryl-NR_x—, optionally substituted cycloalkyl-O—, optionally substituted heterocycloalkyl-

O—, optionally substituted aryl-O—, optionally substituted heteroaryl-O—; e.g., wherein each optional substituent independently represents an occurrence of R_y;

Q is absent or optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted (heteroaryl)alkyl, optionally substituted aralkyl, optionally substituted (cycloalkyl)alkyl, —NR_3R_4, —O—R_3 or —S—R; e.g., wherein each optional substituent independently represents an occurrence of R_z;

W is N or CH;

R_1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted heterocycloalkyl, optionally substituted aralkyl, optionally substituted (heteroaryl)alkyl-, optionally substituted alkoxyalkyl, optionally substituted aminoalkyl, or —$(CH_2)_m$—R_2; e.g., wherein each optional substituent independently represents halo, hydroxy, alkoxy, amino, nitro, cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

R_2 is hydrogen, —NR_aR_b, alkoxy, hydroxy, optionally substituted heteroaryl or optionally substituted heterocycloalkyl; e.g., wherein each optional substituent independently represents an occurrence of R_y;

each R_3 and R_4 is independently selected from optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted aralkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heteroaryl)alkyl and optionally substituted (heterocycloalkyl)alkyl; e.g., wherein each optional substituent is independently selected from alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, nitro, cycloalkyl, (cycloalkyl)alkyl, aryl, aralkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, heteroaryl and (heteroaryl)alkyl;

each R_a and R_b is independently selected from hydrogen, alkyl, aminoalkyl, acyl and heterocyclyl; or R_a and R_b are taken together with the nitrogen to which they are attached to form an optionally substituted ring;

R_x is hydrogen, alkyl, hydroxy, hydroxyalkyl, acyl or cycloalkyl;

each R_y and R_x is independently selected from hydroxy, hydroxyalkyl, halo, alkyl, oxo, haloalkyl, alkoxy, alkenyloxy, amino, nitro, cyano, —SH, —S(alkyl), glycinate, ester, thioester, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, and (heteroaryl)alkyl; optionally wherein the hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are further substituted by one or more substituents selected from alkyl, halo, alkenyl, amino, nitro, cycloalkyl and (cycloalkyl)alkyl; or

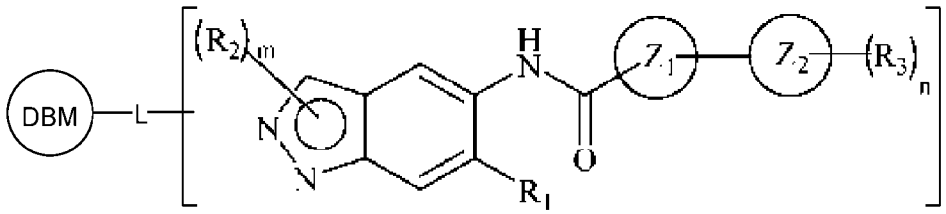
R_y and R_z taken together with the atoms to which they are attached form an alkyl chain having 1-10 carbon atoms; optionally wherein 1-3 carbon atoms are replaced by O, NH or S;

m is 1, 2, or 3; and

n is 1 or 2;

or each of the variables A, B, Q, W, R_1, and n is as defined and described in WO 2017/009798 which is herein incorporated by reference in its entirety.

[00384] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bb-3**



I-bb-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring Z_1 is an optionally substituted heteroaryl;

Ring Z_2 is an optionally substituted heterocycloalkyl, optionally substituted heteroaryl or a direct bond;

R_1 is alkyl, cyano, —NR_aR_b or optionally substituted groups selected from cycloalkyl, aryl or heterocyclyl; wherein the substituent, at each occurrence, independently is alkyl, alkoxy, halogen, hydroxyl, hydroxyalkyl, amino, aminoalkyl, nitro, cyano, haloalkyl, haloalkoxy, —OCO—CH_2—O-alkyl, —OP(O)(O-alkyl)$_2$ or —CH_2—OP(O)(O-alkyl)$_2$;

R_2, at each occurrence, independently is an optionally substituted group selected from alkyl or cycloalkyl; wherein the substituent, at each occurrence, is independently halogen, alkoxy, hydroxyl, hydroxyalkyl, haloalkyl or haloalkoxy;

R_3, at each occurrence, independently is hydrogen, halogen, alkyl, haloalkyl, haloalkoxy, alkoxy, —NR_aR_b, hydroxyl or hydroxyalkyl;

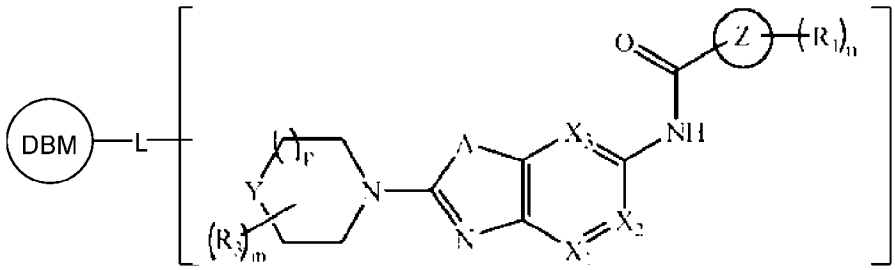
R_a is hydrogen or alkyl;

R_b is hydrogen, alkyl, acyl, hydroxyalkyl, —SO_2-alkyl or optionally substituted cycloalkyl;

m and n are independently 1 or 2;

or each of the variables R_1, R_2, R_3, m, n, Z_1, and Z_2 is as defined and described in WO 2015/104662 which is herein incorporated by reference in its entirety.

[00385] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bb-4**:



I-bb-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X_1 and X_3 independently are CH or N; X_2 is CR_2 or N; provided one and not more than one of X_1, X_2 or X_3 is N;

A is O or S;

Y is $—CH_2—$ or O;

Ring Z is aryl or heterocyclyl;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $—NR_aR_b$;

R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $—NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl;

R_3, at each occurrence, is alkyl or hydroxyl;

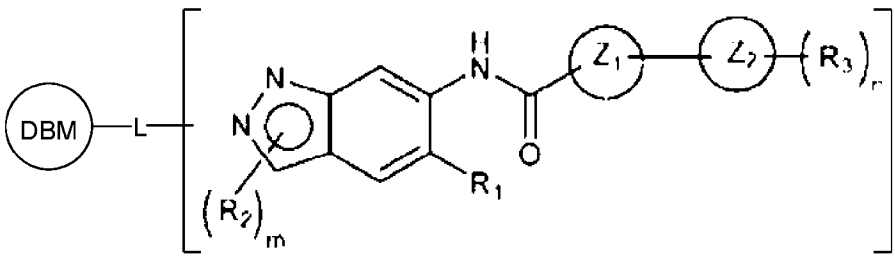
R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

m and n are independently 0, 1 or 2;

p is 0 or 1;

or each of the variables A, R_1, R_3, m, n, p, X_1, X_2, X_3, Y, and Z is as defined and described in WO 2015/104688 which is herein incorporated by reference in its entirety.

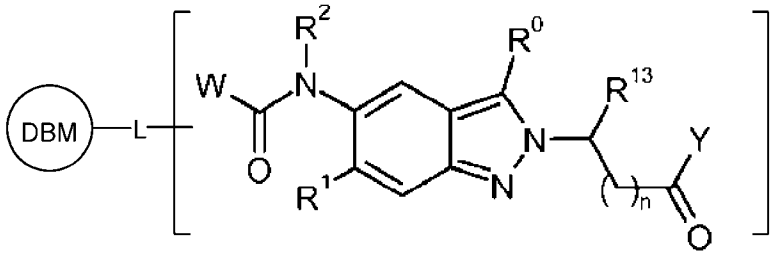
[00386] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bb-5**



I-bb-5

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of the variables R_1, R_2, R_3, m, n, Z_1, and Z_2 is as defined and described in WO 2015/193846 which is herein incorporated by reference in its entirety.

[00387] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bb-6**



I-bb-6

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Z_1 is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or is absent;

Z_2 is optionally substituted cycloalkyl, aryl or heterocyclyl;

R_1 is hydrogen, optionally substituted alkyl, amino, halogen, cyano, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

R_2 at each occurrence is hydrogen, halogen, amino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

R_3 at each occurrence is hydroxy, halogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl or —NR_aR_b;

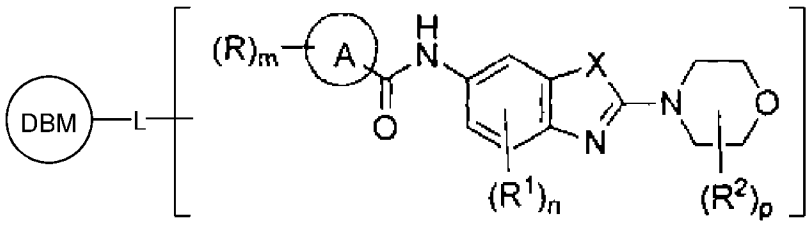
R_a and R_b, independently for each occurrence, are hydrogen, optionally substituted alkyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

m at each occurrence, is 0, 1 or 2; and

n at each occurrence, is 0, 1, or 2;

or each of the variables R^0, R^1, R^2, R^{13}, n, W, and Y is as defined and described in WO 2015/091426 which is herein incorporated by reference in its entirety.

[00388] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bbb-7**:



I-bb-7

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is selected from O, S, and NH;

A is selected from aryl or heteroaryl;

R at each occurrence is independently selected from hydrogen, cyano, halo, hydroxy, -$N0_2$, -NR^3R^4, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyi, optionally substituted heterocycloalkyl or optionally substituted heteroaryl; wherein the optional substituent, in each occurrence, is independently selected from halo, alkyl, haloalkyl, cyano, -NR^5R^6or -$COOR^7$;

R^1 at each occurence is independently selected from hydrogen, halogen, alkyl, aryl, heterocycloalkyl, heterocycloalkylalkyi, heteroaryl, Y-arylalkyl or -Y-cycloalkyl; wherein cycloalkyi, aryl, heterocycloalkyl, heterocycloalkylalkyi, heteroaryl and arylalkyl can be optionally substituted with hydroxy, alkyl, haloalkyl, cyano or halo;

Y is selected from direct bond, O, -C(O)- or NR^7;

R^2 at each occurence is independently selected from hydrogen, carboxy, cyano, hydroxy, hydroxyalkyl, alkyl, aryl, heteroaryl, -$S0^2R^5$ or oxo;

R^3 and R^4 are independently selected from hydrogen, hydroxyalkyl, aminoalkyl, optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted aryl; wherein the optional substituent, in each occurrence, is independently selected from halo, haloalkyl or -$COOR^7$;

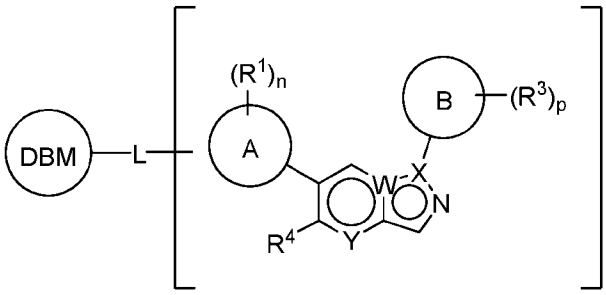
R^5 and R^6 are independently selected from hydrogen, alkyl, COR^7 or -$COOR^7$;

R^7at each occurrence is independently selected from hydrogen or alkyl; and

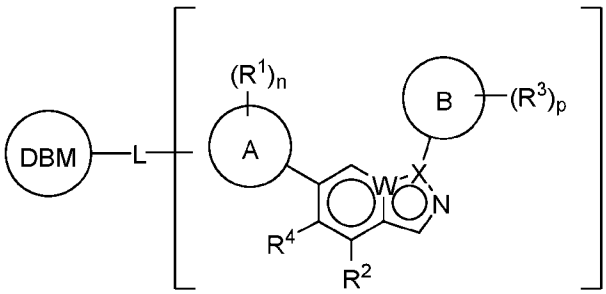
m, n and p are selected from 1, 2 or 3;

or each of the variables R^1, R^2, R, m, n, p, X, and A is as defined and described in WO 2013/042137 which is herein incorporated by reference in its entirety.

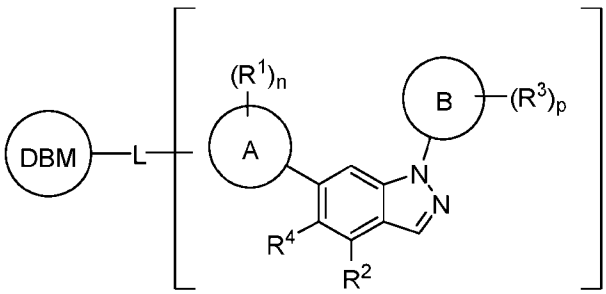
[00389] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-cc-1**, **I-cc-2**, **I-cc-3**, or **I-cc-4**:



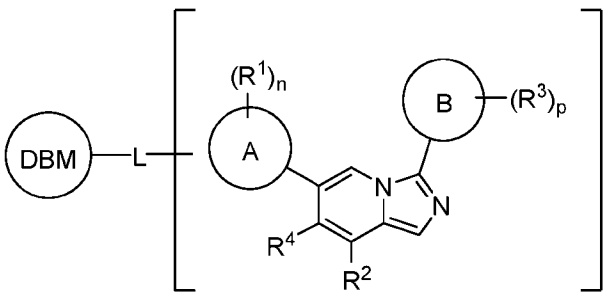
I-cc-1



I-cc-2



I-cc-3



I-cc-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is selected from phenyl and 5- or 6-membered heteroaryl;

Ring B is selected from phenyl and 5- or 6-membered heteroaryl;

n is 0, 1, or 2;

p is 0, 1, or 2;

one of W and X is N, and the other of W and X is C;

Y is N or C—R^2;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 6-membered saturated heterocyclyl, halo, —CN, —$C(R^{1a})$=$NR(OR^{1a})$, —$C(R^{1a})$=$N(R^{1a})$, —$C(O)R^{1a}$, —$C(O)_2R^{1a}$, —$C(O)N(R^{1a})_2$, —NO_2, —$N(R^{1a})_2$, —$N(R^{1a})C(O)R^{1a}$, —$N(R^{1a})C(O)_2R^{1a}$, —$N(R^{1a})C(O)N(R^{1a})_2$, —$N(R^{1a})S(O)_2R^{1a}$, —OR^{1a}, —$OC(O)R^{1a}$, —$OC(O)N(R^{1a})_2$, —SR^{1a}, —$S(O)R^{1a}$, —$S(O)_2R^{1a}$, —$S(O)N(R^{1a})_2$, and —$S(O)_2N(R^{1a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, and 3- to 6-membered saturated heterocyclyl are optionally substituted with one or more R^{10}; or two R^1 substituents, together with their intervening atoms, form a C_{5-7}cycloalkyl or a saturated 5- to 7-membered heterocyclic ring, wherein said C_{5-7}cycloalkyl or a saturated 5- to 7-membered heterocyclic ring are optionally substituted with one or more R^{15};

R^{1a} in each occurrence is independently selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 3- to 6-membered monocyclic heterocyclyl wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 3- to 6-membered monocyclic heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{10};

R^{10} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3- to 6-membered heterocyclyl, halo, —CN, —$C(R^{10a})$=$NR(OR^{10a})$, —$C(R^{10a})$=$N(R^{10a})$, —$C(O)R^{10a}$, —$C(O)_2R^{10a}$, —$C(O)N(R^{10a})_2$, —NO_2, —$N(R^{10a})_2$, —$N(R^{10a})C(O)R^{10a}$, —$N(R^{10a})C(O)_2R_{10a}$, —$N(R^{10a})C(O)N(R^{10a})_2$, —$N(R^{10a})S(O)_2R^{10a}$, —$OR^{10a}$, —$OC(O)R^{10a}$, —$OC(O)N(R^{10a})_2$, —$SR^{10a}$, —$S(O)R^{10a}$, —$S(O)_2R^{10a}$, —$S(O)N(R^{10a})_2$, and —$S(O)_2N(R^{10a})_2$;

R^{10a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo;

R^{15} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3- to 6-membered heterocyclyl, halo, —CN, —$C(R^{15a})$=$NR(OR^{15a})$, —$C(R^{15a})$=$N(R^{15a})$, —$C(O)R^{15a}$, —$C(O)_2R^{15a}$, —$C(O)N(R^{15a})_2$, —NO_2, —$N(R^{15a})_2$, —$N(R^{15a})C(O)R^{15a}$, —$N(R^{15a})C(O)_2R^{15a}$, —$N(R^{15a})C(O)N(R^{15a})_2$, —$N(R^{15a})S(O)_2R^{15a}$, —$OR^{15a}$, —$OC(O)R^{15a}$, —$OC(O)N(R^{15a})_2$, —$SR^{15a}$, —$S(O)R^{15a}$, —$S(O)_2R^{15a}$, —$S(O)N(R^{15a})_2$, and —$S(O)_2N(R^{15a})_2$;

R^{15a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo;

R^{2} is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered carbocyclyl, 3- to 7-membered heterocyclyl, halo, —CN, —$C(R^{2a})$=$NR(OR^{2a})$, —$C(R^{2a})$=$N(R^{2})$, —$C(O)R^{2a}$, —$C(O)_2R^{2a}$, —$C(O)N(R^{2a})_2$, —NO_2, —$N(R^{2a})_2$, —$N(R^{2a})C(O)R^{2a}$, —$N(R^{2a})C(O)_2R^{2a}$, —$N(R^{2a})C(O)N(R^{2a})_2$, —$N(R^{2a})S(O)_2R^{2a}$, —OR^{2a}, —$OC(O)R^{2a}$, —$OC(O)N(R^{2a})_2$, —SR^{2a}, —$S(O)R^{2a}$, —$S(O)_2R^{2a}$, —$S(O)N(R^{2a})_2$, and —$S(O)_2N(R^{2a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered carbocyclyl, and 3-7 membered heterocyclyl are optionally substituted with one or more R^{20};

R^{2a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^{20};

R^{20} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, 3- to 7-membered saturated heterocyclyl, halo, —CN, —$C(R^{20a})$=$NR(OR^{20a})$, —$C(R^{20a})$=$N(R^{20a})$, —$C(O)R^{20a}$, —$C(O)_2R^{20a}$, —$C(O)N(R^{20a})_2$, —NO_2, —$N(R^{20a})_2$, —$N(R^{20a})C(O)R^{20a}$, —$N(R^{20a})C(O)_2R^{20a}$, —$N(R^{20a})C(O)N(R^{20a})_2$, —$N(R^{20a})S(O)_2R^{20a}$, —$OR^{20a}$, —$OC(O)R^{20a}$, —$OC(O)N(R^{20a})_2$, —$SR^{20a}$, —$S(O)R^{20a}$, —$S(O)_2R^{20a}$, —$S(O)N(R^{20a})_2$, and —$S(O)_2N(R^{20a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, and 3-7 membered saturated heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{25};

R^{20a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with R^{25};

R^{25} is selected from halo and —OR^{25a};

R^{25a} is selected from H and C_{1-6}alkyl;

R^{3} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 6-membered saturated heterocyclyl, halo, —CN, —$C(R^{3a})$=$NR(OR^{3a})$, —$C(R^{3a})$=$N(R^{3a})$, —$C(O)R^{3a}$, —$C(O)_2R^{3a}$, —$C(O)N(R^{3a})_2$, —NO_2, —$N(R^{3a})_2$, —$N(R^{3a})C(O)R^{3a}$, —$N(R^{3a})C(O)_2R^{3a}$, —$N(R^{3a})C(O)N(R^{3a})_2$, —$N(R^{3a})S(O)_2R^{3a}$, —OR^{3a}, —$OC(O)R^{3a}$, —$OC(O)N(R^{3a})_2$, —SR^{3a}, —$S(O)R^{3a}$, —$S(O)_2R^{3a}$, —$S(O)N(R^{3a})_2$, and —$S(O)_2N(R^{3a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, and 3- to 6-membered saturated heterocyclyl are optionally substituted with one or more R^{30};

R^{3a} in each occurrence is independently selected from H, C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3- to 6-membered heterocyclyl, wherein said C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{30};

R^{30} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3- to 6-membered heterocyclyl, halo, —CN, —$C(R^{30a})$=$NR(OR^{30a})$, —

$C(R^{30a})$=$N(R^{30a})$, —$C(O)R^{30a}$, —$C(O)_2R^{30a}$, —$C(O)N(R^{30a})_2$, —NO_2, —$N(R^{30a})_2$, —$N(R^{30a})C(O)R^{30a}$, —$N(R^{30a})C(O)_2R^{30a}$, —$N(R^{30a})C(O)N(R^{30a})_2$, —$N(R^{30a})S(O)_2R^{30a}$, —$OR^{30a}$, —$OC(O)R^{30a}$, —$OC(O)N(R^{30a})_2$, —$SR^{30a}$, —$S(O)R^{30a}$ $S(O)_2R^{30a}$, —$S(O)N(R^{30a})_2$, and —$S(O)_2N(R^{30a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carboyclyl, 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{35};

R^{30a} in each occurrence is independently selected from H and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with one or more R^{35};

R^{35} in each occurrence is independently selected from halo and —OR^{35a};

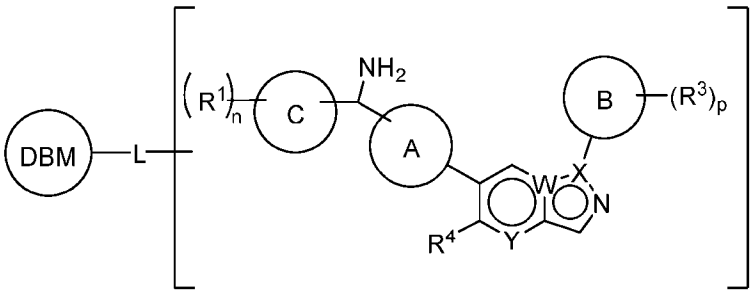
R^{35a} in each occurrence is independently selected from H and C_{1-6}alkyl;

R^4 is selected from H, halo, C_{1-6}alkyl, $N(R^{4a})_2$, and —OR^{4a}; and

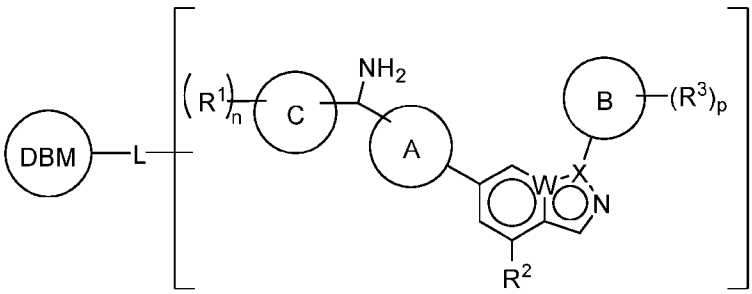
R^{4a} in each occurrence is independently selected from H and C_{1-6}alkyl;

or each of the variables R^1, R^2, R^3, R^4, A, B, W, X, Y, n, and p is as defined and described in WO 2016/011390 which is herein incorporated by reference in its entirety.

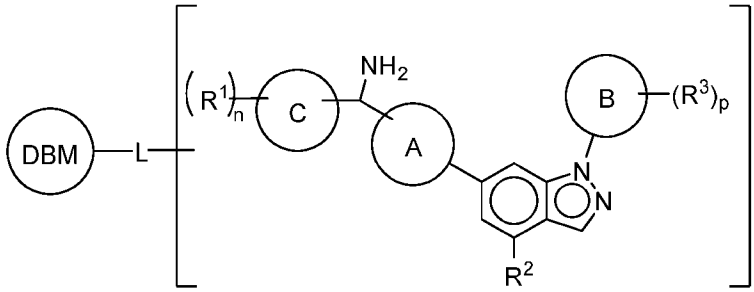
[00390] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-dd-1**, **I-dd-2**, **I-dd-3**, or **I-dd-4**:



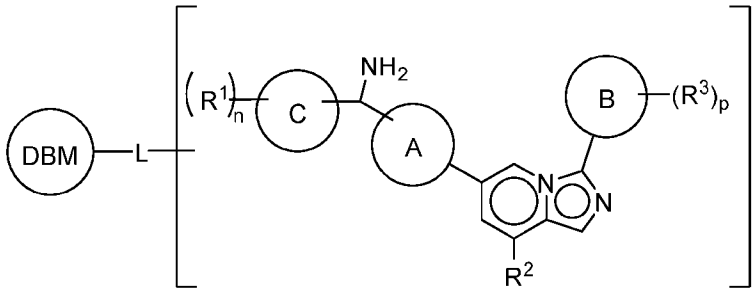
I-dd-1



I-dd-2



I-dd-3



I-dd-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is selected from phenyl and 5- or 6-membered heteroaryl;

Ring B is selected from phenyl and 5- or 6-membered heteroaryl;

Ring C is a 3- to 6-membered carbocyclyl,

n is 1, 2 or 3;

p is 0, 1, or 2;

one of W and X is N, and the other of W and X is C;

Y is N or C-R^2;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, -CN, -$C(R^{la})$=$NR(OR^{la})$, - $C(R^{la})$=$N(R^{la})$, - $C(O)R^{la}$, -$C(O)_2R^{la}$, -$C(O)N(R^{la})_2$, -NO_2, -$N(R^{la})_2$, -$N(R^{la})C(O)R^{la}$, - $N(R^{la})C(O)_2R^{la}$, - $N(R^{la})C(O)N(R^{la})_2$, -$N(R^{la})S(O)_2R^{la}$, -OR^{la}, -$OC(O)R^{la}$, - $OC(O)N(R^{la})_2$, -SR^{la}, -$S(O)R^{la}$, -$S(O)_2R^{la}$, -$S(O)N(R^{la})_2$, and -$S(O)_2N(R^{la})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one or more R^{10};

R^{la} in each occurrence is independently selected from H or C_{1-6}alkyl wherein said C_{1-6}alkyl in each occurrence are optionally and independently substituted with one or more R^{10};

R^{10} in each occurrence is independently selected from halo, -CN, -$C(R^{10a})$=$NR(OR)^{10a}$, -$C(R^{10a})$=$N(R^{10a})$, - $C(O)R^{10a}$, -$C(O)_2R^{10a}$, -$C(O)N(R^{10a})_2$, -NO_2, -$N(R^{10a})_2$, - $N(R^{10a})C(O)R^{10a}$, -$N(R^{10a})C(O)_2R^{10a}$, -

$N(R^{10a})C(O)N(R^{10a})_2$, $-N(R^{10a})S(O)_2R^{10a}$, $-OR^{10a}$, $-OC(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O)_2R^{10a}$, $-S(O)N(R^{10a})_2$, and $-S(O)_2N(R^{10a})_2$;

R^{10a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo;

R is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered carbocyclyl, 3-to 7-membered heterocyclyl, halo, -CN, $-C(R^{2a})=NR(OR^{2a})$, $-C(R^{2a})=N(R^{2a})$, $-C(O)R^{2a}$, $-C(O)_2R^{2a}$, $-C(O)N(R^{2a})_2$, $-NO_2$, $-N(R^{2a})_2$, $-N(R^{2a})C(O)R^{2a}$, $-N(R^{2a})C(O)_2R^{2a}$, $-N(R^{2a})C(O)N(R^{2a})_2$, $-N(R^{2a})S(O)_2R^{2a}$, $-OR^{2a}$, $-OC(O)R^{2a}$, $-OC(O)N(R^{2a})_2$, $-SR^{2a}$, $-S(O)R^{2a}$, $-S(O)_2R^{2a}$, $-S(O)N(R^{2a})_2$, and $-S(O)_2N(R^{2a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-to 7-membered carbocyclyl, and 3-7 membered heterocyclyl are optionally substituted with one or more R^{20};

R^{2a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R 20 ;

R^{20} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, 3-to 7-membered saturated heterocyclyl, halo, -CN, $-C(R^{20a})=NR(OR^{20a})$, $-C(R^{20a})=N(R^{20a})$, $-C(O)R^{20a}$, $-C(O)_2R^{20a}$, $-C(O)N(R^{20a})_2$, $-N0_2$, $-N(R^{20a})_2$, $-N(R^{20a})C(O)R^{20a}$, $-N(R^{20a})C(O)_2R^{20a}$, $-N(R^{20a})C(O)N(R^{20a})_2$, $-N(R^{20a})S(O)_2R^{20a}$, $-OR^{20a}$, $-OC(O)R^{20a}$, $-OC(O)N(R^{20a})_2$, $-SR^{20a}$, $-S(O)R^{20a}$, $-S(O)_2R^{20a}$, $-S(O)N(R^{20a})_2$, and $-S(O)_2N(R^{20a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, and 3-7 membered saturated heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{25};

R^{20a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with R^{25};

R^{25} is selected from halo and $-OR^{25a}$;

R^{25a} is selected from H and C_{1-6}alkyl;

R is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3-to 6-membered saturated heterocyclyl, halo, -CN, $-C(R^{3a})=NR(OR^{3a})$, $-C(R^{3a})=N(R^{3a})$, $-C(O)R^{3a}$, $-C(O)_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-NO_2$, $-N(R^{3a})_2$, $-N(R^{3a})C(O)R^{3a}$, $-N(R^{3a})C(O)_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})_2$, $-N(R^{3a})S(O)_2R^{3a}$, $-OR^{3a}$, $-OC(O)R^{3a}$, $-OC(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)N(R^{3a})_2$, and $-S(O)_2N(R^{3a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, and 3-to 6-membered saturated heterocyclyl are optionally substituted with one or more R^{30};

R^{3a} in each occurrence is independently selected from H, C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3-to 6-membered heterocyclyl, wherein said C_{1-6}alkyl, 3- to 6- membered carbocyclyl, and 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{30};

R^{30} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3-to 6-membered heterocyclyl, halo, -CN, - $C(R^{30a})=NR(OR^{30a})$, $-C(R^{30a})=N(R^{30a})$, - $C(O)R^{30a}$, $-C(O)_2R^{30a}$, $-C(O)N(R^{30a})_2$, $-NO_2$, - $N(R^{30a})_2$, $-N(R^{30a})C(O)R^{30a}$, $-N(R^{30a})C(O)_2R^{30a}$, - $N(R^{30a})C(O)N(R^{30a})_2$, - $N(R^{30a})S(O)_2R^{30a}$, $-OR^{30a}$, $-OC(O)R^{30a}$, $-OC(O)N(R^{30a})_2$, $-SR^{30a}$, $-S(O)R^{30a}$, $-S(O)_2R^{30a}$, - $S(O)N(R^{30a})_2$, and $-S(O)_2N(R^{30a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{35};

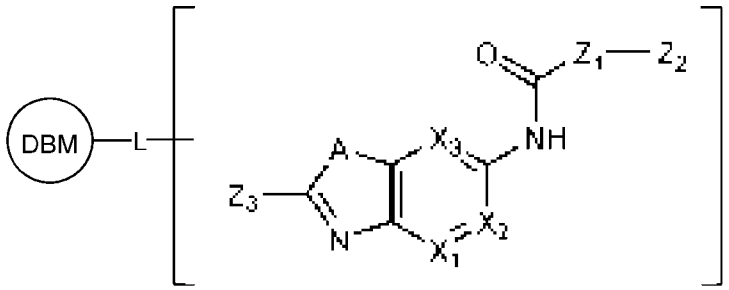
R^{30a} in each occurrence is independently selected from H and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with one or more R^{35};

R^{35} in each occurrence is independently selected from halo and $-OR^{35a}$; and

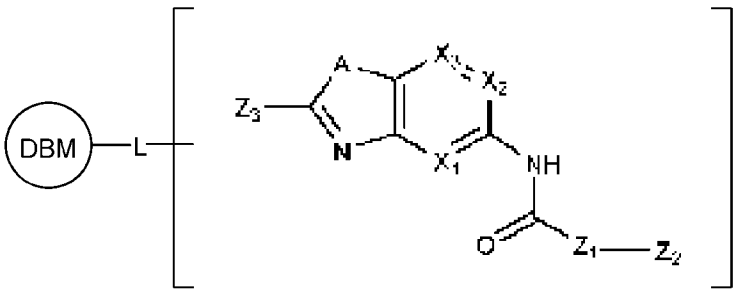
R^{35a} in each occurrence is independently selected from H and C_{1-6}alkyl;

or each of the variables R^1, R^2, R^3, A, B, C, W, X, Y, n, and p is as defined and described in WO 2017/127430 which is herein incorporated by reference in its entirety.

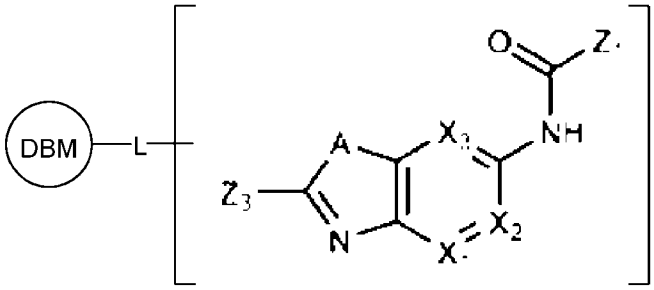
[00391] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ee-1**, **I-ee-2**, **I-ee-3**, or **I-ee-4**:



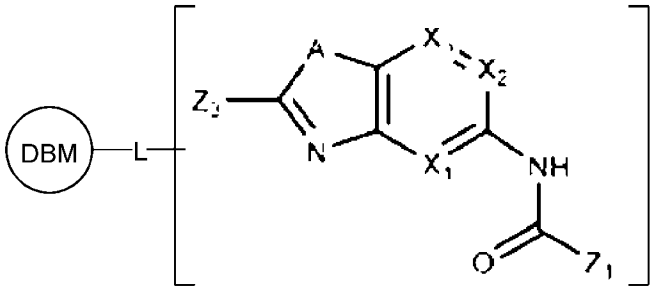
I-ee-1



I-ee-2



I-ee-3



I-ee-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

each X_1, X_2 and X_3 are independently CR^2 or N;

A is O, S, S(O) or $S(O)_2$;

Z_1 is optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted aralkyl-, optionally substituted heteroaralkyl-, optionally substituted (cycloalkyl)alkyl-, optionally substituted aryloxy-, optionally substituted heteroaryloxy-, optionally substituted heterocycloalkyloxy-, optionally substituted cycloalkyloxy-, optionally substituted aryl-NR′—, optionally substituted heteroaryl-NR′—, optionally substituted heterocycloalkyl-NR′—, optionally substituted cycloalkyl-NR′—, optionally substituted aryl-S—, optionally substituted heteroaryl-S—, optionally substituted heterocycloalkyl-S—, optionally substituted cycloalkyl-S—, optionally substituted (cycloalkyl)alkyl-NR′—, optionally substituted aralkyl-NR′—, optionally substituted (heterocycloalkyl)alkyl-NR′—, optionally substituted heteroaralkyl-NR′—, optionally substituted (cycloalkyl)alkyl-S—, optionally substituted aralkyl-S—, optionally substituted (heterocycloalkyl)alkyl-S—, optionally substituted heteroaralkyl-S—, optionally substituted (cycloalkyl)alkyl-O—, optionally substituted aralkyl-O—, optionally substituted (heterocycloalkyl)alkyl-O—, optionally substituted heteroaralkyl-O—; e.g., wherein each optional substituent independently represents an occurance of R_x;

Z_2 is absent or optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted aryloxy-, optionally substituted heteroaryloxy-, optionally substituted cycloalkyloxy-, optionally substituted heterocycloalkyloxy-, optionally substituted (cycloalkyl)alkyl-, optionally substituted aralkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted heteroaralkyl-, optionally substituted (cycloalkyl)alkyl-NR″—, optionally substituted aralkyl-NR″—, optionally substituted (heterocycloalkyl)alkyl-NR″—, optionally substituted heteroaralkyl-NR″—, optionally substituted (cycloalkyl)alkyl-O—, optionally substituted aralkyl-O—, optionally substituted (heterocycloalkyl)alkyl-O—, optionally substituted heteroaralkyl-O—, optionally substituted (cycloalkyl)alkyl-S—, optionally substituted aralkyl-S—, optionally substituted (heterocycloalkyl)alkyl-S— or optionally substituted heteroaralkyl-S—; e.g., wherein each optional substituent independently represents an occurance of R_y;

Z_3 is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted aryloxy-, optionally substituted heteroaryloxy-, optionally substituted cycloalkyloxy-, optionally substituted heterocycloalkyloxy-, optionally substituted (cycloalkyl)alkyl-, optionally substituted aralkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted heteroaralkyl-, optionally substituted (cycloalkyl)-NR′″—, optionally substituted aryl-NR′″—, optionally substituted heteroaryl-NR′″—, optionally substituted heterocycloalkyl-NR′″—, optionally substituted aryl-S—, optionally substituted heteroaryl-S—, optionally substituted cycloalkyl-S—, optionally substituted heterocycloalkyl-S—, optionally substituted (cycloalkyl)alkyl-NR′″—, optionally substituted aralkyl-NR′″—, optionally substituted (heterocycloalkyl)alkyl-NR′″—, optionally substituted heteroaralkyl-NR′″—, optionally substituted (cycloalkyl)alkyl-O—, optionally substituted aralkyl-O—, optionally substituted (heterocycloalkyl)alkyl-O—, optionally substituted heteroaralkyl-O—, optionally substituted (cycloalkyl)alkyl-S—, optionally substituted aralkyl-S—, optionally substituted (heterocycloalkyl)alkyl-S— or optionally substituted heteroaralkyl-S—; e.g., wherein each optional substituent independently represents an occurance of R_z;

each R^2 is independently selected from hydrogen, alkyl, haloalkyl, halo, cyano, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl-, optionally substituted cycloalkyloxy-, optionally substituted aryl, optionally substituted aralkyl-, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted heteroaralkyl-, —NR_aR_b, —O—R_3 and —S—R_3; e.g., wherein each optional substituent independently represents alkyl, alkoxy, halo, haloalkyl,

hydroxy, hydroxyalkyl, —SH, —S(alkyl), cyano, amido, amino, carboxylate, glycinate, alaninate, oxo, aryl, cycloalkyl, heterocycloalkyl or heteroaryl;

each R′, R″ and R‴ is independently selected from hydrogen, alkyl, hydroxy, hydroxyalkyl, acyl and cycloalkyl;

each R_x, R_y and R_z is independently selected from alkyl, alkenyl, alkynyl, halo, hydroxy, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, —SH, —S(alkyl), cyano, amido, carboxylic acid, carboxylate, ester, thioester, alkoxycarbonyl, —C(O)NH(alkyl), oxo, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-, aryl, aralkyl-, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, heteroaralkyl-, —NR_aR_b, —O—R_4 or —S—R_4; optionally wherein the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl are further substituted by one or more substituents selected from halo, haloalkyl, amino, hydroxy, alkyl, cyano, nitro, alkenyl, aminoalkyl, hydroxyalkyl and haloalkoxy;

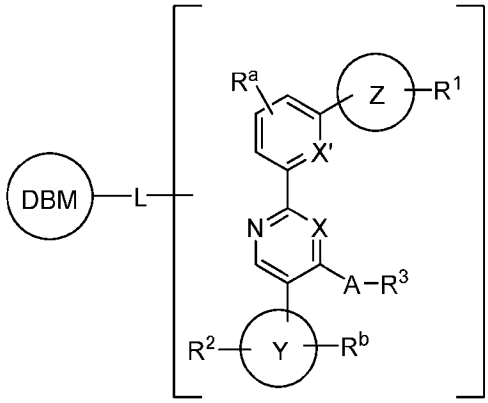
each R_a and R_b is independently selected from hydrogen, alkyl, aminoalkyl, acyl, aminoacyl, halo, haloalkyl, hydroxy, haloalkoxy, hydroxyalkyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl-, (heterocycloalkyl)alkyl-, aralkyl-, and (heteroaryl)alkyl-; optionally wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are further substituted by one or more substituents selected from alkyl, halo, alkenyl, cyano, hydroxy, hydroxyalkyl, alkoxy, amino and nitro; or

R_a and R_b are taken together along with the atoms which they are attached to form a 3 to 8 membered optionally substituted ring; and

each R_3 and R_4 is independently selected from hydrogen, alkyl, aminoacyl, phosphate, phosphonate, alkylphosphate, alkoxycarbonyl, cycloalkyl, (cycloalkyl)alkyl-, aryl, heteroaryl, heterocycloalkyl, aralkyl-, heteroaralkyl and (heterocycloalkyl)alkyl-;

or each of the variables X_1, X_2, X_3,, Z_1, Z_2, Z_3, and A is as defined and described in WO 2017/009806 which is herein incorporated by reference in its entirety.

[00392] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ff-1**:



I-ff-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is CR or N;

A is O, S, SO_2, SO, —NRC(O), —$NRSO_2$, or N(R); or A is absent;

R^3 is —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)N(R)_2$, —$NRSO_2R$, or —$N(R)_2$; or

when A is —NRC(O), —$NRSO_2$, or N(R); then R and R^3, together with the atoms to which each is attached, may form a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

X′ is CR or N;

Ring Z is a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

R^1 is —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)N(R)_2$, —$NRSO_2R$, or —$N(R)_2$;

R^a is absent, —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)N(R)_2$, —$NRSO_2R$, or —$N(R)_2$;

Ring Y is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 2-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)N(R)_2$, —$NRSO_2R$, or —$N(R)_2$;

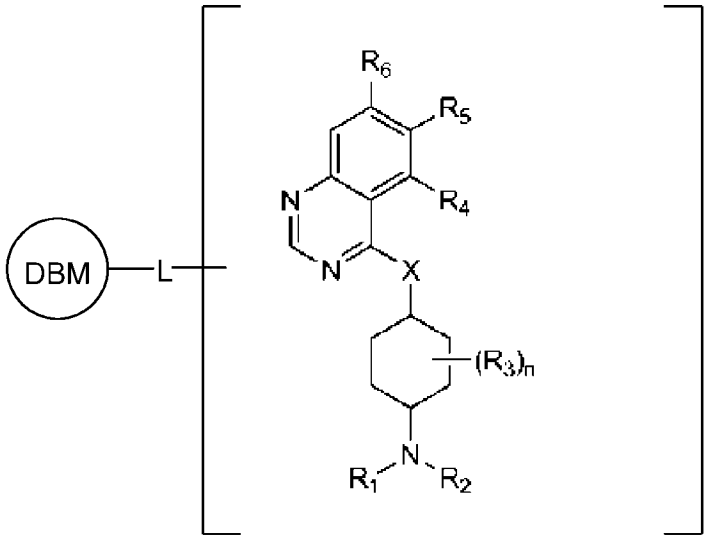
R^b is absent, —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)N(R)_2$, —$NRSO_2R$, or —$N(R)_2$;

each R is independently hydrogen, C_{1-6} aliphatic, C_{3-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or

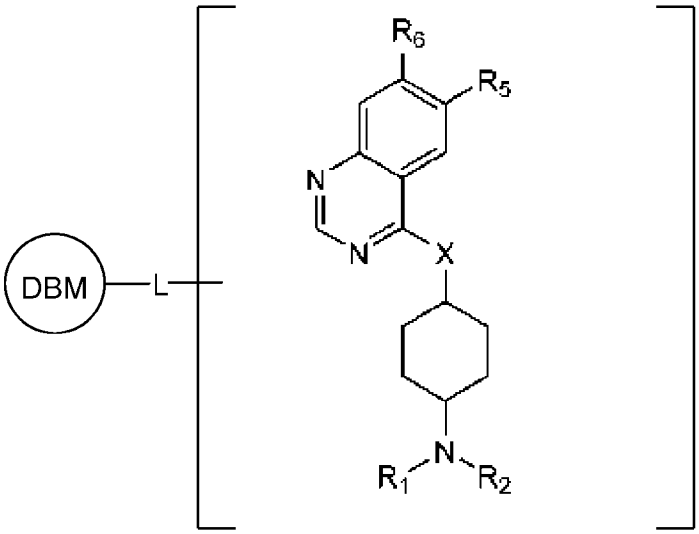
two R groups on the same atom are taken together with the atom to which they are attached to form a C_{3-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

or each of the variables A, R^1, R^2, R^3, R^a, R^b, X, X', Y and Z is as defined and described in WO 2016/081679 which is herein incorporated by reference in its entirety.

[00393] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-gg-1** or **I-gg-2**:



I-gg-1



I-gg-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is NH or O;

b is 0 or 1;

n is 0, 1, 2, 3 or 4;

R_1 and R_2 are independently H, (C_1-C_4)alkyl and heterocyclyl, or $R_1$and R_2 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic (fused, bridged or spirocyclic) heterocycle containing 3-8 carbon atoms optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said alkyl and heterocycle are optionally substituted with one or more substituents selected from R_a;

R_3 is (C_1-C_4)alkyl wherein two adjacent alkyl groups can join together and form a bridged moiety of 3-6 carbon atoms;

R_4 is absent, halo or O_b(C_1-C_4)alkyl;

R_5 is selected from C_1-C_4 alkyl and C_2-C_4 alkenyl which are optionally substituted with one or more substituents selected from R_b;

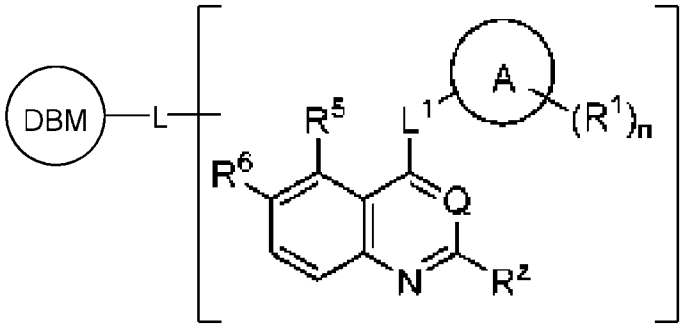
R_6 is absent, halo, or O(C_1-C_4)alkyl;

R_a is halo, oxo, OH, O_b(C_1-C_4)alkyl, CF_3, SO_2(C_1-C_4)alkyl, or heterocyclyl, said heterocyclyl optionally substituted with one or more substituents independently selected from F, and (C_1-C_4)alkyl; and

R_b is independently selected from OH, halo, O_b(C_1-C_4)alkyl, and CN;

or each of the variables R_1, R_2, R_3, R_4, R_5, R_6, X and n is as defined and described in WO 2016/053769 which is herein incorporated by reference in its entirety.

[00394] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-gg-3**:



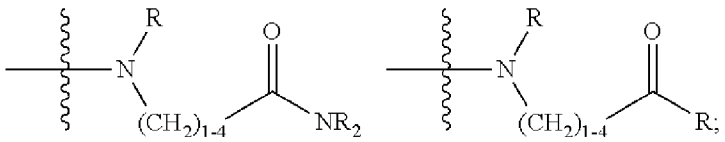
I-gg-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Q is =N— or =CH—;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 is independently —R^2, halogen, —CN, —NO_2, —OR, —SR, —NR_2, —$S(O)_2R$, —$S(O)_2NR_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)NR_2$, —C(O)N(R)OR, —N(R)C(O)OR, —$N(R)C(O)NR_2$, Cy, or —$N(R)S(O)_2R$; or $R^1$is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^5 and R^6 is independently hydrogen or $-L^2(R^4)_p—R^x$; or

R^5 and R^6 are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —NR_2, —$S(O)_2R$, —$S(O)_2NR_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)NR_2$, —N(R)C(O)R, —$N(R)C(O)NR_2$, —C(O)N(R)OR, —N(R)C(O)OR, —$N(R)S(O)_2NR_2$, —$N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^x is hydrogen, —R^2, —CN, —NO_2, halogen, —$C(O)NR_2$, —C(O)OR, —C(O)R, —NR_2, —NH[Ar], —OR, or —$S(O)_2NR_2$;

R^z is hydrogen, —R^2, —CN, —NO_2, halogen, —$C(O)NR_2$, —C(O)OR, —C(O)R, —NR_2, —NH[Ar], —OR, or —$S(O)_2NR_2$;

[Ar] is an optionally substituted phenyl or an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

m is 0-4;

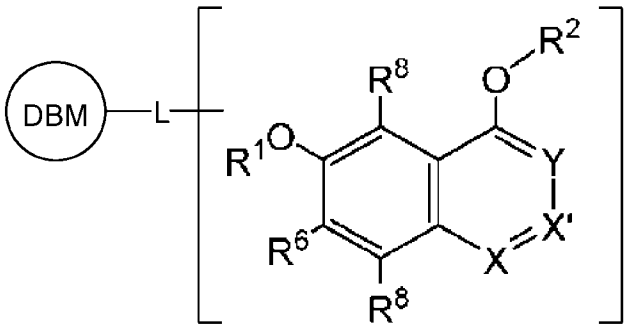
n is 0-4; and

p is 0-2;

or each of the variables R^5, R^6, L^1, A, R^1, n, Q, and R^z is as defined and described in WO 2015/164374

which is herein incorporated by reference in its entirety.

[00395] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-gg-4**:



I-gg-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X and X′ are each independently CR^8, N or $—N^+—O^-$; Y is independently N, $—N^+—O^-$ or $CR^{8'}$; provided that at least one of X, X′ or Y is neither N nor $—N^+—O^-$ and that no more than one of X, X′ or Y is $—N^+—O^-$;

R^1 is C_1-C_6alkyl; C_2-C_6alkenyl; C_2-C_6alkynyl; $—(CR^{3a}R^{3b})_m$-(3- to 7-membered cycloalkyl); $—(CR^{3a}R^{3b})_m$-(3- to 7-membered heterocycloalkyl) having one to three heteroatoms; $—(CR^{3a}R^{3b})_m$-(5- to 10-membered heteroaryl), having one to three heteroatoms; or $—(CR^{3a}R^{3b})_m—C_6$-C_{12}aryl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl or aryl is optionally substituted with one to five halogen, deuterium, $—OR^5$, $—SR^5$, $—NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl, C_3-C_6cycloalkyl or —C_1-C_6alkoxy;

R^2 is $—(CR^{3a}R^{3b})_m$-(3- to 10-membered cycloalkyl); $—(CR^{3a}R^{3b})_m$-(3- to 10-membered heterocycloalkyl) having one to three heteroatoms; $—(CR^{3a}R^{3b})_m$-(5- to 10 membered heteroaryl) having one to three heteroatoms; or $—(CR^{3a}R^{3b})_m—C_6$-C_{12}aryl; wherein said cycloalkyl, heterocycloalkyl, heteroaryl or aryl is optionally substituted with one to five R^4; and wherein, if the heteroatom on said heterocycloalkyl and heteroaryl is N, said N is

optionally substituted with $R^{4'}$; or R^2 is C_1-C_6alkyl, wherein said alkyl is optionally substituted with NH_2, OH or cyano;

R^{3a} and R^{3b} for each occurrence are independently hydrogen or C_1-C_3alkyl;

R^4 for each occurrence is independently a bond, deuterium halogen, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, oxo, $—OR^5$, $—SR^5$, $—S(O)R^9$, $—S(O)_2R^9$, $—NR^{11a}R^{11b}$, $—C(O)R^{10}$, $—(CR^{3a}R^{3b})_n$-(3- to 7-membered cycloalkyl), $—(CR^{3a}R^{3b})_n$-(4- to 10-membered heterocycloalkyl), having one to three heteroatoms,

—$(CR^{3a}R^{3b})_n$-(5- to 10 membered heteroaryl), having one to three heteroatoms, or —$(CR^{3a}R^{3b})_n$—C_6-C_{12}aryl wherein said alkyl, cycloalkyl, heterocycloalkyl, heteroaryl or aryl is each optionally and independently substituted with one to five deuterium, halogen, OR^5, —SR^5, —$NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl, C_3-C_6cycloalkyl or —C_1-C_6alkoxy; or two R^4 taken together with the respective carbons to which each are bonded form a 3- to 6-membered cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl is optionally substituted with one to three halogen, deuterium, —OR^5, —SR^5, —$NR^{11a}R^{11b}$, cyano or C_1-C_6alkyl or C_1-C_6alkoxy, wherein the alkyl or alkoxy is optionally substituted with halogen, deuterium, —OR^5, —SR^5, —$NR^{11a}R^{11b}$, or cyano; and wherein, if a heteroatom on said heterocycloalkyl is N, said N is optionally substituted with $R^{4'}$;

$R^{4'}$ is independently C_1-C_6alkyl, C_2-C_6alkenyl, —$C(O)R^{10}$, —$S(O)_2R^9$, —$(CR^{3a}R^{3b})_n$-(3- to 7-membered cycloalkyl), —$(CR^{3a}R^{3b})_n$-(4- to 10-membered heterocycloalkyl) or $C(O)(CH_2)_tCN$; wherein said alkyl, alkenyl, cycloalkyl, or heterocycloalkyl is each optionally and independently substituted with one to five deuterium, halogen, OH, cyano or C_1-C_6alkoxy; or R^4 and $R^{4'}$ taken together with the respective atoms to which each are bonded form a 3- to 6-membered cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl is optionally substituted with one to three halogen, deuterium, —OR^5, —SR^5, —$NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl or C_1-C_6alkoxy, wherein the alkyl or alkoxy is optionally substituted with halogen, deuterium, —OR^5, —SR^5, —$NR^{11a}R^{11b}$, or cyano;

R^5 is independently hydrogen or C_1-C_6alkyl, wherein said alkyl is optionally substituted with halogen, deuterium, C_1-C_6alkoxy, C_1-C_6alkylthiolyl, —$NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl or C_3-C_6cycloalkyl; or two R^5 taken together with the oxygen atoms to which they are bonded form a 5- or 6-membered heterocycloalkyl;

R^6 is —$C(O)NHR^7$, CO_2R^7 or cyano;

R^7 is hydrogen or C_1-C_6alkyl;

each R^8 is independently hydrogen, halogen, cyano, —OR^5, —SR^5, —$NR^{11a}R^{11b}$, C_6alkyl, C_3-C_6cycloalkyl, 3- to 10-membered heterocycloalkyl or 5- to 6-membered heteroaryl or aryl, wherein said alkyl, cycloalkyl, heterocycloalkyl, heteroaryl or aryl is optionally substituted with one to three halogen, —$NR^{11a}R^{11b}$, OR^5, —SR^5, cyano, C_1-C_3 alkyl, —$C(O)R^{10}$ or oxo;

$R^{8'}$ is hydrogen, deuterium, halogen, cyano, —OR^5, —SR^5 or $NR^{11a}R^{11b}$;

R^9 is —$(CR^{3a}R^{3b})_p$—(C_1-C_3alkyl), —$(CR^{3a}R^{3b})_p$-(4- to 6-membered cycloalkyl), —$(CR^{3a}R^{3b})_p$-(4- to 6-membered heterocycloalkyl) or —$(CR^{3a}R^{3b})_p$—(C_5-C_9aryl), wherein said alkyl, cycloalkyl, heterocycloalkyl or aryl are each optionally substituted with fluoro or C_1-C_3alkyl;

R^{10} is C_1-C_6alkyl, wherein said alkyl is optionally substituted with deuterium, halogen, OH, C_1-C_6alkoxy or cyano;

R^{11a} and R^{11b} are each independently hydrogen or C_1-C_6alkyl, wherein said alkyl is optionally substituted with deuterium, C_1-C_6alkoxy or cyano; and if C_2-C_6alkyl, said alkyl is optionally substituted with deuterium, C_1-C_6alkoxy, cyano, halogen or OH;

m is independently 0, 1, 2 or 3;

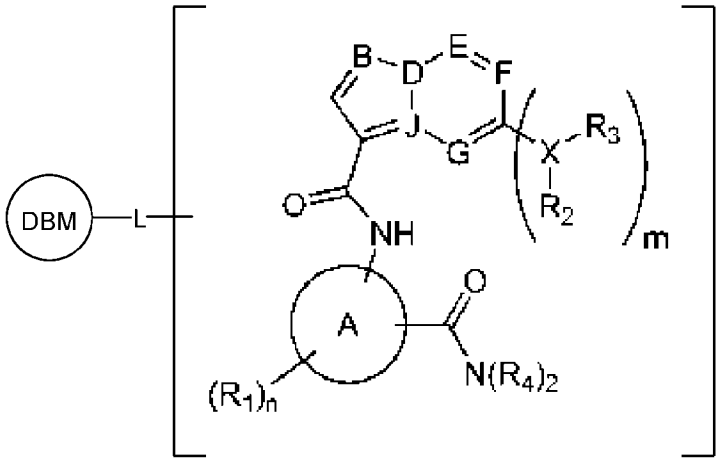
n is independently 0, 1, 2 or 3;

p is independently 0 or 1; and

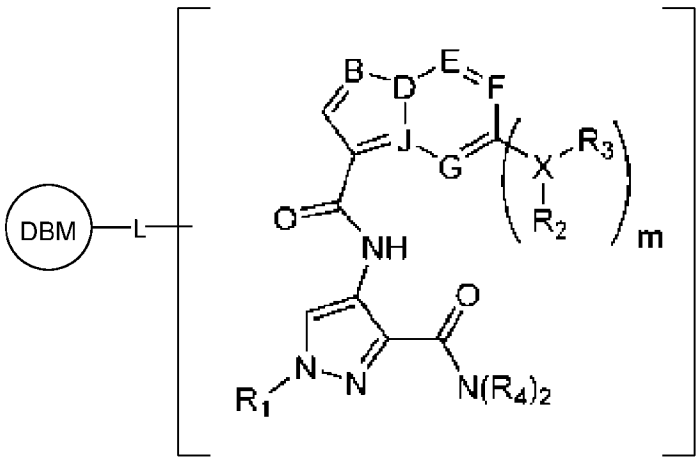
t is 1, 2 or 3;

or each of the variables R^1, R^2, R^6, R^8, X, X', and Y is as defined and described in WO 2015/150995 which is herein incorporated by reference in its entirety.

[00396] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-1** or **I-hh-2**:



I-hh-1



I-hh-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

B is CH, N or S; D is CH or N; E is CH or N; F is CH or N; G is CH or N; and J is C or N, wherein when B is S then D is CH, E is N, F is CH, G is N and J is C;

X is O, S, CH_2 or N;

m is 0 or 1; n is 0, 1 or 2;

Ring A is pyridinyl, pyrazolyl, thiophenyl, furanyl or phenyl;

R_1 is independently selected from $(C_1$-$C_4)$alkyl, pyrimidine, piperidine and phenyl, each optionally substituted with $(C_1$-$C_4)$alkyl, OH, halo, $O(C_1$-$C_4)$alkyl, methylpiperidine, $S(O)_2R_c$, $C(O)N(R_b)_2$, or $C(O)O(C_1$-$C_4)$alkyl;

R_2 is absent or H and R_3 is independently selected from: $(C_1$-$C_4)$alkyl, pyranyl, cyclopentyl, cyclohexyl, cycloheptyl, thiopyranyl, pyrazolyl, piperidinyl, morpholinyl, piperazinyl each optionally substituted with one or more substituents independently selected from halo, OH, oxo, $N(R_b)_2$, oxopyrrolidinyl, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form piperazine or morpholine, each optionally substituted with oxo;

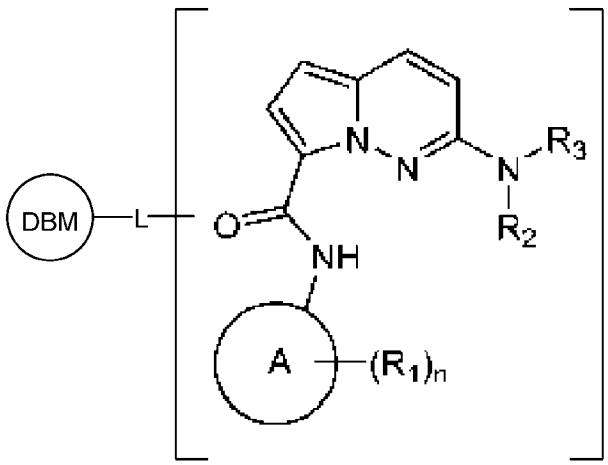
R_4 is independently H or methyl;

R_b is independently selected from H and $(C_1$-$C_4)$alkyl; and

R_c is methyl;

or each of the variables A, B, D, E, F, G, J, X, R_1, R_2, R_3, R_4, m, and n is as defined and described in WO 2016/144844 which is herein incorporated by reference in its entirety.

[00397] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-3**:



I-hh-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is aryl or heterocyclyl;

n is 0, 1, 2, 3 or 4;

R_1 is independently selected from: $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

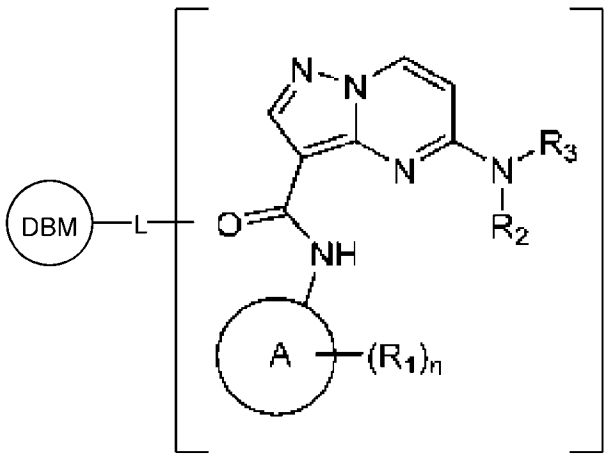
R_2 is H and R_3 is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with $(C_3\text{-}C_6)$cycloalkyl and CF_3; and

R_b is independently selected from H and $(C_1\text{-}C_4)$alkyl;

or each of the variables A, R_1, R_2, R_3 and n is as defined and described in WO 2016/144847 which is herein incorporated by reference in its entirety.

[00398] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-4**:



I-hh-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is aryl or heterocyclyl;

n is 0, 1, 2, 3 or 4;

R_1 is independently selected from: $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN and halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

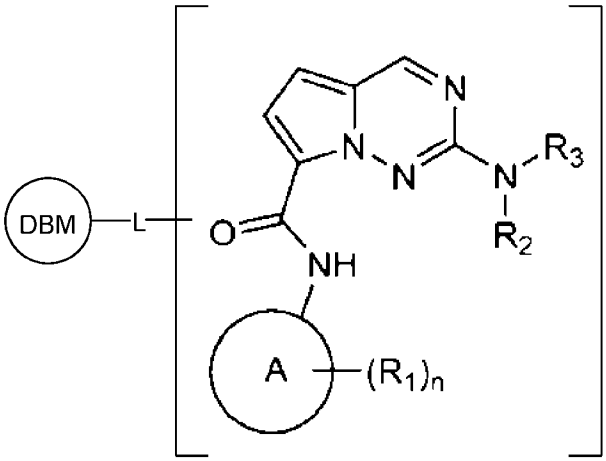
R_2 is H and R_3 is independently selected from: $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with $(C_3$-$C_6)$cycloalkyl or CF_3; and

R_b is independently selected from H and $(C_1$-$C_4)$alkyl;

or each of the variables A, R_1, R_2, R_3 and n is as defined and described in WO 2016/144846 which is herein incorporated by reference in its entirety.

[00399] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-5**:



I-hh-5

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is aryl or heterocyclyl;

n is 0, 1, 2, 3 or 4;

R_1 is independently selected from: $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

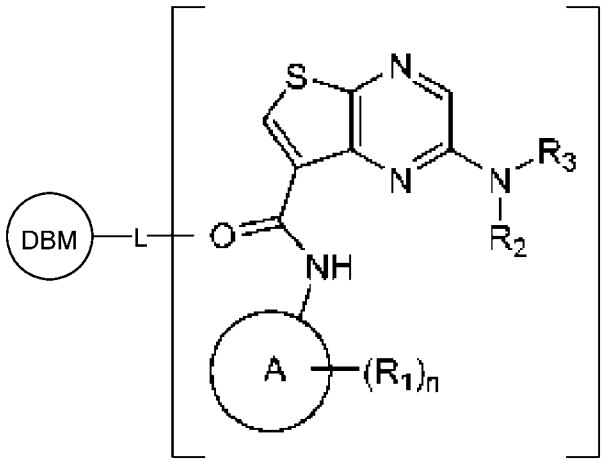
R_2 is H and R_3 is independently selected from: $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with $(C_3$-$C_6)$cycloalkyl and CF_3; and

R_b is independently selected from H and (C_1-C_4)alkyl;

or each of the variables A, R_1, R_2, R_3 and n is as defined and described in WO 2016/144848 which is herein incorporated by reference in its entirety.

[00400] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-6**:



I-hh-6

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is aryl or heterocyclyl;

n is 0, 1, 2, 3 or 4;

R_1 is independently selected from: (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

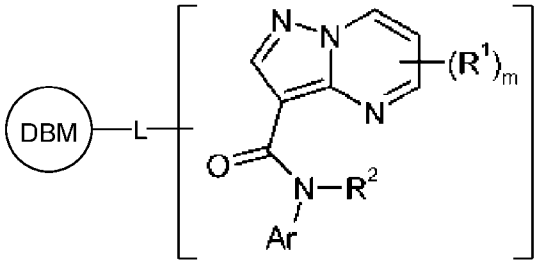
R_2 is H and R_3 is independently selected from: (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with (C_3-C_6)cycloalkyl and CF_3; and

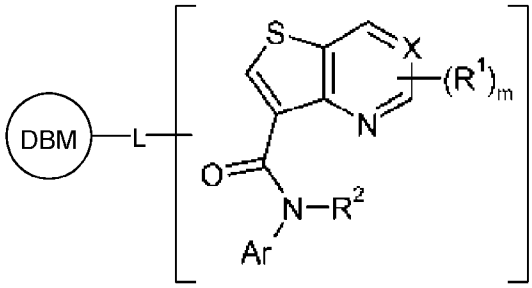
R_b is independently selected from H and (C_1-C_4)alkyl;

or each of the variables A, R_1, R_2, R_3 and n is as defined and described in WO 2016/144849 which is herein incorporated by reference in its entirety.

[00401] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-7** or **I-hh-8**:



I-hh-7



I-hh-8

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is N or CH

m is 1 or 2;

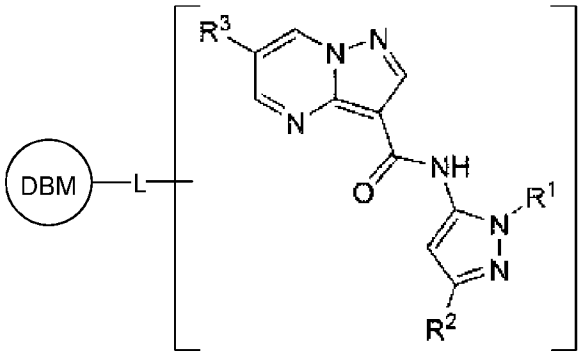
Ar is optionally substituted aryl or optionally substituted heteroaryl;

R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyl, hydroxy-C_{1-6}alkyl, C_{1-6}alkyl-amino, amino-C_{1-6}alkyl, amino-C_{1-6}alkyl-amino, hydroxy-C_{1-6}alkylamino, C_{3-6}cycloalkylamino, amino-C_{3-6}cycloalkylamino, amino-C_{3-6}heterocycloalkylamino, aminocarbonyl, halo, hydroxy-C_{1-6}alkyl, or hydroxy-C_{1-6}alkoxy; and

R^2 is hydrogen or C_{1-6}alkyl;

or each of the variables R^1, R^2, m, and X is as defined and described in WO 2012/007375 which is herein incorporated by reference in its entirety.

[00402] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hh-9**



I-hh-9

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

R^1 is aryl, heteroaryl, heterocyclyl or (C_{1-6} alkyl)R^6, wherein said aryl, heteroaryl, and heterocyclyl groups are optionally substituted with one or two substituents selected from the group consisting of halo, cyano, R^4, C_{3-8} cycloalkyl, C_{1-3} aminoalkyl, C_{1-3}hydroxyalkyl, OR^4, NR^4R^5, NR^4COR^6, $NR^4SO_2R^6$, $SO_2NR^4R^5$, $CONR^4R^5$and $CONR^4R^5$;

R^2 is aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl or (C_{1-6} alkyl)R^6, wherein said aryl, heteroaryl, cycloalkyl and heterocyclyl groups are optionally substituted with one or two substituents selected from the group consisting of halo, cyano, oxo, hydroxyl, imino, hydroxyimino, R^4, OR^4, O(C_{3-8} cycloalkyl), (C=O)OR^4, SO_mR^6, SO_mR^4, NR^4R^5, $SO_2NR^4R^5$ and $NR^4SO_2R^6$;

R^3 is halo, cyano, oxo, hydroxyl, imino, hydroxyimino, R^4, OR^4, C_{3-8}cycloalkyl, SO_mR^6, $SO_mR^4NR^4R^5$ or (C=O)NR^4R^5, $NR^4(CO)R^6$, $SO_mNR^4R^5$ and $NR^4SO_2R^6$;

R^4 is hydrogen or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to three halo or hydroxyl;

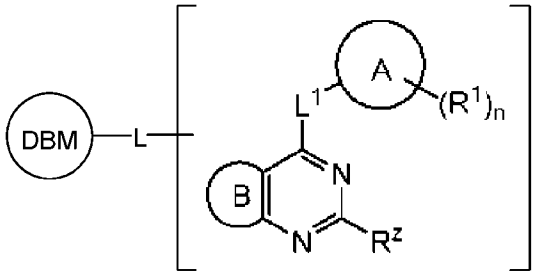
R^5 is hydrogen or C_{1-6} alkyl, wherein said alkyl is optionally substituted with halo or hydroxyl;

R^6 is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl;

m is an integer from zero to two;

or each of the variables R^1, R^2, and R^3 is as defined and described in WO 2012/129258 which is herein incorporated by reference in its entirety.

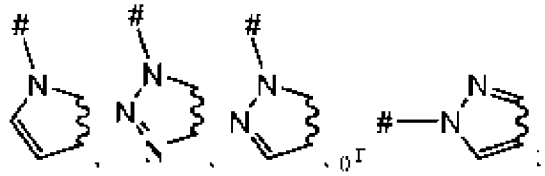
[00403] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-1**:



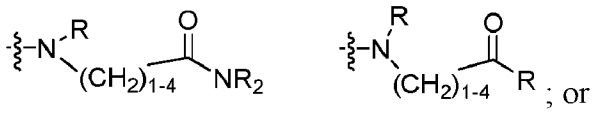
I-ii-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is  ;

wherein ~~~ represents the portion of the ring fused to the pyrimidine ring and # is $-L^2(R^4)_P-R^X$; each R^1 and $R^{1'}$ is independently $-R^2$, halogen, -CN, $-NO_2$, -OR, -SR, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, -C(O)N(R)OR, -N(R)C(O)OR, $-N(R)C(O)N(R)_2$, Cy, or $-N(R)S(O)_2R$; or $R^1$is selected from one of the following formulae:



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently an optionally substituted group selected from Ci-6aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^4 is independently halogen, -CN, $-NO_2$, -OR, -SR, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, - N(R)C(O)R,

$-N(R)C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)S(O)_2N(R)_2$, $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^x is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$;

[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms indepently selected from nitrogen, oxygen, and sulfur, wherein [Ar] is substituted by m instances of R^1;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -N(R)-, -N(R)C(O)-, - C(O)N(R)-, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or $-S(O)_2-$;

L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -N(R)-, -N(R)C(O)-, - C(O)N(R)-, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or $-S(O)_2-$;

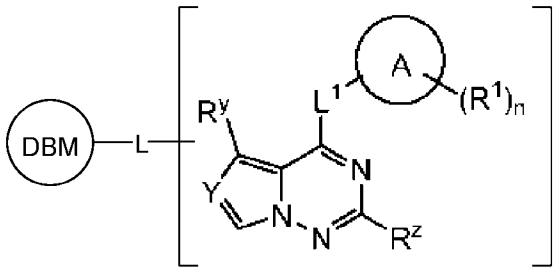
m is 0-4;

n is 0-4; and

p is 0-2;

or each of the variables A, B, L^1, R^1, R^z, and n is as defined and described in WO 2017/004133 which is herein incorporated by reference in its entirety.

[00404] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-2**:



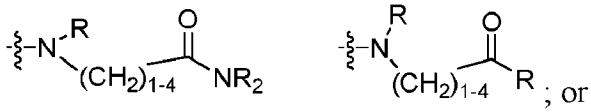
I-ii-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Y is N or C-R^x;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 and R^y is independently -R^2, halogen, -CN, -NO_2, -OR, -SR, -$N(R)_2$, -$S(O)_2R$, -$S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)N(R)_2$, -C(O)N(R)OR, -N(R)C(O)OR, -$N(R)C(O)N(R)_2$, Cy, or -$N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from Ci-6 aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or: two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently an optionally substituted group selected from Ci-$_6$aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^x and R^y is independently hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, - H[Ar], -OR, or $-S(O)_2N(R)_2$; or

R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$;

[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said [Ar] is substituted by m instances of R^r;

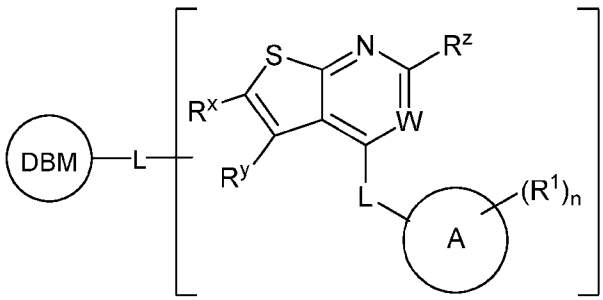
L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -N(R)-, -N(R)C(O)-, - C(O)N(R)-, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or $-S(O)_2-$;

m is 0-4; and

n is 0-4;

or each of the variables A, L^1, R^1, R^y, R^z, Y, and n is as defined and described in WO 2017/004134 which is herein incorporated by reference in its entirety.

[00405] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-3**



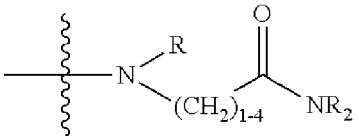
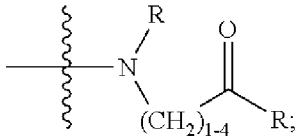
I-ii-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 0-4;

each R^1 is independently —R, halogen, —CN, —NO_2, —OR, —CH_2OR, —SR, —$N(R)_2$, —SO_2R, —$SO_2N(R)_2$, —SOR, —C(O)R, —CO_1R, —$C(O)N(R)_2$, —C(O)N(R)—OR, —NRC(O)R, —$NRC(O)N(R)_2$, Cy, or —$NRSO_2R$; or R^1 is selected from one of the following formulas:

or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, aryl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

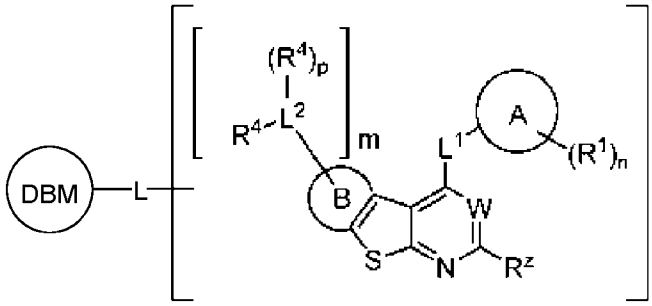
R^z is —R, —CN, —NO_2, halogen, —$C(O)N(R)_2$, —C(O)OR, —C(O)R, —$N(R)_2$, —OR, or —$SO^2N(R)_2$;

Ring B is an unsubstituted 4-8 membered partially unsaturated carbocyclic fused ring; and

L is a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —NR—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)SO_2$—, —$SO_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

or each of the variables R^x, R^y, R^z, R^1, n, L, A, and W is as defined and described in WO 2012/097013 which is herein incorporated by reference in its entirety.

[00406] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-4**



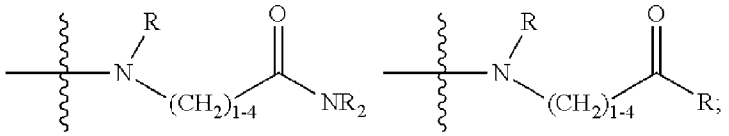
I-ii-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 0-4;

each R^1 is independently —R, halogen, —CN, —NO_2, —OR, —CH_2OR, —SR, —$N(R)_2$, —SO_2R, —$SO_2N(R)_2$, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —C(O)N(R)—OR, —NRC(O)OR, —$NRC(O)N(R)_2$, Cy, or —$NRSO_2R$; or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

Ring B is a cyclopento or cyclohexo fused ring;

m is 1-2;

p is 0-2;

W is N;

R^z is R, CN, NO_2, halogen, —C(O)N(R)$_2$, —C(O)OR, —C(O)R, —N(R)C(O)OR, —NRC(O)N(R)$_2$, —OR, or —SO_2N(R)$_2$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, —SO_2N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

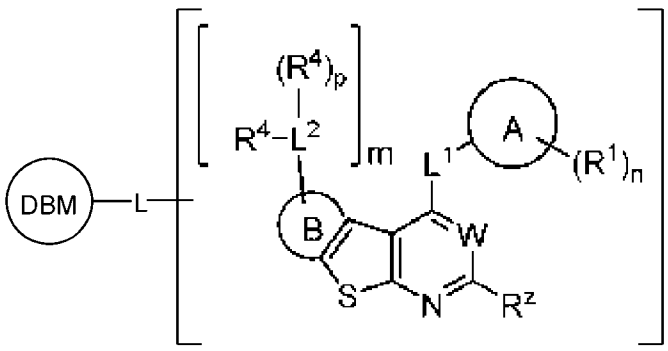
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, —SO_2N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —N(R)$_2$, —SO_2R, —SO_2N(R)$_2$, —SOR, —C(O)R, —CO_2R, —C(O)N(R)$_2$, —NRC(O)R, —NRC(O)N(R)$_2$, —C(O)N(R)OR, —N(R)C(O)OR, —N(R)S(O)$_2$N(R)$_2$, —NRSO_2R, or an optionally substituted group selected from C_{1-6}aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two -L^2(R^4)$_p$—R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or each of the variables R^1, R^4, R^z, L^1, L^2, m, n, p, W, A, and B is as defined and described in WO 2013/106535 which is herein incorporated by reference in its entirety.

[00407] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-5**



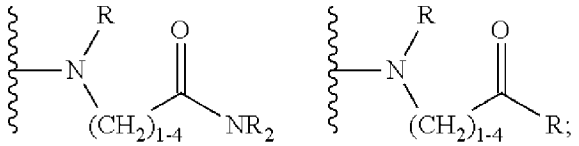
I-ii-5

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0-4;

each R^1 is independently —R, halogen, —CN, —NO_2, —OR, —CH_2OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —C(O)N(R)—OR, —N(R)C(O)R, —N(R)C(O)OR, —$N(R)C(O)N(R)_2$, Cy, or —$N(R)S(O)_2R$, or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a benzo fused ring and a 5-6 membered heteroaromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said Ring B may be optionally substituted by one or more oxo, thiono, or imino groups;

m is 0-4;

p is 0-2;

W is N or —$C(R^3)$—;

R^z is R, CN, NO_2, halogen, —C(O)N(R)$_2$, —C(O)OR, —C(O)R, —N(R)$_2$, —N(R)C(O)OR, —N(R)C(O)N(R)$_2$, —OR, or —S(O)$_2$N(R)$_2$;

R^3 is hydrogen, halogen, —CN, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N(R)$_2$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)S(O)$_2$—, —S(O)$_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —S(O)$_2$—;

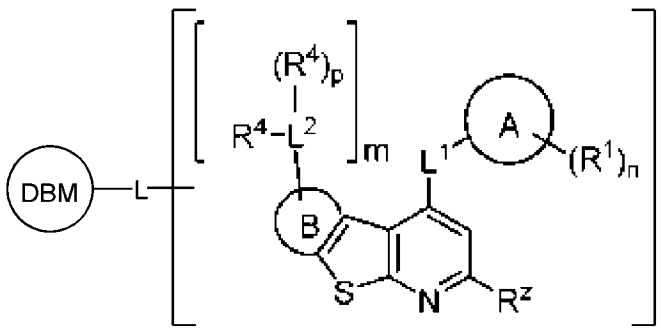
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)S(O)$_2$—, —S(O)$_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —S(O)$_2$—; and

each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —N(R)$_2$, —S(O)$_2$R, —S(O)$_2$N(R)$_2$, —S(O)R, —C(O)R, —CO_2R, —C(O)N(R)$_2$, —N(R)C(O)R, —N(R)C(O)N(R)$_2$, —C(O)N(R)OR, —N(R)C(O)OR, —N(R)S(O)$_2$N(R)$_2$, —N(R)S(O)$_2$R, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two -L^2(R^4)$_p$—R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

or each of the variables R^1, R^4, R^z, L^1, L^2, m, n, p, W, A, and B is as defined and described in WO 2014/011902 which is herein incorporated by reference in its entirety.

[00408] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-6**



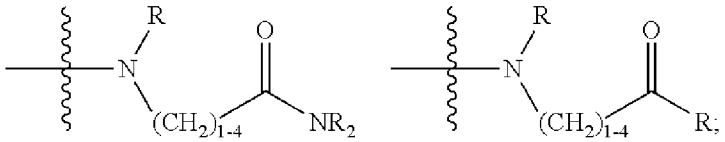
I-ii-7

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0-4;

each R^1 is independently —R, halogen, —CN, —NO_2, —OR, —CH_2OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)N(R)_2$, —C(O)N(R)—OR, —N(R)C(O)R, —N(R)C(O)OR, —$N(R)C(O)N(R)_2$, Cy, or —$N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 4-8 membered partially unsaturated carbocyclic fused ring and a 4-7 membered partially unsaturated heterocyclic fused ring having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur; wherein said Ring B may be optionally substituted by one or more oxo, thiono, or imino groups;

m is 0-4;

p is 0-2;

R^z is —R, —CN, —NO_2, halogen, —$C(O)N(R)_2$, —C(O)OR, —C(O)R, —$N(R)_2$, —N(R)C(O)OR, —$N(R)C(O)N(R)_2$, —OR, or —$S(O)_2N(R)_2$;

R^3 is hydrogen, halogen, —CN, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N(R)$_2$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)S(O)$_2$—, —S(O)$_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —S(O)$_2$—;

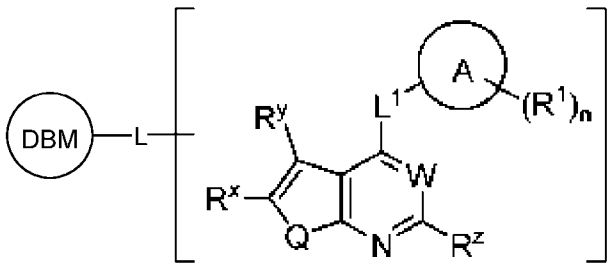
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)S(O)$_2$—, —S(O)$_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —S(O)$_2$—; and

each R^4 is independently halogen, —CN, —NO$_2$, —OR, —SR, —N(R)$_2$, —S(O)$_2$R, —S(O)$_2$N(R)$_2$, —S(O)R, —C(O)R, —C(O)OR, —C(O)N(R)$_2$, —N(R)C(O)R, —N(R)C(O)N(R)$_2$, —C(O)N(R)OR, —N(R)C(O)OR, —N(R)S(O)$_2$N(R)$_2$, —N(R)S(O)$_2$R, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two -L^2(R^4)$_p$—R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

or each of the variables R^1, R^4, R^z, L^1, L^2, m, n, p, A, and B is as defined and described in WO 2014/011906 which is herein incorporated by reference in its entirety.

[00409] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-8**



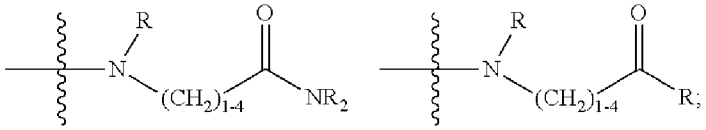
I-ii-8

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0-4;

each R^1 is independently —R, halogen, —CN, —NO_2, —OR, —CH_2OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)N(R)_2$, —C(O)N(R)—OR, —N(R)C(O)R, —N(R)C(O)OR, —$N(R)C(O)N(R)_2$, Cy, or —$N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

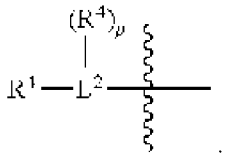
each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each of R^x and R^y is independently —R, halogen, —CN, —NO_2, —OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)N(R)_2$, —N(R)C(O)R, —$N(R)C(O)N(R)_2$, or —$N(R)S(O)_2R$, or:

R^x and R^y are taken together with their intervening atoms to form Ring B substituted with m occurrences of



;

Ring B is selected from a benzo fused ring, a 4-8 membered partially unsaturated carbocyclic fused ring, a 4-8 membered partially unsaturated heterocyclic fused ring having one or two heteroatoms

independently selected from nitrogen oxygen and sulfur, and a 5-6 membered heteroaromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said Ring B may be optionally substituted by one or more oxo, thiono, or imino groups;

m is 0-4;

p is 0-2;

Q is —O— or —N(R)—

W is N or —C(R^3)—;

R^z is —R, —CN, —NO_2, halogen, —C(O)N($R)_2$, —C(O)OR, —C(O)R, —N($R)_2$, —N(R)C(O)OR, —N(R)C(O)N($R)_2$, —OR, or —$S(O)_2$N($R)_2$;

R^3 is hydrogen, halogen, —CN, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N($R)_2$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)$S(O)_2$—, —$S(O)_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

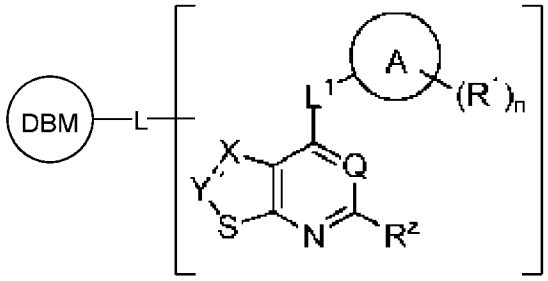
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)$S(O)_2$—, —$S(O)_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—; and

each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —N($R)_2$, —$S(O)_2$R, —$S(O)_2$N($R)_2$, —S(O)R, —C(O)R, —C(O)OR, —C(O)N($R)_2$, —N(R)C(O)R, —N(R)C(O)N($R)_2$, —C(O)N(R)OR, —N(R)C(O)OR, —N(R)$S(O)_2$N($R)_2$, —N(R)$S(O)_2$R, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two -L^2($R^4)_p$—R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

or each of the variables R^x, R^y, R^z, A, W, R^1, n, Q, and A is as defined and described in WO 2014/011911 which is herein incorporated by reference in its entirety.

[00410] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ii-9**



I-ii-9

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

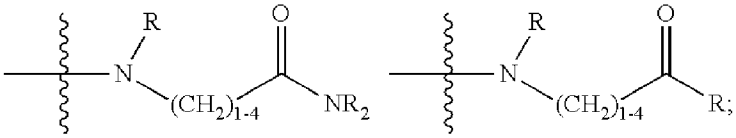
Q is CH, C—CN, or N;

X is C-$L^2(R^4)_p$—R^x and Y is N; or

X is N and Y is C—Rx;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 and $R^{1'}$ is independently —R^2, halogen, —CN, —NO_2, —OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)N(R)_2$, —C(O)N(R)OR, —N(R)C(O)OR, —$N(R)C(O)N(R)_2$, Cy, or —$N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)N(R)_2$, —$N(R)C(O)R$, —$N(R)C(O)N(R)_2$, —$C(O)N(R)OR$, —$N(R)C(O)OR$, —$N(R)S(O)_2N(R)_2$, —$N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^x is hydrogen, —R^2, —CN, —NO_2, halogen, —$C(O)N(R)_2$, —C(O)OR, —C(O)R, —$N(R)_2$, —NH[Ar], —OR, or —$S(O)_2N(R)_2$;

R^z is hydrogen, —R^2, —CN, —NO_2, halogen, —$C(O)N(R)_2$, —C(O)OR, —C(O)R, —$N(R)_2$, —NH[Ar], —OR, or —$S(O)_2N(R)_2$;

[Ar] is a phenyl or heteroaromatic ring substituted by m instances of $R^{1'}$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

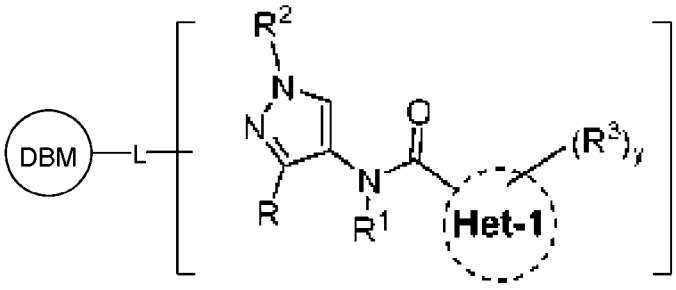
m is 0-4;

n is 0-4; and

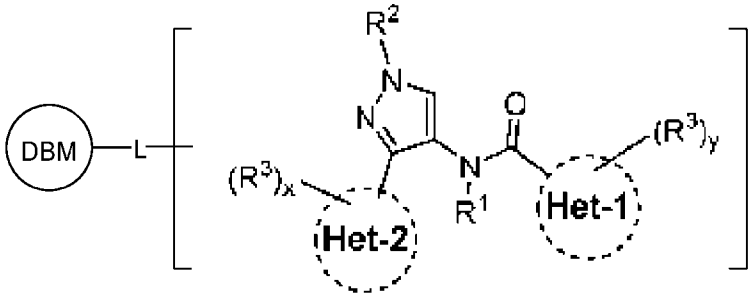
p is 0-2;

or each of the variables X, Y, L^1, A, R^1, n, and R^z is as defined and described in WO 2015/048281 which is herein incorporated by reference in its entirety.

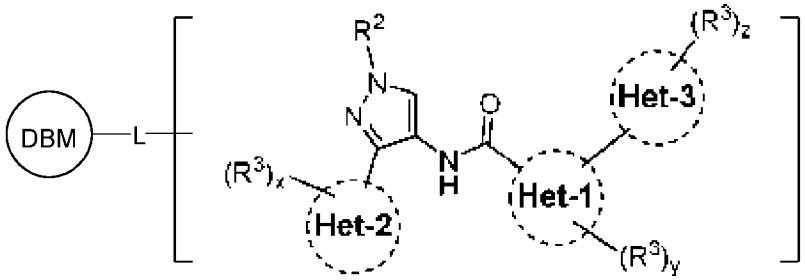
[00411] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-jj-1**, **I-jj-2**, or **I-jj-3**:



I-jj-1



I-jj-2



I-jj-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

R is aliphatic, heteroaliphatic, heteroaryl, aryl, halo, amide or CN;

R^1 is H, aliphatic or heteroaliphatic;

or R and R^1, together with the atoms to which they are attached, form a heterocyclyl ring;

R^2 is H, aliphatic, heteroaliphatic, heterocycloaliphatic, aryl, amide, heterocyclyl or araliphatic;

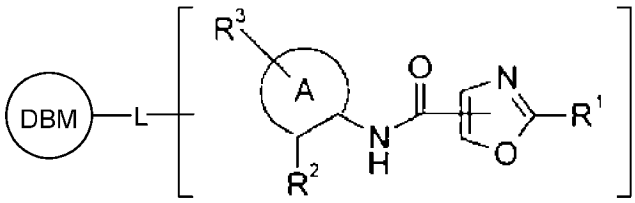
each R^3 independently is H, aliphatic, halogen, heteroaliphatic, —O-aliphatic, heterocyclyl, aryl, araliphatic, —O-heterocyclyl, hydroxyl, nitro, cyano, carboxyl, carboxyl ester, acyl, amide, amino, sulfonyl, sulfonamide, sulfanyl, sulfinyl, haloalkyl, alkylphosphate, or alkylphosphonate;

y is from 1 to 6;

or each of the variables R, R^1, R^2, R^3, Het-1, Het-2, Het-3, x, y, and z is as defined and described in WO

2016/172560 which is herein incorporated by reference in its entirety.

[00412] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-jj-4**:



I-jj-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is a monocyclic heteroaryl;

R^1 is one to three optionally substituted with R^{10} monocyclic or bicyclic heteroaryl;

R^2 is, $-C(O)NH_2$, $-C(O)NH-R^0$, $-C(O)NH-R^{00}-OH$, $-C(O)NH-R^{00}-OR^0$, $-C(O)N(R^0)_2$, -C(O)NH- cycloalkyl, -C(O)NH-heterocycloalkyl, -C(O)NH-(pyrazolyl optionally substituted with R^0), $-C(O)-R^0$, -C(O)-cycloalkyl, $-S(O)_2NH_2$, $-S(O)_2NH-R^0$, -S(O)2NH-cycloalkyl, $-R^{00}-OH$, $-R^{00}-OR^0$, $-R^{00}-($ morpholin-4-yl) phenyl, oxadiazolyl, or tetrazolyl optionally substituted with R^0, wherein oxadiazolyl in R^2 is, R^0, R^{00}-OH or may be substituted with R^0-OR^0;

R^3 is, H, R^0, halogeno-lower alkyl, cycloalkyl, heterocycloalkyl, phenyl, pyridyl, pyrimidinyl, pyrazinyl, $-C(O)N(R^0)_2$, $-R^{00}$-cycloalkyl, $-R^{00}$-heterocycloalkyl, $-R^{00}$-phenyl, $-R^{00}$-OH or a $-R^{00}-OR^0$, wherein the cycloalkyl in R^3, heterocycloalkyl, phenyl and pyridyl, R^0, halogen, $-C(O)OR^0$, $-C(O)-R^0$, -OH, $-OR^0$, $-S(O)_2-R^0$, -O-halogeno-lower alkyl, $-OR^{00}-$(morpholin-4-yl), $-R^{00}-OH$, $-R^{00}-OR^0$, morpholin-4-yl or, $-R^{00}-$(morpholin-4-yl) may be substituted;

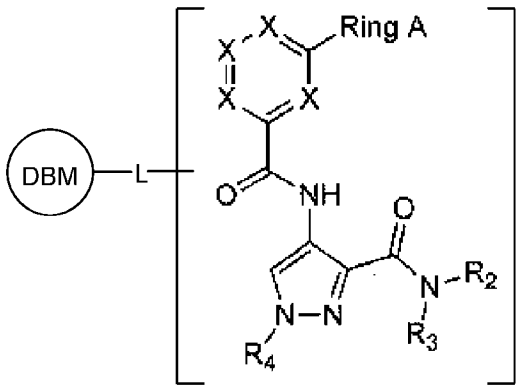
R^{10} may be the same or different from each other, R^0, halogen, halogeno-lower alkyl, cycloalkyl, $-OR^0$, optionally substituted amino, -O-halogeno-lower alkyl, $-R^{00}-OH$, $-R^{00}-OR^0$ or, $-R^{00}-$ is optionally amino substituted,

R^0 is the same or different from each other, lower alkyl,

R^{00} are identical or different from each other, it is a lower alkylene;

or each of the variables R^1, R^2, R^3, and A is as defined and described in WO 2011/043371 which is herein incorporated by reference in its entirety.

[00413] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-jj-5**:



I-jj-5

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is CH or N;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;

Ring A is (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkenyl, aryl or heterocycle optionally substituted with one to three substituents independently selected from R_1;

R_1 is selected from: H, oxo, $(C{=}O)_aO_b(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkenyl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkynyl, CO_2H, halo, OH, $O_b(C_1$-$C_6)$fluoroalkyl, $(C{=}O)_aNR_5R_6$, CN, $(C{=}O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_mNR_5R_6$, SH, $S(O)_m$—$(C_1$-$C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;

R_2 and R_3 are independently selected from: H, $(C{=}O)_aO_bC_1$-C_{10} alkyl, $(C{=}O)_aO_b$aryl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $(C{=}O)_aO_b$ heterocyclyl, CO_2H, CN, O_bC_1-C_6 fluoroalkyl, $O_a(C{=}O)_bNR_5R_6$, CHO, $(N{=}O)R_5R_6$, $S(O)_mNR_5R_6$, SH, $S(O)_m$—$(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_bC_3$-C_8 cycloalkyl, optionally substituted with one or more substituents selected from R_1; or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R_1;

R_4 is selected from: $(C_1$-$C_6)$alkyl and $(C_3$-$C_6)$cycloalkyl, optionally substituted with R_a;

R_5 and R_6 are independently selected from: H, oxo, $(C{=}O)_aO_b(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkenyl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkynyl, CO_2H, $O_b(C_1$-$C_6)$fluoroalkyl, $(C{=}O)_aN(R_a)_2$, CN, $(C{=}O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_m N(R_a)_2$, SH, $S(O)_m$—$(C_1$-$C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl,

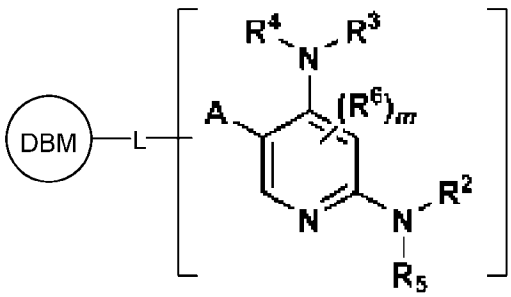
said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from R_b, OH, $(C_1$-$C_6)$alkoxy, halogen, cyclopropyl, CO_2H, CN, $O_a(C{=}O)_b(C_1$-$C_6)$alkyl, oxo, and $N(R_b)_2$; and

R_b is independently selected from H and $(C_1$-$C_6)$alkyl;

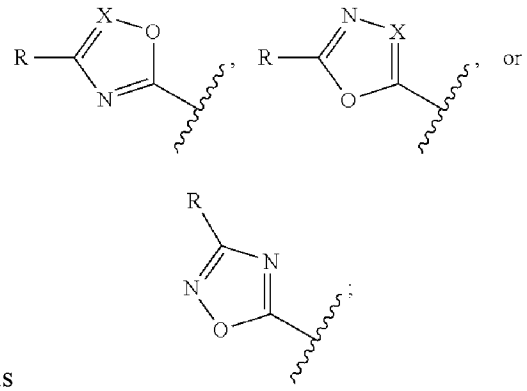
or each of the variables R_2, R_3, R_4, X, and Ring A is as defined and described in WO 2014/058691 which is herein incorporated by reference in its entirety.

[00414] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-1**:



I-kk-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:



A is

X is N or C—R^7;

R is hydrogen, R^1, halogen, cyano, nitro, —OR^1, —C(=O)—R^1, —C(=O)O—R^1, —C(=O)NR^{11}—R^1, —$S(=O)_2$—R^1, —$NR^{11}C(=O)$—R^1, —$NR^{11}C(=O)NR^{11}R^{11}$, —$NR^{11}C(=O)O$—$R^1$, —$NR^{11}S(=O)_2R^1$ or —$NR^{11}R^{11}$;

R^1 is $C_{1\text{-}6}$ alkyl substituted with 0-4 R^{1a}, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^{1a}, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^{1a}, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^{1a}, $C_{6\text{-}10}$ aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted

with 0-3 R^{1a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)R^c$, $—S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $—(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^2 is C_{6-10} aryl substituted with 0-4 R^{2a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 1-4 R^{2a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a};

R^{2a} at each occurrence is independently selected from hydrogen, =O, halo, OCF_3, CN, NO_2, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)R^c$, $—S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $—(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $—(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

R^3 is C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{3a}, C_{2-6} alkynyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}, C_{6-10} aryl substituted with 0-3 R^{3a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a} or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a};

R^{3a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)R^c$, $—S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6}haloalkyl, $—(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $—(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^4 and R^5 are independently selected from hydrogen, C_{1-4} alkyl substituted with 0-1 R^f, (CH_2)-phenyl substituted with 0-3 R^d, and a $—(CH_2)$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

R^6 and R^7 are independently at each occurrence is selected from hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)_2R^c$, $—S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6}haloalkyl, $—(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a, provided R^6 and $R^7$are not both hydrogen;

R^{11} at each occurrence is independently hydrogen, R^e, C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl substituted with 0-3 R^d, or $—(CH_2)$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^d; or

R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an optionally substituted heterocycle;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)R^c$, $—S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $—(CH_2)_r$-3-14 membered carbocycle, or $—(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; or two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $—O—(CH_2)_n—O—$, or $—O—CF_2—O—$, wherein n is selected from 1 or 2;

R^b is hydrogen, R^e, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6}haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $—OR^e$, $—(CH_2)_rC(O)R^c$, $—NR^eR^e$, $—NR^eC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^e is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^f is hydrogen, halo, NH_2, OH, or $O(C_{1-6}$alkyl);

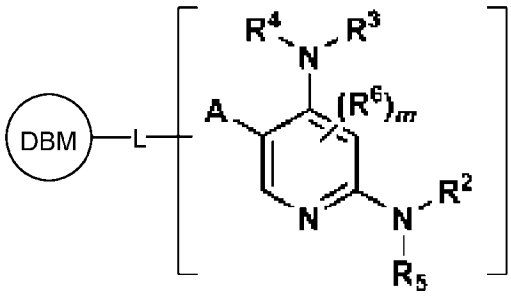
p is 0, 1, or 2;

r is 0, 1, 2, 3, or 4; and

m is 0, 1, or 2;

or each of the variables R^2, R^3, R^4, R_5, R^6, A, and *m* is as defined and described in WO 2013/106612 and WO 2013/106614 which is herein incorporated by reference in its entirety.

[00415] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-2**:



I-kk-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

A is a triazole optionally substituted by 0-2 R;

X is N or C—R^7;

R is hydrogen, R′, halogen, cyano, nitro, —OR^1, —C(=O)—R^1, —C(=O)O—R^1, —C(=O)NR^{11}—R^1, —$S(=O)_2$—R^1, —$NR^{11}C(=O)$—R′, —$NR^{11}C(=O)NR^{11}R^1$, —$NR^{11}C(=O)O$—R′, —$NR^{11}S(=O)_2R^1$ or —$NR^{11}R^1$;

R^1 is C_{1-6} alkyl substituted with 0-4 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10}cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —S(C)$R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^2 is C_{6-10} aryl substituted with 0-4 R^{2a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 1-4 R^{2a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a};

R^{2a} at each occurrence is independently selected from hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —

$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —$S(O)R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, 0, and $S(O)_p$ substituted with 0-2 R^a;

R^3 is C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{3a}, C_{2-6} alkynyl substituted with 0-3 R^{3a}, C_{3-10}cycloalkyl substituted with 0-3 R^{3a}, C_{6-10} aryl substituted with 0-3 R^{3a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 $R^{3'}$ or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a};

R^{3a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —$S(O)R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6}haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^4 and R^5 are independently selected from hydrogen, C_{1-4} alkyl substituted with 0-1 R^f, (CH_2)-phenyl substituted with 0-3 R^d, and a —(CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

R^6 and R^7 are independently at each occurrence is selected from hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —$S(O)R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6}haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a, provided R^6 and R^7 are not both hydrogen;

R^{11} at each occurrence is independently hydrogen, R^c, C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl substituted with 0-3 R^d, or —(CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^d; or

R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an optionally substituted heterocycle;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)R^c$, $—S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $—(CH_2)_r$-3-14 membered carbocycle, or $—(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; or two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $—O—(CH_2)_n—O—$, or $—O—CF_2—O—$, wherein n is selected from 1 or 2;

R^b is hydrogen, R^e, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $—OR^e$, $—(CH_2)_rC(O)R^c$, $—NR^eR^e$, $—NR^eC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^e is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^f is hydrogen, halo, NH_2, OH, or $O(C_{1-6}$alkyl);

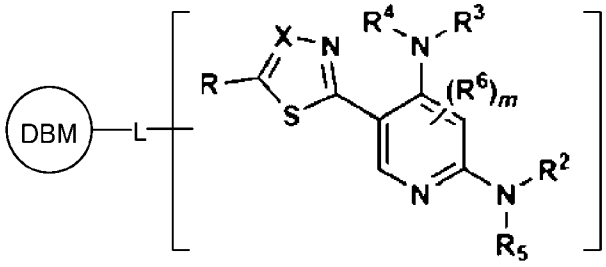
p is 0, 1, or 2;

r is 0, 1, 2, 3, or 4; and

m is 0, 1, or 2;

or each of the variables R^2, R^3, R^4, R_5, R^6, A, and *m* is as defined and described in WO 2013/106614 which is herein incorporated by reference in its entirety.

[00416] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-4**:



I-kk-4

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is N or $C—R^7$;

R is R^1, halogen, cyano, nitro, —O—R^1, —C(=O)—R^1, —C(=O)O—R^1, —C(=O)NR^{11}—R^1, —S(=O)$_2$—R^1, —NR^{11}C(=O)—R^1, —NR^{11}C(=O)NR^{11}—R^1, —NR^{11}C(=O)O—R^1, —NR^{11}S(=O)$_2$—R^1, or —NR^{11}—R^1;

R^1 is C_{1-6} alkyl substituted with 0-4 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10}cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —S(O)$R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$substituted with 0-3 R^a;

R^2 is C_{6-10} aryl substituted with 0-4 R^{2a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a};

R^{2a} at each occurrence is independently selected from hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —S(O)$R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

R^3 is C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{3a}, C_{2-6} alkynyl substituted with 0-3 R^{3a}, C_{3-10}cycloalkyl substituted with 0-3 R^{3a}, C_{6-10} aryl substituted with 0-3 R^{3a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a};

R^{3a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —S(O)$R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each

comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^4 and R^5 are independently selected from hydrogen, C_{1-4} alkyl substituted with 0-1 R^f, (CH_2)-phenyl substituted with 0-3 R^d, and a —(CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

R^6 and R^7 are independently at each occurrence is selected from hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —$S(O)R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a, provided R^6 and R^7 are not both hydrogen;

R^{11} at each occurrence is independently R^e, C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl substituted with 0-3 R^d, or —(CH_2)-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^d;

alternatively, R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an optionally substituted azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or 4-(C_{1-6} alkyl)piperazinyl;

R^a is R^d, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —$S(O)_2R^c$, —$S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, —$(CH_2)_r$-3-14 membered carbocycle, or —$(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; alternatively two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula —O—$(CH_2)_n$—O—, or —O—CF_2—O—, wherein n is selected from 1 or 2;

R^b is R^c, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6}cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CH_2)_rC(O)R^c$, —NR^eR^e, —$NR^eC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^e is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^f is hydrogen, halo, NH_2, OH, or O(C_{1-6}alkyl);

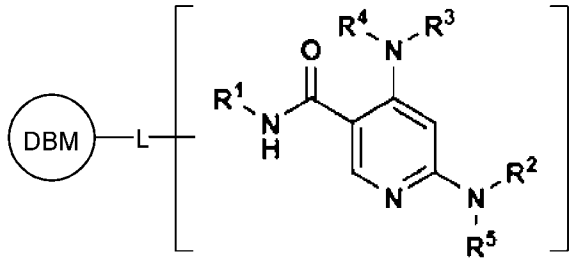
p is 0, 1, or 2;

r is 0, 1, 2, 3, or 4; and

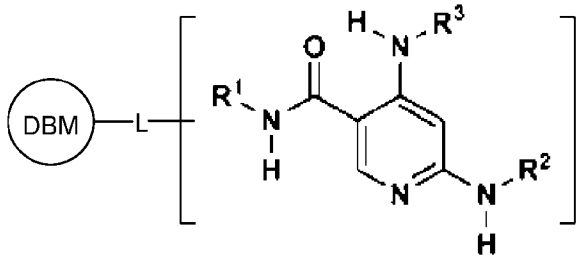
m is 0, 1, or 2;

or each of the variables R, R^2, R^3, R^4, R_5, R^6, X, and *m* is as defined and described in WO 2013/106641 which is herein incorporated by reference in its entirety.

[00417] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-5** or **I-kk-6**:



I-kk-5



I-kk-6

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

R^1 is:

(a) $C_{2\text{-}3}$ hydroxyalkyl substituted with zero to 4 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CN, —CF_3, —OCH_3, and cyclopropyl;

(b) $C_{1\text{-}3}$ alkyl substituted with —O($C_{1\text{-}3}$ alkyl) and zero to 4 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CN, —CF_3, and cyclopropyl;

(c) $C_{4\text{-}8}$ alkyl substituted with zero to 7 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CF_3, —CN—OCH_3, cyclopropyl, and —OP(O)$(OH)_2$;

(d) —$(CH_2)_{2\text{-}4}$NHC(O)($C_{1\text{-}6}$ alkyl), —$(CH_2)_2$CH(CH_3)NHC(O)($C_{1\text{-}6}$alkyl), —$(CH_2)_2$CH(CH_3)NHC(O)$(CH_2)_{0\text{-}1}$NH($C_{1\text{-}6}$ alkyl), or —$(CH_2)_2$CH(CH_3)NHC(O)$(CH_2)_{0\text{-}1}$N($C_{1\text{-}4}$ alkyl)$_2$;

(e) cyclohexyl substituted with zero to 2 substituents independently selected from —OH, —OCH_3, C_{1-6} alkyl, C_{1-6}hydroxyalkyl, —$C(O)NH_2$, —$C(O)NH(C_{1-3}$ alkyl), —$C(O)NH(C_{1-6}$hydroxyalkyl), —$C(O)NH(C_{3-6}$ cycloalkyl), —$C(O)NH(C_{3-6}$ fluoro cycloalkyl), —$NHC(O)(C_{1-3}$ alkyl), —$NHC(O)O(C_{1-3}$ alkyl), —$NHS(O)_2CH_3$, —$S(O)_2NH_2$, —$S(O)_2(C_{1-3}$ alkyl), —$S(C_{1-3}$ alkyl), thiazolyl, methyl pyrazolyl, and C_{1-3} alkyl substituted with —OH and cyclopropyl;

(f) —$(CH_2)_2$(phenyl) wherein said phenyl is substituted with —$C(O)NH_2$, —$C(O)NH(C_{1-3}$ alkyl), or —$S(O)_2NH_2$; or

(g) piperidinyl substituted with —$C(O)(C_{1-3}$ alkyl);

R^2 is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazolyl, thiazolyl, or triazolyl, each substituted with zero to 2 substituents independently selected from F, Cl, —OH, —CN, C_{1-3} alkyl, —$CH_2C(O)OCH_3$, —$O(C_{1-3}$alkyl), —NH_2, —$NH(C_{1-3}$ alkyl), —NH(cyclopropyl), —$C(O)NH_2$, —$NHC(O)(C_{1-3}$ alkyl), —NH(tetrahydropyranyl), hydroxypyrrolidinyl, =O, —O(piperidinyl), and pyridinyl; and

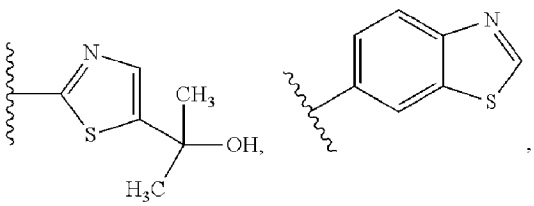
R^3 is:

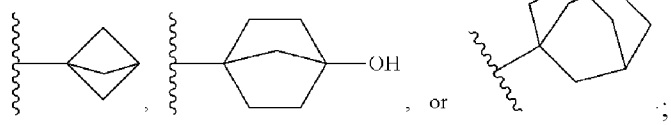
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, —OH, —CH_3, —CF_3, and C_{3-6}cycloalkyl;

(b) C_{3-6} cycloalkyl substituted with zero to 2 substituents independently selected from F, —OH, C_{1-3} hydroxyalkyl, —CH_3, —CF_2H, —NH_2, and —$C(O)OCH_2CH_3$;

(c) oxetanyl, tetrahydropyranyl, or fluoro tetrahydropyranyl;

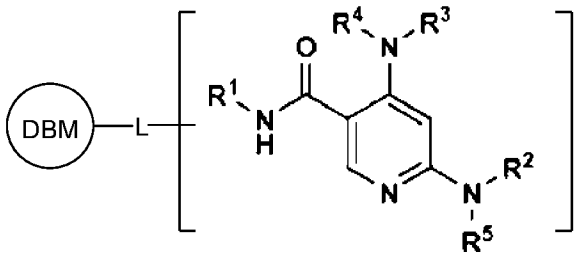
(d) phenyl substituted with zero to 2 substituents independently selected from —OH, —CN, —$O(C_{1-3}$ alkyl), C_{1-3} hydroxyalkyl, —$C(O)NH_2$, —$S(O)_2NH_2$, —$NHS(O)_2(C_{1-3}$ alkyl), pyrazolyl, imidazolyl, and methyl tetrazolyl; or



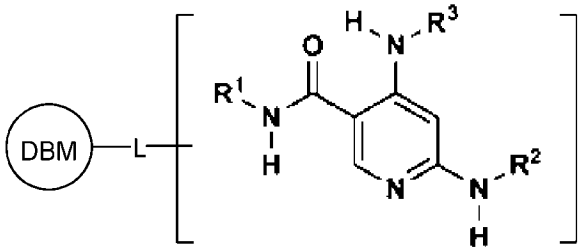
(e) 

or each of the variables R^1, R^2, R^3, R^4, and R^5 is as defined and described in WO 2014/075657 which is herein incorporated by reference in its entirety.

[00418] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-7** or **I-kk-8**:



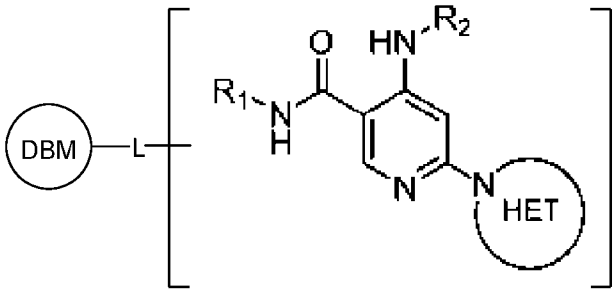
I-kk-7



I-kk-8

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein each of the variables R^1, R^2, R^3, R^4, and R^5 is as defined and described in WO 2014/075675 which is herein incorporated by reference in its entirety.

[00419] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-9**:



I-kk-9

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

HET is a heteroaryl selected from pyrazolyl, indolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-b]pyridinyl, pyrazolo[3,4-d]pyrimidinyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, imidazo[4,5-b]pyridinyl, and purinyl, wherein said heteroaryl is substituted with R_a and R_b;

R_a is H, F, Cl, Br, —CN, —OH, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4}hydroxyalkyl, C_{1-4} alkoxy, —NH_2, —$NH(C_{1-4}$ alkyl), —$N(C_{1-4}$ alkyl)$_2$, —$NH(C_{1-4}$ hydroxyalkyl), —$NH(C_{1-4}$ fluoroalkyl), —$NH(C_{1-6}$ hydroxy-fluoroalkyl), —$C(O)NH_2$, —$CH_2NHC(O)(C_{1-6}$ alkyl), —$CH_2NHC(O)(C_{1-6}$hydroxyalkyl), —$CH_2NHC(O)NH(C_{1-6}$ alkyl), —$CH_2NHC(O)NHCH_2$(phenyl), —$CH_2NHC(O)N(C_{1-4}$ alkyl)$_2$, —$CH_2NHC(O)O(C_{1-4}$ alkyl), —$CH_2NHC(O)(C_{3-6}$ cycloalkyl), —$CH_2NHC(O)$(tetrahydrofuranyl), —$CH_2NHC(O)CH_2(C_{3-6}$ cycloalkyl), —$CH_2NHC(O)CH_2$(tetrahydropyranyl), —$CH_2NHC(O)CH_2$(phenyl), —$NHC(O)(C_{1-4}$ alkyl), pyrrolidinyl, hydroxypyrrolidinyl, or pyridazinyl;

R_b is H or —NH_2;

R_1 is:

(i) C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-8} hydroxy-fluoroalkyl, —(C_{1-6} alkylenyl)O(C_{1-4} alkyl), —(C_{1-6} alkylenyl)O(C_{1-4}fluoroalkyl), —(C_{1-6} fluoroalkylenyl)O(C_{1-4} alkyl), —(C_{1-6}fluoroalkylenyl)O(C_{1-4} deuteroalkyl), —(C_{1-6} fluoroalkylenyl)O(C_{1-4}fluoroalkyl), —(C_{1-4} fluoroalkylenyl)C(C_{3-6} cycloalkyl)$_2$(OH), —(C_{1-4}alkylenyl)NHC(O)(C_{1-4} alkylenyl)OC(O)(C_{1-3} alkyl), —(C_{1-6}alkylenyl)NHS(O)$_2$(C_{1-4} alkyl), —(C_{1-6} alkylenyl)P(O)(C_{1-4} alkoxy)$_2$, —(C_{1-6} fluoroalkylenyl)NH(C_{1-4} alkyl), —(C_{1-6} alkylenyl)C(O)NH(C_{1-4} alkyl), —(C_{1-6} fluoroalkylenyl)C(O)NH(C_{1-4} alkyl), —(C_{1-6}fluoroalkylenyl)C(O)NH(C_{1-4} hydroxyalkyl), or —(C_{1-6}fluoroalkylenyl)OP(O)(OH)$_2$;

(ii) —(C_{1-3} alkylenyl)R_x, —(C_{1-3} fluoroalkylenyl)R_x, —(C_{1-3}alkylenyl)C(O)R_x, —(C_{1-3} alkylenyl)C(O)NHR_x, —(C_{1-3}fluoroalkylenyl)C(O)R_x, or —CH_2CF=(tetrahydropyranyl), wherein R_x is a cyclic group selected from C_{3-6} cycloalkyl, tetrazolyl, 1,1-dioxidotetrahydrothiophenyl, 1,1-dioxidothiomorpholinyl, oxadiazolyl, piperidinyl, piperazinyl, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, imidazolyl, morpholinyl, phenyl, and triazinyl, wherein each cyclic group is substituted with zero to 3 substituents independently selected from F, —OH, —CH_3, —$C(CH_2)_2$OH, —OCH_3, —C(O)CH_2CN, —$S(O)_2CH_3$, —$S(O)_2NH_2$, —NHC(O)CH_3, —$N(S(O)_2CH_3)_2$, —CH_2CH_2(acetamidophenyl), —CH_2CH_2(methoxyphenyl), —CH_2CH_2(sulfamoylphenyl), oxetanyl, benzyl, and morpholinyl;

(iii) C_{3-6} cycloalkyl or C_{4-6} cycloalkenyl, each substituted with zero to 3 substituents independently selected from F, —OH, —CN, C_{1-3}alkyl, C_{1-3} alkoxy, —$S(C_{1-3}$ alkyl), —NO_2, —$S(O)_2(C_{1-3}$ alkyl), C_{1-4}hydroxyalkyl, —$C(C_{1-3}$ alkyl)(OH)(C_{3-6} cycloalkyl), —CH_2C(O)NH(C_{1-3} alkyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)(C_{1-4}hydroxyalkyl), —C(O)NH(C_{1-3} alkyl), —C(O)NH(C_{1-3} deuteroalkyl), —C(O)NH(C_{3-6} cycloalkyl), —

$NHC(O)O(C_{1-3}$ alkyl), —$NHS(O)_2(C_{1-3}$alkyl), pyridinyl, imidazolyl, pyrazolyl, methylimidazolyl, methylpyrazolyl, and thiazolyl;

(iv) tetrahydropyranyl, piperidinyl, pyrazolyl, phenyl, pyridinyl, or pyrimidinyl, each substituted with zero to 1 substituent selected from —OH, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, C_{1-3}alkoxy, —$C(O)(C_{1-4}$ alkyl), —$S(O)_2(C_{1-4}$ alkyl), —$S(O)_2NH(C_{1-4}$ alkyl), —$NH(C_{1-3}$ alkyl), —$N(C_{1-3}$ alkyl)$_2$, —$O(C_{1-3}$ alkylenyl)$N(C_{1-3}$ alkyl)$_2$, —CH_2(morpholinyl), azetidinyl, oxetanyl, tetrahydropyranyl, morpholinyl, piperazinyl, piperidinyl, methylpiperazinyl, methoxypiperidinyl, pyridinyl, pyrimidinyl, methylsulfonyl azetidinyl, and —C(O)(methylsulfonyl azetidinyl); or

(v) pyrrolo[2,3-c]pyridinyl, bicyclo[2.2.1]heptan-1-ol, tetrahydrobenzo[d]thiazol-2-amine, or 1,3-diazaspiro[4.5]decane-2,4-dione; and

R_2 is:

(i) C_{1-7} alkyl or C_{2-6} alkenyl, each substituted with zero to three substituents independently selected from F, —OH, and —CN; —$(C_{1-4}$ alkylenyl)$O(C_{1-4}$ alkyl), —$(C_{1-4}$ alkylenyl)$O(C_{1-4}$ fluoroalkyl), —$(C_{1-6}$ alkylenyl)NH_2, —$(C_{1-6}$ alkylenyl)$S(O)_2(C_{1-3}$ alkyl), —$(C_{1-6}$fluoroalkylenyl)$NH(C_{1-3}$ alkyl), or —$(C_{1-6}$ alkylenyl)$NHC(O)(C_{1-4}$fluoroalkyl);

(ii) —$(C_{1-4}$ alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, oxazolyl, pyridinyl, tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

(iii) C_{3-6} cycloalkyl, azetidinyl, oxetanyl, furanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl, each substituted with zero to 3 substituents independently selected from F, —OH, C_{1-3}alkyl, C_{1-3} hydroxyalkyl, —$C(O)(C_{1-3}$ alkyl), —$C(O)(C_{1-3}$ fluoroalkyl), —$C(O)(C_{1-3}$ cyanoalkyl), —$C(O)O(C_{1-3}$ alkyl), —$C(O)NH_2$, —$C(O)NH(C_{1-3}$ alkyl), —C(O)(difluorophenyl), —NH_2, —$NH(C_{1-3}$ alkyl), —$NH(C_{1-3}$ fluoroalkyl), —NH(oxetanyl), —$NHC(O)(C_{1-3}$ alkyl), —$NHC(O)(C_{1-3}$ fluoroalkyl), —$NHC(O)(C_{3-6}$ cycloalkyl), —NHC(O)(fluorophenyl), —$S(O)_2(C_{1-3}$ alkyl), imidazolyl, phenyl, pyrimidinyl, fluoropyrimidinyl, chloropyrimidinyl, and methoxypyrimidinyl;

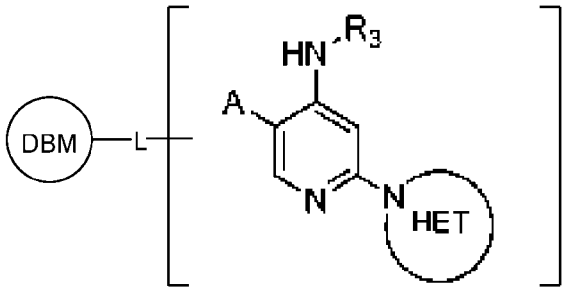
(iv) adamantanyl, hydroxyadamantanyl, benzo[d]imidazolyl, benzo[d]oxazolyl, benzo[d]triazolyl, benzothiazolyl, bicyclo[1.1.1]pentanyl, or hydroxy-bicyclo[2.2.1]heptanyl; or

(v) phenyl, pyrazolyl, thiazolyl, thiadiazolyl, or indazolyl, each substituted with 0 to 2 substituents independently selected from F, Cl, —OH, —CN, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} fluoroalkyl, C_{1-4}cyanoalkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, —$(C_{1-3}$ alkylenyl)$O(C_{1-3}$alkyl), —$(C_{1-3}$ alkylenyl)$O(C_{1-3}$ fluoroalkyl), —$C(O)NH_2$, —$C(O)NH(C_{1-3}$ alkyl), —

$NHC(O)(C_{1-3}$ alkyl), —$NHC(O)S(O)_2(C_{1-3}$alkyl), —$S(O)_2NH_2$, —$S(O)_2(C_{1-3}$ alkyl), pyrazolyl, methyl pyrazolyl, imidazolyl, triazolyl, methyl tetrazolyl, ethyl tetrazolyl, phenyl, pyrimidinyl, fluoropyrimidinyl, and tetrahydropyranyl;

or each of the variables R_1, R_2, and HET is as defined and described in WO 2015/103453 which is herein incorporated by reference in its entirety.

[00420] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kk-10**:



I-kk-10

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

HET is a heteroaryl selected from pyrrolo[2,3-b]pyridinyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-b]pyridinyl, pyrazolo[3,4-d]pyrimidinyl, imidazolo[4,5-b]pyridinyl, and imidazolo[4,5-d]pyrimidinyl, wherein said heteroaryl is attached to the pyridinyl group in the compound of Formula (I) by a nitrogen ring atom in said heteroaryl and wherein said heteroaryl is substituted with zero to 2 R_b;

A is pyrazolyl, imidazolyl, triazolyl, isoxazolyl, oxadiazolyl or dihydroisoxazolyl, each substituted with R_a;

R_3 is C_{2-3} alkyl, C_{2-3} fluoroalkyl, C_{3-4} hydroxyalkyl, or a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and pyrazolyl, wherein said cyclic group is substituted with zero to 2 substituents independently selected from F, —OH, C_{1-2} alkyl, and —CH_2CHF_2;

R_a is:

(i) H, F, C_1, —OH, —CN, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-4} cyanoalkyl, C_{1-6} hydroxyalkyl, C_{1-5} hydroxy-fluoroalkyl, C_{2-4} alkenyl, C_{1-6}aminoalkyl, —$(CH_2)_{1-3}NHR_y$, —$(CH_2)_{1-3}NR_yR_y$, —$CH_2CH(OH)$(phenyl), —$CH(CH_2OH)$(phenyl), —$CH_2CH(OH)CH_2$(phenyl), —$CH_2CH(OH)CH_2O$(methoxyphenyl), —$CH_2CH(NH_2)CH_2$(phenyl), —$(CH_2CH_2O)_4H$, —$(CH_2)_{1-3}O(C_{1-3}$ alkyl), —$CH_2CH(OH)CH_2O(C_{1-3}$alkyl), —$CH_2C(O)(C_{1-3}$ alkyl), —$CH_2C(O)NR_yR_y$, —$(CH_2)_{1-3}NR_yC(O)(C_{1-3}$ alkyl), —$CH_2C(O)O(C_{1-3}$ alkyl), —$C(O)NH_2$, —$CH_2NR_yC(O)NH_2$, —

$(CH_2)_{1-2}NR_yC(O)O(C_{1-2}$ alkyl), —$(CR_yR_y)_{1-5}OC(O)CH_2NR_yR_y$, —$CH_2CH_2S(O)_2CH_3$, —$CH_2S(O)_2(C_{1-3}$ alkyl), —$CH_2S(O)_2$(phenyl), or —NH(aminocyclohexyl); or

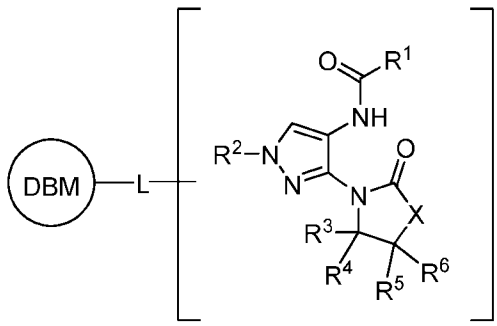
(ii) —$(CH_2)_{0-3}R_z$ or —$(CH_2)_{0-1}C(O)R_z$, wherein R_z is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperazinyl, pyrrolyl, pyrrolidinonyl, morpholinyl, pyrrolidinyl, phenyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, dioxopyrimidinyl, benzo[d]imidazolyl, benzo[d]thiazolyl, 1,3-dioxolanyl, or 8-azabicyclo[3.2.1]octanyl, each substituted with zero to 4 substituents independently from F, —CN, —OH, —NR_yR_y, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-3} hydroxyalkyl, —CH(phenyl)$_2$, —$O(C_{1-4}$ alkyl), —$C(O)(C_{1-4}$ alkyl), —$C(O)(C_{1-4}$ deuteroalkyl), —$C(O)(C_{1-5}$ hydroxyalkyl), —$C(O)(C_{1-3}$ fluoroalkyl), —$C(O)(C_{3-6}$cycloalkyl), —$C(O)O(C_{1-3}$ alkyl), —$C(O)NR_yR_y$, —C(O)(phenyl), —C(O)(pyridinyl), —$C(O)CH_2(C_{3-6}$ cycloalkyl), —$C(O)O(C_{1-4}$ alkyl), —$NH(C_{1-4}$ alkyl), —$NH(C_{1-3}$ fluoroalkyl), —$NHC(O)CH_3$, —$NHC(O)O(C_{1-3}$ alkyl), —$NHC(O)OC(CH_3)_3$, —$S(O)_2(C_{1-3}$ alkyl), —$OS(O)_2(C_{1-3}$ alkyl), methyl oxadiazolyl, and pyrimidinyl;

each R_b is independently selected from H, Cl, —CN, —NH_2, and —$C(O)NH_2$, wherein said heteroaryl is attached to the pyridinyl group by a nitrogen atom in said heteroaryl; and

each R_y is independently H or C_{1-2} alkyl;

or each of the variables R_3, A, and HET is as defined and described in WO 2016/210034 which is herein incorporated by reference in its entirety.

[00421] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-II-1**:



I-II-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

R^1 is an optionally substituted aromatic heterocyclic group or an optionally substituted C_{6-14} aryl group;

R^2 is a hydrogen atom or a substituent;

R^3 and R^4 are independently a hydrogen atom or a substituent, or $R^3$and R^4 in combination optionally form an optionally substituted ring;

R^5 and R^6 are independently a hydrogen atom or a substituent, or R^5 and R^6 in combination optionally form an optionally substituted ring;

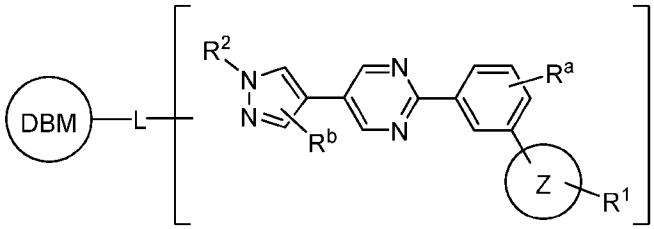
X is CR^7R^8, NR^9, O or S;

R^7 and R^8 are independently a hydrogen atom or a substituent, or R^7 and R^8 in combination optionally form an optionally substituted ring; and

R^9 is a hydrogen atom or a substituent;

or each of the variables R^1, R^2, R^3, R^4, R^5, R^6, and X is as defined and described in WO 2015/068856 which is herein incorporated by reference in its entirety.

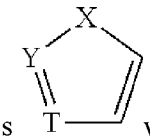
[00422] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-mm-1**:



I-mm-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

R^1 denotes absent, A or Q-Het,

Z is  wherein:

X denotes O, S or N,

Y denotes C or N,

T denotes C or N, or

Z denotes a pyridine or a pyridazine group,

R^a is absent, OR^3, CF_3, Hal, or NO_2,

R^b is absent, A, or COHet,

R^2 denotes H, Het, Q-Het, Cyc, A or OA,

each Het is independently a 4-9 membered monocyclic ring or a fused, spiro or bridged bicyclic ring, which is saturated, unsaturated, or aromatic, which contains 1 to 3 heteroatoms independently selected from N, O, and S, and a group CO, SO or SO_2, and wherein 1 or 2 H atoms may be replaced by A, OA, COA, CN, Hal, NO_2, OR^3, SOA and/or SO_2A,

Cyc denotes a 4-8 saturated carbocyclic ring optionally containing a group SO, SO_2, or CO, and optionally substituted once or twice by a group selected from $CO(NR^3)_2$, COHet, OR^3, Het^1, A, CH_2Het^1, NH_2, NHCOA, OCH_2Cyc^1, SO_2A and —SA(=NH)(=O),

each Q is independently a linear or branched alkylene, having 1 to 6 carbon atoms wherein 1-5 H atoms may be replaced by a group independently selected from OR^3, Hal, and $N(R^3)_2$, and wherein 1 or 2 CH_2 groups may be replaced by a group independently selected from CO, SO, SO_2 and NR^3, or Q denotes a 4-8-membered bivalent heterocyclic ring, which is saturated, unsaturated or aromatic and which contains 1 to 3 heteroatoms independently selected from N, O and S,

each A is independently a linear or branched alkyl having 1 to 10 carbon atoms wherein 1 to 7 H atoms may be replaced by a group independently selected from —OR^3, Hal, $NHSO_2A$, SO_2A, SOA, and $N(R^3)_2$, and wherein 1, 2 or 3 non-adjacent —CH_2— groups may be replaced by a group independently selected from —CO—, NR^3 and —O—,

each Hal is independently F, Cl, Br or I,

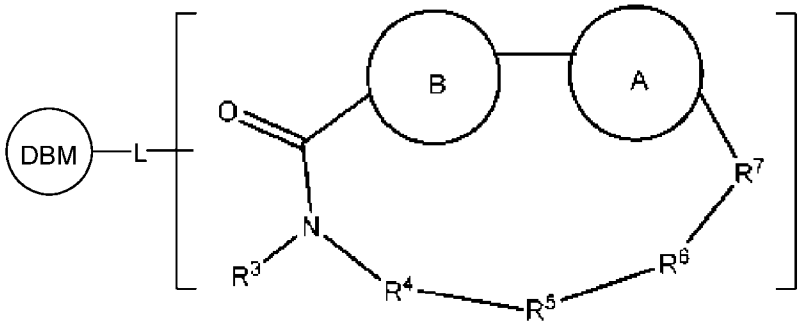
each R^3 is independently H or C_1-C_6-alkyl wherein 1 H atom may be replaced by a group selected from OH, O—C_1-C_6-alkyl, and Hal,

each Het^1 is independently a five- or six membered saturated monocyclic heterocycle which contains 1-3 N- and/or O-atoms, which optionally is monosubstituted by A,

Cyc^1 denotes cycloalkyl with 3-7 atoms;

or each of the variables R^1, R^2, R^a, R^b, and Z is as defined and described in WO 2014/008992 which is herein incorporated by reference in its entirety.

[00423] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-nn-1**:



I-nn-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Ring A is phenylene or 5- to 6-membered heteroarylene containing 1-3 heteroatoms chosen from O, S, and N, wherein ring A is optionally substituted with lower alkyl that is further optionally substituted,

Ring B is phenylene, 5- to 6-membered heterocycloalkylene containing 1-3 heteroatoms chosen from O, S, and N, or 5- to 6-membered heteroarylene containing 1-3 heteroatoms chosen from O, S, and N, wherein ring B is optionally substituted with lower alkyl that is further optionally substituted,

R^3 is chosen from hydrogen, lower alkyl optionally substituted with alkoxy, amino, N-(alkyl)amino, N,N-(dialkyl)amino, or phenyl, heterocycloalkyl, and heteroaryl,

wherein phenyl, heterocycloalkyl, and heteroaryl are optionally substituted with one or two groups independently chosen from lower alkyl and wherein alkoxy is optionally substituted with tri(alkyl)silyl,

R^4 is chosen from heteroarylene and arylene, each of which is optionally substituted, or R^4 and R^3 taken together with the nitrogen to which they are bound, form an optionally substituted 3- to 7-membered heterocycloalkyl ring, or R^4 is an alkylene chain having 1-3 carbon atoms that is optionally substituted with one or two groups independently chosen from lower alkyl and cycloalkyl, each of which groups is optionally substituted with hydroxyl or alkoxy, or R^4 is absent,

R^5 is chosen from $C(O)NR^{51}$, NR^{52}, and O or R^5 is absent, provided that if R^4 is absent, then R^5 is absent,

R^6 is an alkylene or alkenylene chain having one or two double bonds,

wherein the alkylene or alkenylene chain has 2 to 10 carbon atoms,

wherein the alkylene or alkenylene chain is optionally substituted with one or two groups independently chosen from lower alkyl and cycloalkyl, each of which groups is optionally substituted with hydroxyl or alkoxy, and

further wherein one or two of the carbon atoms in the alkylene chain is optionally replaced by an O, S, SO, SO_2, or NR^{61}, and

wherein two of the carbon atoms in the alkylene chain, are optionally connected by a two or three carbon atom alkylene chain to form a 5- to 7-membered ring.

R^7 is chosen from NR^{71} and O or R^7 is absent,

R^{51} is chosen from hydrogen and lower alkyl,

R^{52} is chosen from hydrogen, lower alkyl, and —$C(O)OR^{81}$,

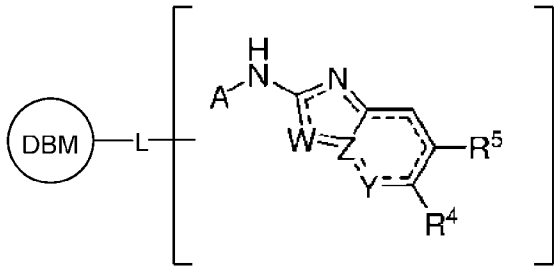
R^{61} is chosen from hydrogen, lower alkyl, and —$C(O)OR^{81}$,

R^{71} is chosen from hydrogen, lower alkyl, and —$C(O)OR^{81}$, and

R^{81} is lower alkyl;

or each of the variables R^3, R^4, R^5, R^6, R^7, A and B is as defined and described in WO 2014/143672 which is herein incorporated by reference in its entirety.

[00424] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-oo-1**:



I-oo-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

=== is a single or double bond;

W is selected from CH, CH—CH, O, S, NR^6, and CO;

Y is N or CR^9;

Z is N or C, and Z is N if W is CH and Y is CR^9;

R^4 is selected from hydrogen, halogen, OR^6, CN, NR^7R^8, CH_2OR^6, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, an optionally substituted carbocycle, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6heteroalkyl, an optionally substituted C_1-C_6 alkenyl, an optionally substituted C_1-C_6 alkynyl, CO_2R^6, SO_3R^6, SO_2R^6 and $SO_2NR^7R^8$;

R^5 is selected from hydrogen, halogen, OR^6, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_1-C_6haloheteroalkyl, an optionally substituted C_1-C_6 alkenyl, and an optionally substituted C_1-C_6 alkynyl;

or R^4 and R^5 are linked to form an optionally substituted non-aromatic ring;

each R^6 is independently selected from an optionally substituted aryl, an optionally substituted heteroaryl, and an optionally substituted non-aromatic ring, each optionally fused with a substituted aryl or a substituted heteroaryl, hydrogen, an optionally substituted C_1-C_{10}alkyl, an optionally substituted C_1-C_{10} haloalkyl, and an optionally substituted C_1-C_{10} heteroalkyl;

each R^7 and R^8 is independently selected from an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, each optionally fused with a substituted aryl or a substituted heteroaryl, hydrogen, an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_1-C_{10} haloalkyl, an optionally substituted C_1-C_{10} alkenyl, an optionally substituted C_1-

C_{10} alkynyl, and an optionally substituted C_1-C_{10} heteroalkyl, or R^7 and R^8 are linked to form an optionally substituted non-aromatic ring;

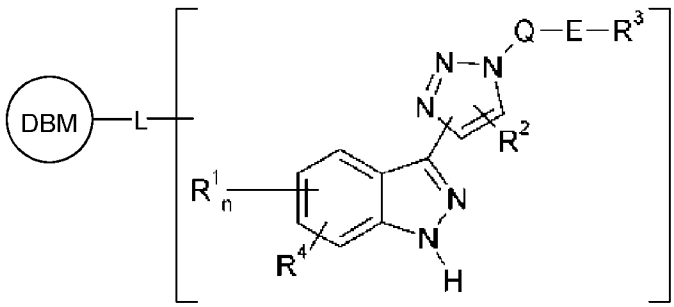
R^9 is selected from hydrogen, halogen, OR^6, CN, NR^7R^8, CH_2OR^6, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_1-C_6 alkenyl, an optionally substituted C_1-C_6 alkynyl, CO_2R^6, SO_3R^6, and $SO_2NR^7R^8$;

A is an optionally substituted aryl or an optionally substituted heteroaryl group;

each optionally substituted group is either unsubstituted or substituted with one or more groups independently selected from alkyl, heteroalkyl, alkenyl, alkynyl, haloalkyl, heterohaloalkyl, aryl, arylalkyl, heteroaryl, non-aromatic ring, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, =O, =S, amino, and protected derivatives of amino groups;

or each of the variables R^4, R^5, A, W, Y, and Z is as defined and described in WO 2012/068546 which is herein incorporated by reference in its entirety.

[00425] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-pp-1**:



I-pp-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

Q denotes Ar or Het;

E denotes —$(CH_2)_mCO$—, —$(CH_2)_mSO_2$, —$(CH_2)_q$—, —$(CH_2)_mNHCO$—, or a single bond;

R^1 denotes H, OH, NH—C_1-C_6-alkyl, OC_1-C_6-alkyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, Cyc, Hal, Het^1, O-Het^1, CO-Het^1, NH-Het^1, CO—Ar^1, O—Ar^1, Ar^1, NH—Ar^1, —$(CH_2)_qHet^1$, —CONH—$(CH_2)_qHet^1$, —CONH-Het^1, —$(CH_2)_qO$-Het^1, —$(CH_2)_qO$—Ar^1, —$(CH_2)_qAr^1$, —CONH—$(CH_2)_qAr^1$, —CONH—Ar^1, —CONHC_3-C_6-cycloalkyl, —$(CH_2)_q$Hal, —$(CH_2)_q$Cyc, CF_3, —

$(CH_2)_sNH—(CH_2)_q$-Het^1, $—(CH_2)_sNH—(CH_2)_q—Ar^1$, wherein NH—$C_1$-$C_6$-alkyl, OC_1-C_6-alkyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl may be substituted by 1 to 3 groups independently selected from OC_1-C_3-alkyl, OH, $CONH_2$, NH_2;

R^2 denotes H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, Hal, CF_3, preferably H;

R^3 denotes Het^1, Ar^1, NR^aR^b, COOH, $—(CH_2)_qHet^1$, $—(CH_2)_qAr^1$, $—(CH_2)_qNR^aR^b$, $—(CH_2)_qCOOH$, or C_1-C_6-alkyl wherein 1 to 3 hydrogen atoms may be independently replaced by OH or CF_3;

R^4 denotes H, C_1-C_6-alkyl, C_2-C_6-alkenyl, Hal;

R^a denotes H, linear, branched or cyclic C_1-C_6-alkyl;

R^b denotes H, Het^b, Ar^b, $—CO$-Het^b, $—CO—Ar^b$, a C_3-C_8-cycloalkyl or a linear or branched alkyl having 1 to 6 carbon atoms, wherein 1 to 3 hydrogen atoms may be replaced by Het^b, Ar^b, NH_2, $N(C_1$-C_6-alkyl$)_2$, $NH(C_1$-C_6-alkyl$)$, $N(C_1$-C_6-alkyl$)(C_3$-C_8-cycloalkyl$)$, $NH(C_3$-C_8-cycloalkyl$)$, $O(C_1$-C_6-alkyl$)$, CN, OH, CF_3, Hal;

n is 0, 1, 2, 3 or 4;

m is 0, 1, 2, 3 or 4;

q is 1, 2, or 3;

s is 0, 1, 2 or 3;

Hal denotes Cl, Br, I, F, preferably Cl or F;

Ar denotes a divalent monocyclic or fused bicyclic arylen group having 6 to 14 carbon atoms, which may be further substituted with 1 to 4 substitutents selected from Hal, C_1-C_6-alkyl, $—(CH_2)_mOC_1$-C_6-alkyl, CN, OH, NO_2, CF_3, $—(CH_2)_mCOOH$, $—(CH_2)_mCOOC_1$-C_6-alkyl;

Het denotes a divalent monocyclic or fused bicyclic unsaturated, saturated or aromatic heterocyclic group having 1 to 5 heteroatom independently selected from N, O, S and/or a group —C=O, which may be further substituted with 1 to 4 substituent selected from Hal, C_1-C_6-alkyl, $—(CH_2)_mOC_1$-C_6-alkyl, CN, OH, NO_2, CF_3, $—(CH_2)_mCOOH$, $—(CH_2)_mCOOC_1$-C_6-alkyl;

Ar^1 denotes a monocyclic or bicyclic, aromatic carbocyclic ring having 6 to 14 carbon atoms, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, $—CF_3$, $—OCF_3$, $—NO_2$, —CN, perfluoroalkyl, Hal, $—CF_3$, $—OCF_3$, $—NO_2$, —CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, cycloalkyl, —OH, $—OC_1$-C_6-alkyl, $—COC_1$-C_6-alkyl, $—NH_2$, —COH, —COOH, $—CONH_2$, a group R^b such as $—CH_2O(C_1$-C_6-alkyl$)$, $—SO_2NR^aR^b$ or $SO_2(C_1$-C_6alkyl$)$;

Het^1 denotes a monocyclic or bicyclic (fused, bridged or spiro) saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 heteroatom independently selected from N, O, S and/or a CO group, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, $—CF_3$, $—OCF_3$, $—NO_2$, —CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, C_3-C_8-cycloalkyl, —OH, $—OC_1$-C_6-

alkyl, —NH_2, —$N(C_1$-C_6-alkyl)$_2$, —COH, —COOH, —$CONH_2$, —COC_1-C_6-alkyl, —$NHCO(C_3$-C_6cycloalkyl), a group R^b—$SO_2NR^aR^b$ or $SO_2(C_1$-C_6alkyl);

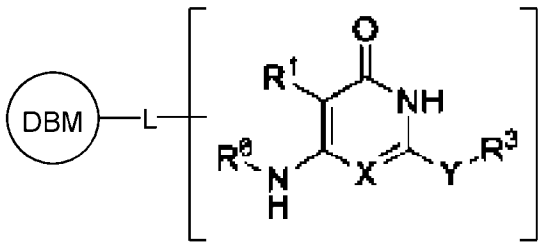
Het^b denotes a monocyclic or bicyclic (fused or spiro) saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 heteroatom independently selected from N, O, S and/or a CO group, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, —OH, —OC_1-C_6-alkyl, —NH_2, —COH, —COOH, —$CONH_2$, or by a linear or branched C_1-C_6-alkyl wherein 1 to 3 hydrogen atoms may be replaced by NH_2, $N(C_1$-C_6-alkyl)$_2$, $NH(C_1$-C_6-alkyl), $N(C_1$-C_6-alkyl)(C_3-C_8-cycloalkyl), $NH(C_3$-C_8-cycloalkyl), $O(C_1$-C_6-alkyl), CN, OH, CF_3, Hal, C_3-C_8-cycloalkyl, or by a 4 to 8-membered heterocyclic ring containing an heteroatom selected from O, S and N;

Ar^b denotes a monocyclic or bicyclic, aromatic carbocyclic ring having 6 to 14 carbon atoms, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, —OH, —OC_1-C_6-alkyl, —NH_2, —COH, —COOH, —$CONH_2$, or by a linear or branched C_1-C_6-alkyl wherein 1 to 3 hydrogen atoms may be replaced by NH_2, $N(C_1$-C_6-alkyl)$_2$, $NH(C_1$-C_6-alkyl), $N(C_1$-C_6-alkyl)(C_3-C_8-cycloalkyl), $NH(C_3$-C_8-cycloalkyl), $O(C_1$-C_6-alkyl), CN, OH, CF_3, Hal, C_3-C_8-cycloalkyl, or by a 4 to 8-membered heterocyclic ring containing an heteroatom selected from O, S and N;

Cyc denotes a saturated or unsaturated carbocyclic ring having 3 to 8 carbon atoms, preferrably 5 or 6 carbon atoms, wherein 1 to 5 H atoms are replaced by Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, cycloalkyl, —OH, —OC_1-C_6-alkyl, —COC_1-C_6-alkyl, —NH_2, —COH, —COOH, —$CONH_2$, a group R^b such as —$CH_2O(C_1$-C_6-alkyl), —$SO_2NR^aR^b$ or $SO_2(C_1$-C_6alkyl);

or each of the variables R^1, R^2, R^3, R^4, n, E, and Q is as defined and described in WO 2012/084704 which is herein incorporated by reference in its entirety.

[00426] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-qq-1**:



I-qq-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in

embodiments herein, and wherein:

X is —N= or —CH=;

Y is selected from the group consisting of —NR^2—, —CH_2—, —CHR— and —O—, such that when Y is —CHR—, R and R^3 together with the carbon to which they are attached optionally form a 4- to 6-membered cycloalkyl, cycloalkenyl or heterocyclic ring, wherein the 4- to 6-membered cycloalkyl, cycloalkenyl, or heterocyclic ring is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$; or when Y is —NR^2—, $R^2$and R^3 together with the nitrogen to which they are attached optionally form a 4- to 6-membered heterocyclic ring, wherein the 4- to 6-membered heterocyclic ring is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$;

R^1 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-8}cycloalkyl, aryl, heterocyclyl, halogen, —$COOR^7$, —NHR^7, —SR^7, —OR^7, —SO_2R^7, —COR^7, —$NHCOR^7$, and —$CONHR^7$; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, CN, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^S$, wherein said —NHR^8 is optionally substituted with —N(C_{1-4}alkyl)NH_2 or —N(C_{3-6} cycloalkyl)NH_2;

R^2 is selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{3-8} cycloalkyl;

R^3 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-8}cycloalkyl, aryl, heterocyclyl, and —$COOR^7$; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$;

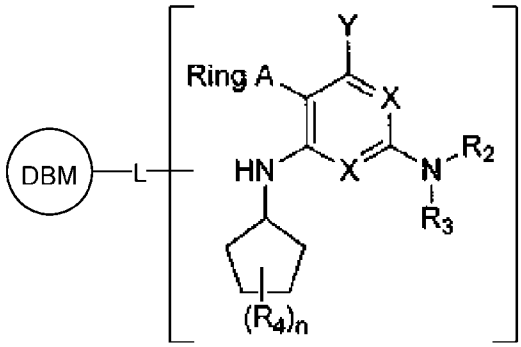
R^6 is selected from the group consisting of C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, heterocyclyl, —$COOR^7$, —SO_2R^7, and —COR^7; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$;

R^7 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-8}cycloalkyl, aryl, and heteroaryl; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6}cycloalkyl, phenyl, CF_3, heterocyclyl,

halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$;

or each of the variables R^1, R^3, R^6, X, and Y is as defined and described in WO 2013/066729 which is herein incorporated by reference in its entirety.

[00427] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-qq-2**:



I-qq-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

X is independently CH or N;

Y is H or methyl;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; n is 0, 1, 2, 3 or 4;

Ring A is (C_3-C_8)cycloalkenyl, aryl or heterocycle optionally substituted with one to three substituents independently selected from R_1;

R_1 is selected from: H, oxo, $(C{=}O)_aO_b(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkenyl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkynyl, CO_2H, halo, OH, $O_b(C_1$-$C_6)$fluoroalkyl, $(C{=}O)_aNR_5R_6$, CN, $(C{=}O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_mNR_5R_6$, SH, $S(O)_m$—$(C_1$-$C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;

R_2 and R_3 are independently selected from: H, $(C{=}O)_aO_bC_1$-C_{10} alkyl, $(C{=}O)_aO_b$aryl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $(C{=}O)_aO_b$ heterocyclyl, CO_2H, CN, O_bC_1-C_6fluoroalkyl, $O_a(C{=}O)_bNR_5R_6$, CHO, $(N{=}O)R_5R_6$, $S(O)_mNR_5R_6$, SH, $S(O)_m$—$(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_bC_3$-C_8 cycloalkyl, optionally substituted with one or more substituents selected from R_1; or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional

heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R_1;

R_4 is independently selected from: $(C_1\text{-}C_6)$alkyl, OH, methoxy, CF_3 and F, said alkyl optionally substituted with OH;

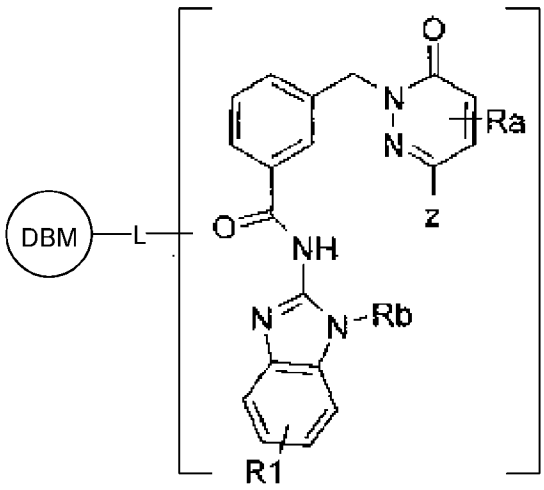
R_5 and R_6 are independently selected from H, $(C{=}O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C{=}O)_aO_b(C_2\text{-}C_{10})$alkynyl, CO_2H, $O_b(C_1\text{-}C_6)$fluoroalkyl, $(C{=}O)_aN(R_a)_2$, CN, $(C{=}O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mN(R_a)_2$, SH, $S(O)_m$—$(C_1\text{-}C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from R_b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, cyclopropyl, CO_2H, CN, $O_a(C{=}O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R_b)_2$; and

R_b is independently selected from H and $(C_1\text{-}C_6)$alkyl;

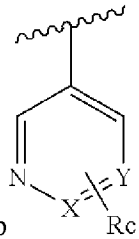
or each of the variables R_2, R_3, R_4, n, X, Y, and Ring A is as defined and described in WO 2014/058685 which is herein incorporated by reference in its entirety.

[00428] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-rr-1**:



I-rr-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:



Z denotes a group Rc ; wherein

X is CH or N;

Y is CH or N;

Ra, Rc, R1 denote each independently H, Hal or A1;

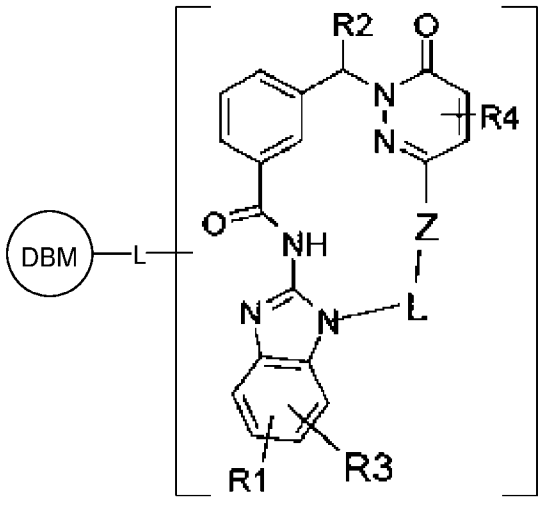
Rb is H or alkyl;

Al is branched or linear alkyl having 1 to 12 C-atoms, wherein one or more, such as 1 to 7, H atoms may be replaced by Hal, ORb, COORb, CN or $N(Rb)_2$ and wherein one or more, preferably 1 to 5 CH_2-groups may be replaced by O, CO, NRb or S, SO, SO_2, 1,2-, 1,3- or 1,4-phenylen, —CH=CH— or —C≡C—; and

Hal denotes F, Cl, Br, I;

or each of the variables R1, Ra, Rb, and z is as defined and described in WO 2014/121931 which is herein incorporated by reference in its entirety.

[00429] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-rr-2**:



I-rr-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein:

R1, R3 denote each, independently of one another H, $(CH_2)_pCON(R5)_2$, OA, Hal, COOH, COOA, $(CH_2)_pNHCOA$, $(CH_2)_pHet1$, $(CH_2)_pNR2R5$, or OH;

R2 denotes H or linear or branched alkyl with 1, 2 or 3 C atoms, wherein one or two H atoms of the alkyl group are optionally replaced by OR6, NR5R6, NHCOR5, CONR5R6;

R4 denotes H or A;

R5 denotes H or linear or branched alkyl with 1, 2 or 3 C atoms;

R6 denotes H or linear or branched alkyl with 1, 2 or 3 C atoms;

Z is absent or denotes Ar-diyl or Het-diyl;

L denotes $(CH_2)_n$ wherein one or two CH_2 groups are optionally replaced by O and/or a CH=CH-group, and/or wherein one or two H atoms are optionally replaced by OR2, NR2R5 or Het1;

Ar-diyl denotes 1,2-, 1,3- or 1,4-phenylen optionally substituted with from 1 to 5 groups independently selected from the group consisting of Hal, CN, —CF_3, —OCF_3, OH, O-A, SO_2-A, COOH, COOA, —CO-A, O-phenyl, SO_2-phenyl, SO_2—CF_3, Het2 and A;

Het-diyl denotes an unsaturated, saturated or aromatic 5- or 6-membered heterocycle comprising 1 to 2 N, O and/or S atoms, which are optionally unsubstituted or mono-, di- or trisubstituted by Hal, CN, —CF_3, —OCF_3, O-A, SO_2-A, COOH, COOA, —CO-A, O-phenyl, SO_2-phenyl, SO_2—CF_3, Het2 and/or A;

A denotes an unbranched or branched alkyl comprising 1 to 10 C atoms, in which 1 to 5 H atoms are optionally replaced by F and/or in which one or two non-adjacent CH_2 groups are optionally replaced by O;

Het1 denotes morpholinyl, piperidinyl or pyrrolidinyl;

Het2 denotes morpholinyl, piperidinyl or pyrrolidinyl;

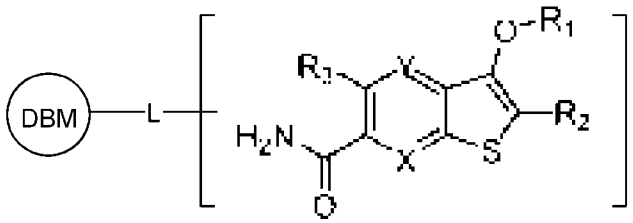
Hal denotes F, Cl, Br, I;

n denotes 1, 2, 3, 4, 5 or 6;

p denotes 0, 1 or 2;

or each of the variables R1, R2, R3, R4, L and Z is as defined and described in WO 2014/121942 which is herein incorporated by reference in its entirety.

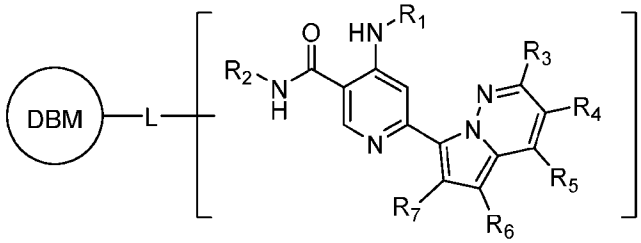
[00430] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula formula **I-zz**:



I-zz

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein X, Y, R_1, R_2, and R_3 are as defined and described in WO 2018/209012, the entirety of which is herein incorporated by reference.

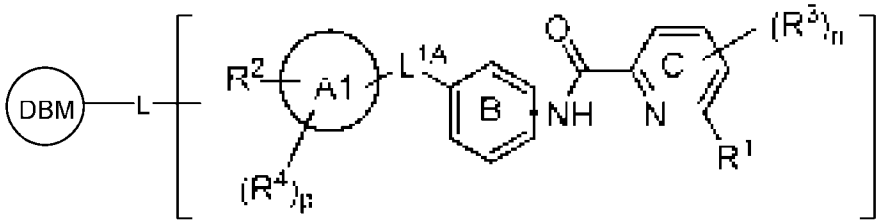
[00431] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula formula **I-aaa**:



I-aaa

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are as defined and described in US 2018/0230157, the entirety of which is herein incorporated by reference.

[00432] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula formula **I-bbb**:

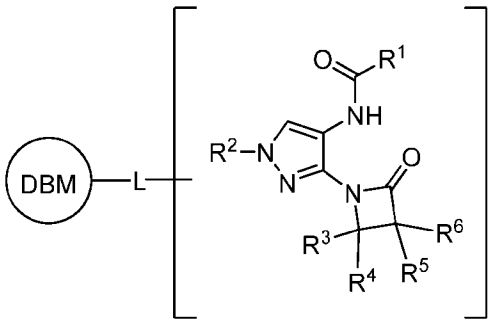


I-bbb

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Ring A1, Ring B, Ring C, L^{1A}, R^1, R^2, R^3, R^4, n, and p are as defined and described in WO 2018/098367, the entirety of which is herein incorporated by reference.

[00433] In certain embodiments, the present invention provides a compound of formula **I**, wherein

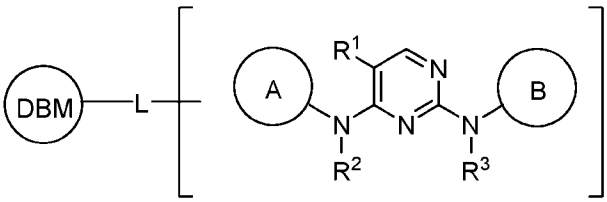
IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula formula **I-ccc**:



I-ccc

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein R^1, R^2, R^3, R^4, R^5, and R^6 are as defined and described in WO 2018/052058, the entirety of which is herein incorporated by reference.

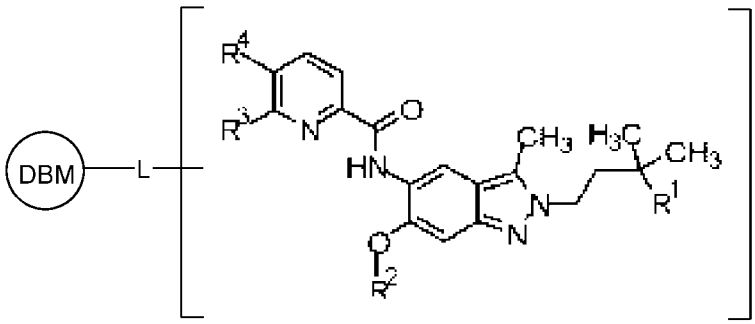
[00434] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ddd**:



I-ddd

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Ring A, Ring B, R^1, R^2, and R^3 are as defined and described in US 2017/0369476, the entirety of which is herein incorporated by reference.

[00435] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-eee**:

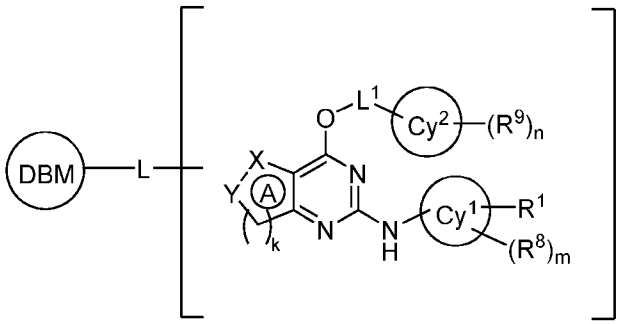


I-eee

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein R^1, R^2, R^3, and R^4 are as defined and described in WO 2017/207385, the

entirety of which is herein incorporated by reference.

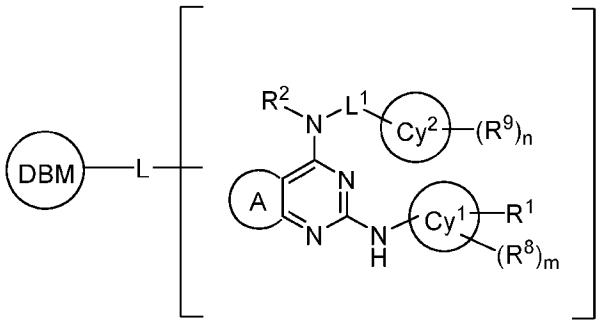
[00436] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-fff**:



I-fff

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Ring A, X, Y, L^1, Cy^1, Cy^2, R^1 R^8, R^9, k, m, and n are as defined and described in WO 2017/205766, the entirety of which is herein incorporated by reference.

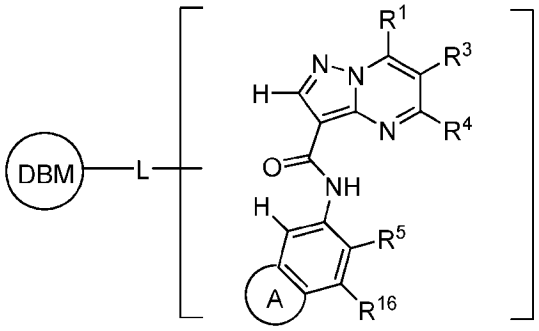
[00437] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula formula **I-ggg**:



I-ggg

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Ring A, L^1, Cy^1, Cy^2, R^1 R^8, R^9, m, and n are as defined and described in WO 2017/205762, the entirety of which is herein incorporated by reference.

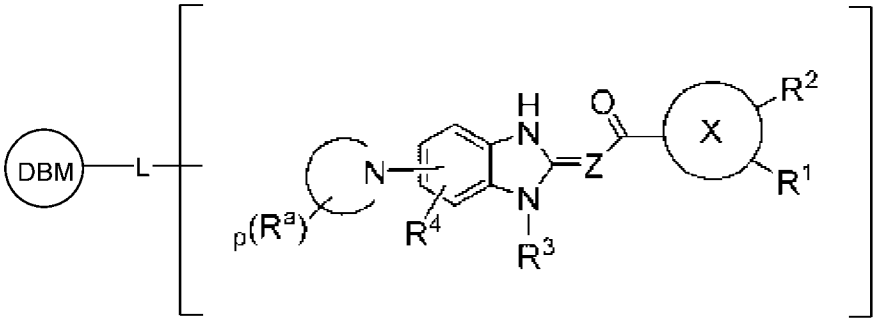
[00438] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-hhh**:



I-hhh

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Ring A, R^1, R^3, R^4, R^5, and R^{16} are as defined and described in WO 2017/108723, the entirety of which is herein incorporated by reference.

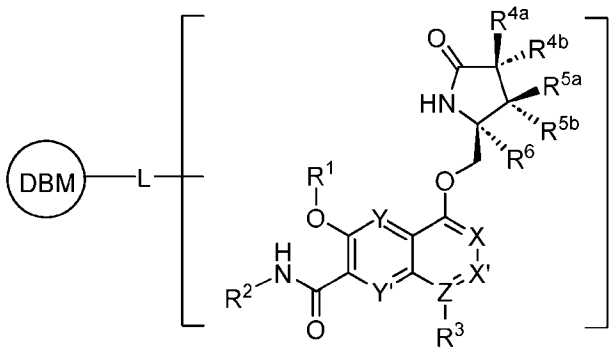
[00439] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-iii**:



I-iii

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Ring X, Z, R^1, R^2, R^3, R^4, R^a and p are as defined and described in WO 2017/049068, the entirety of which is herein incorporated by reference.

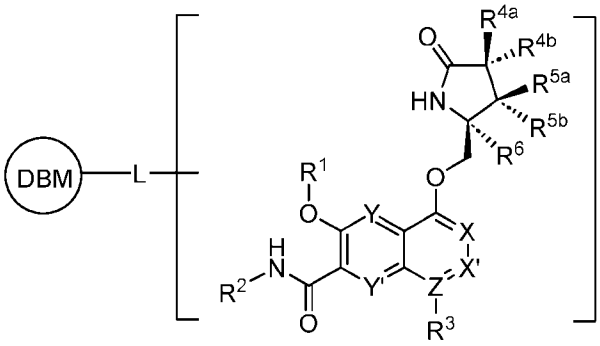
[00440] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-jjj**:



I-jjj

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein X, X', Y, Y', Z, R^1, R^2, R^3, R^{4a}, R^{4b}, R^{5a}, R^{5b} and R^6 are as defined and described in WO 2017/033093, the entirety of which is herein incorporated by reference.

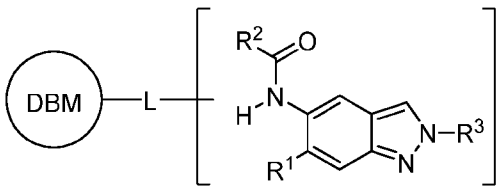
[00441] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-kkk**:



I-kkk

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein X, X', Y, Y', Z, R^1, R^2, R^3, R^{4a}, R^{4b}, R^{5a}, R^{5b} and R^6 are as defined and described in WO 2017/033093, the entirety of which is herein incorporated by reference.

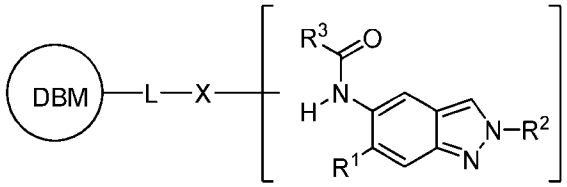
[00442] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-lll**:



I-lll

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, and R^3 is as described and defined in WO 2017/148902 and US 2019/071432, the entirety of each of which is herein incorporated by reference.

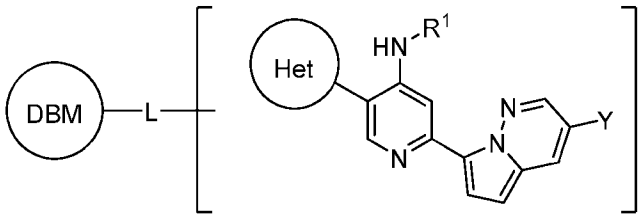
[00443] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-mmm**:



I-mmm

or a pharmaceutically acceptable salt thereof, wherein L, X, and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, and R^3 is as described and defined in WO 2017/108744, the entirety of each of which is herein incorporated by reference.

[00444] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-nnn**:

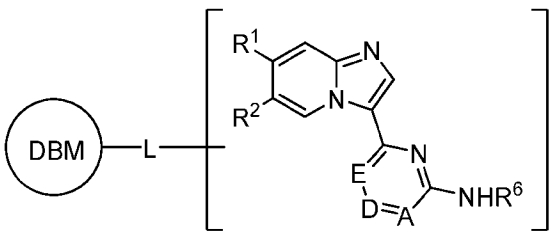


I-nnn

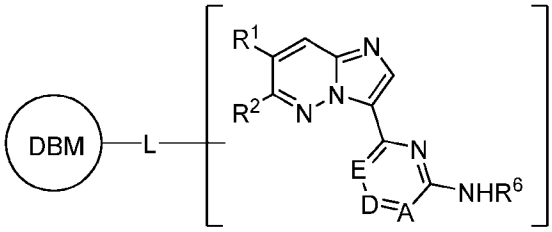
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, and wherein Het is a 5-6 membered heteroaryl having 1-4 heteroatoms selected from nitrogen, oxygen, and sulfur; and each of the variables R^1 and Y is as described and defined in WO 2020/036830, the entirety of each of which is herein incorporated by reference.

[00445] In some embodiments, the present invention provides a compound of **I-nnn** wherein L and DBM are as defined above and described in embodiments herein, and wherein Het is 1,3,4-thiadiazole; R^1 is an optionally substituted C_{1-6} aliphatic or optionally substituted 4-6 membered heterocyclyl; and Y is -CN.

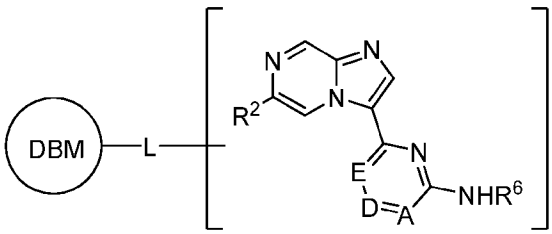
[00446] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula:



I-ooo-1



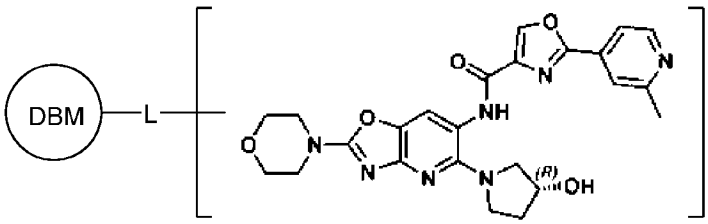
I-ooo-1



I-ooo-1

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/026935 and WO 2023/009833, the entirety of each of which is herein incorporated by reference.

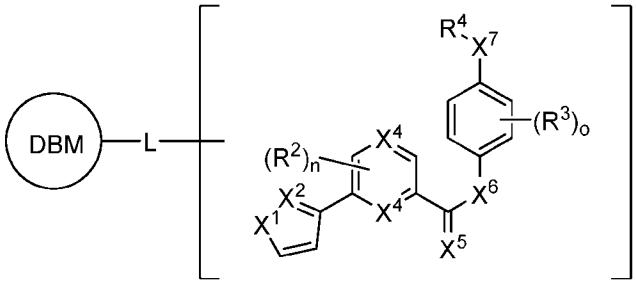
[00447] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ppp**:



I-ppp

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, as described and defined in WO 2022/031330, the entirety of each of which is herein incorporated by reference.

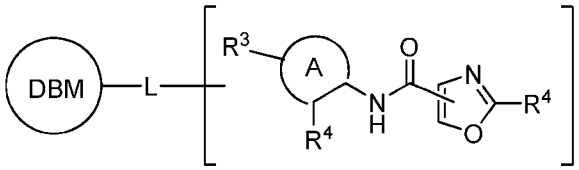
[00448] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-qqq**:



I-qqq

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/020661, the entirety of each of which is herein incorporated by reference.

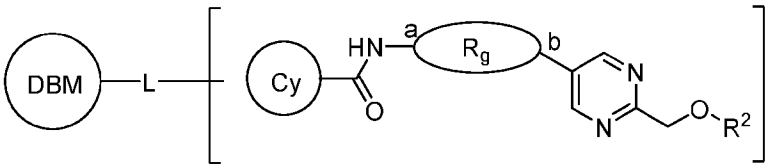
[00449] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-rrr**:



I-rrr

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/006129, the entirety of each of which is herein incorporated by reference.

[00450] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-sss**:

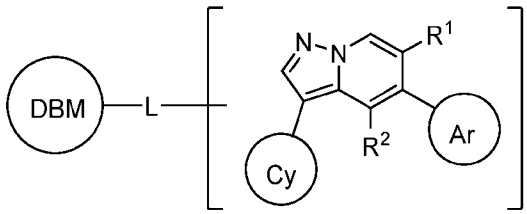


I-sss

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/070289, the entirety of each of which is herein incorporated by reference.

[00451] In certain embodiments, the present invention provides a compound of formula **I**, wherein

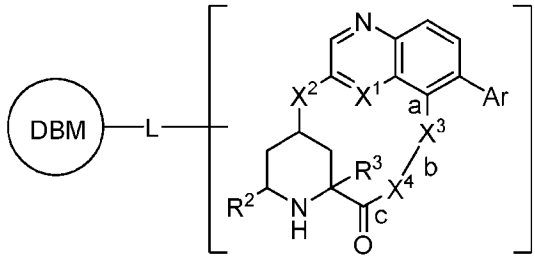
IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ttt**:



I-ttt

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/070288, the entirety of each of which is herein incorporated by reference.

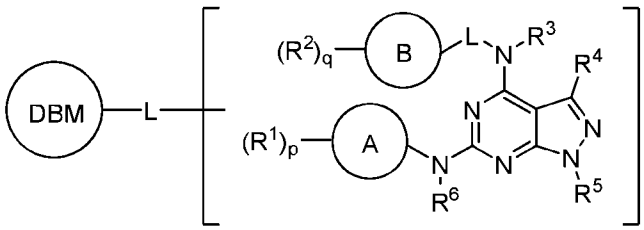
[00452] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-uuu**:



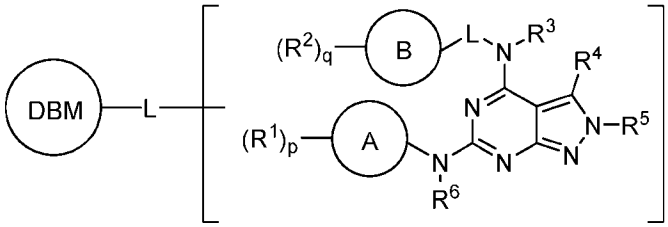
I-uuu

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/070287, the entirety of each of which is herein incorporated by reference.

[00453] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of either formulae:



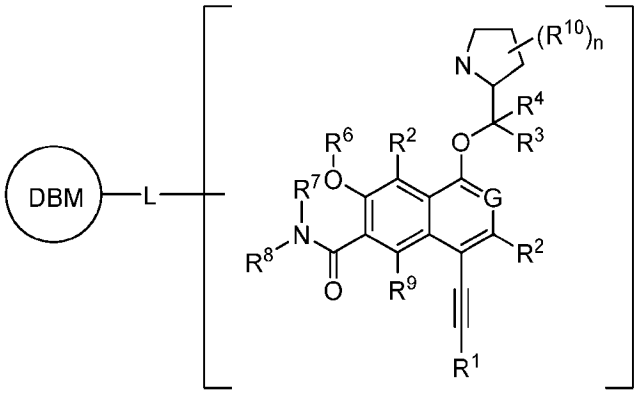
I-vvv-1



I-vvv-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in US 2022/144842, the entirety of each of which is herein incorporated by reference.

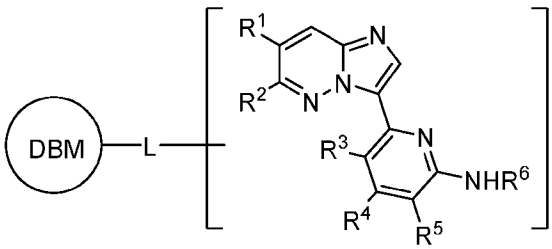
[00454] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-www**:



I-www

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/070287, the entirety of each of which is herein incorporated by reference.

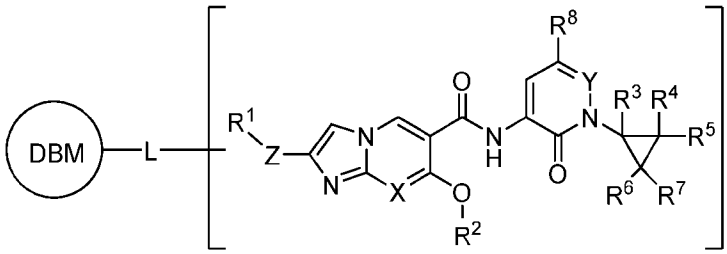
[00455] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-xxx**:



I-xxx

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/135338 and WO 2022/140647, the entirety of each of which is herein incorporated by reference.

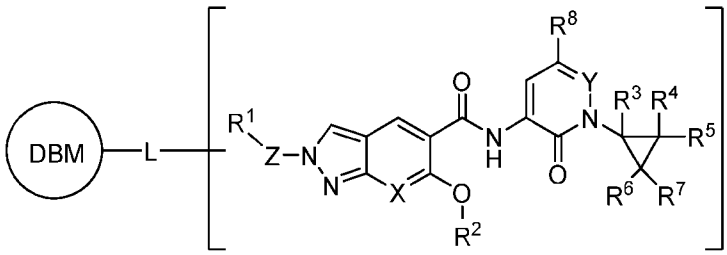
[00456] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-yyy**:



I-yyy

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/140425, the entirety of each of which is herein incorporated by reference.

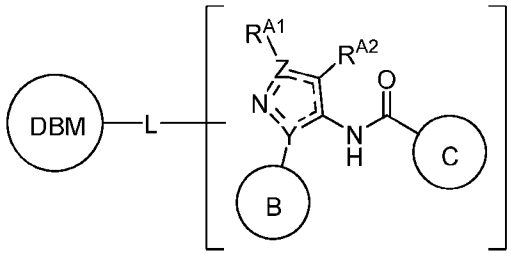
[00457] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-zzz**:



I-zzz

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2022/140415, the entirety of each of which is herein incorporated by reference.

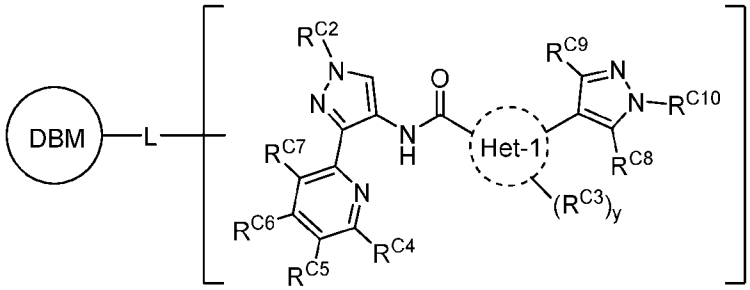
[00458] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-aaaa**:



I-aaaa

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2023/039047, the entirety of each of which is herein incorporated by reference.

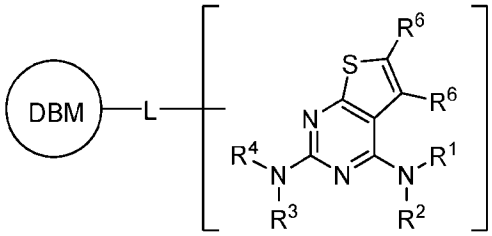
[00459] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-bbbb**:



I-bbbb

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2023/038815, the entirety of each of which is herein incorporated by reference.

[00460] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-cccc**:

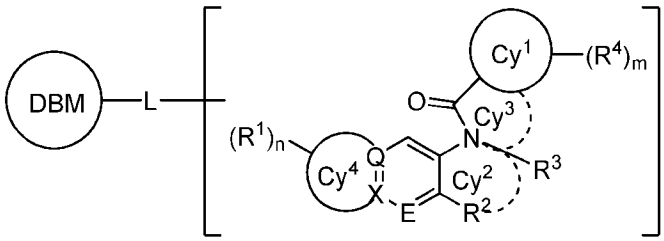


I-cccc

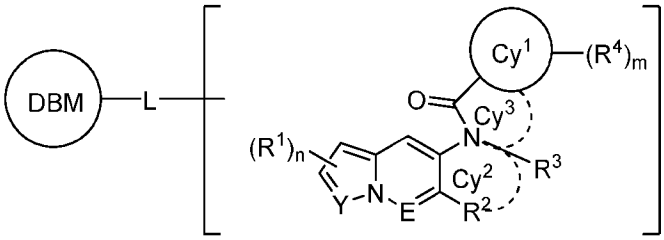
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as

described and defined in WO 2023/075479, the entirety of each of which is herein incorporated by reference.

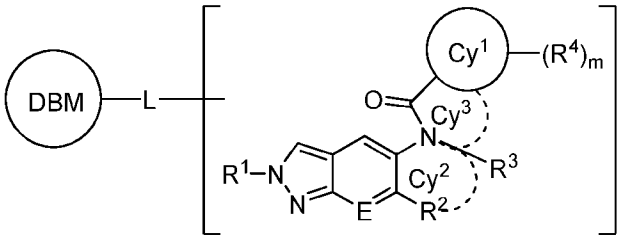
[00461] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formulae:



I-dddd-1



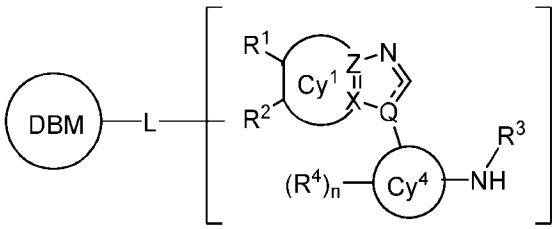
I-dddd-2



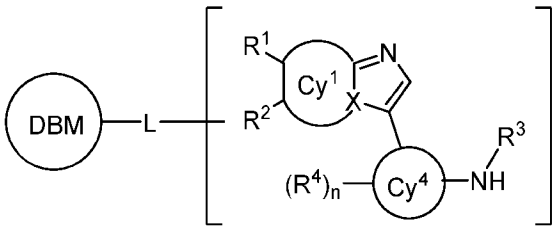
I-dddd-3

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2023/116866, the entirety of each of which is herein incorporated by reference.

[00462] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula:



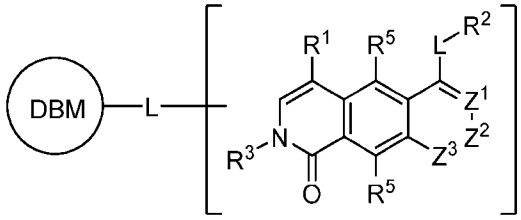
I-eeee-1



I-eeee-2

or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2023/116888, the entirety of each of which is herein incorporated by reference.

[00463] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety as shown below to provide a compound of formula **I-ffff**:

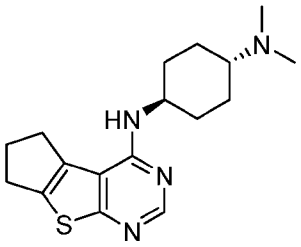


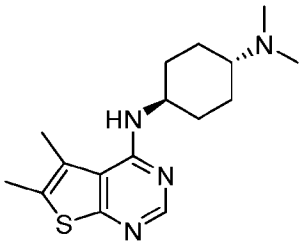
I-ffff

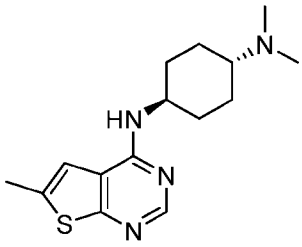
or a pharmaceutically acceptable salt thereof, wherein L and DBM are as defined above and described in embodiments herein, or a pharmaceutically acceptable salt thereof, wherein each of the variables are as described and defined in WO 2023/192479, the entirety of each of which is herein incorporated by reference.

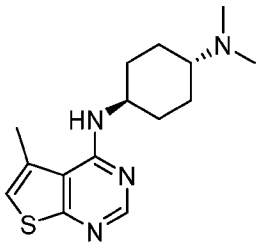
[00464] In some embodiments, IRAK is selected from a moiety recited in Aurigene Discovery Tech. Ltd. Presentation: *Novel IRAK-4 Inhibitors exhibit highly potent anti-proliferative activity in DLBCL cell lines with activation MYD88 L264P mutation*, such as, for example: AU-5850, AU-2807, AU-6686, and AU-5792, wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

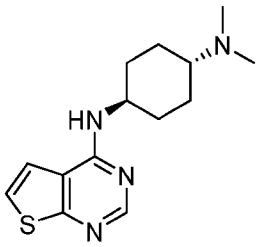
[00465] In some embodiments, IRAK is selected from a moiety recited in Scott, J.S. *et al. Discovery and Optimization of Pyrrolopyrimidine Inhibitors of Interleukin-1 Receptor Associated Kinase 4 (IRAK4) for the Treatment of Mutant MYD88 Diffuse Large B-cell Lymphoma*. J. Med. Chem. Manuscript, Nov, 29 2017, 10.1021/acs.jmedchem.7b01290 such as, for example:

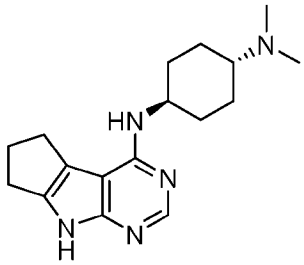

Cmp 1

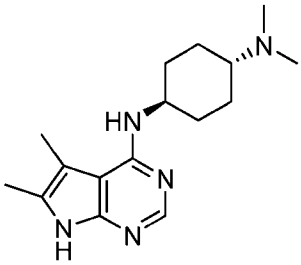

Cmp 2

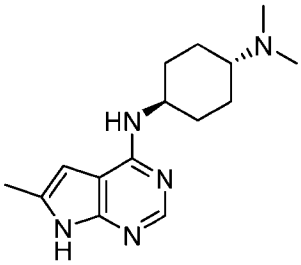

Cmp 3

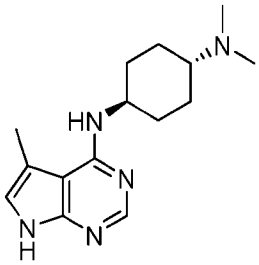

Cmp 4

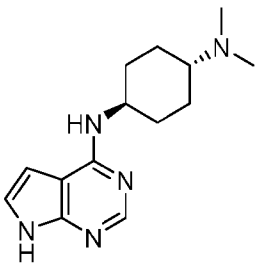

Cmp 5

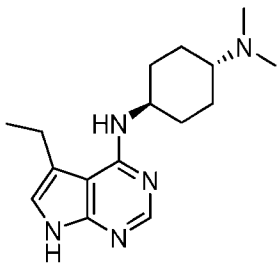

Cmp 6


Cmp 7


Cmp 8


Cmp 9


Cmp 10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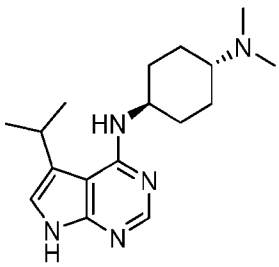
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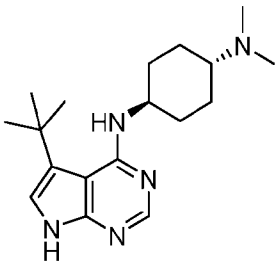

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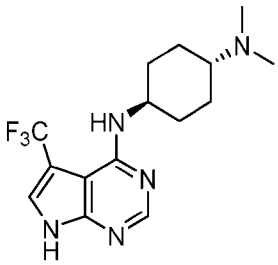

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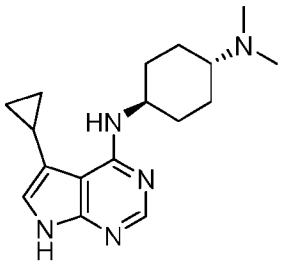

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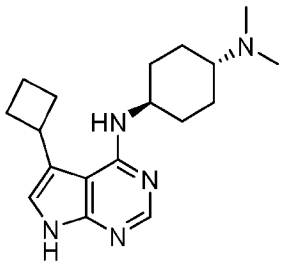

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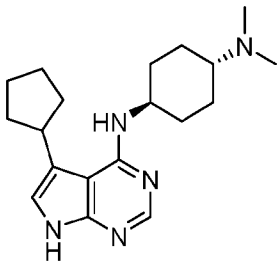

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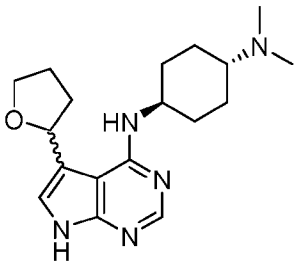

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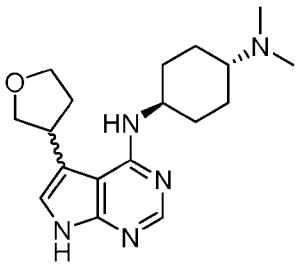

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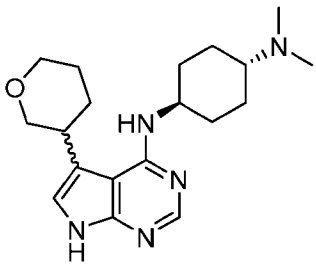

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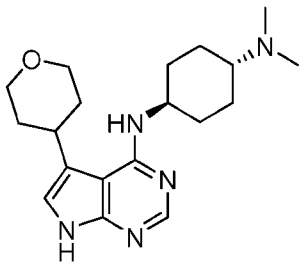

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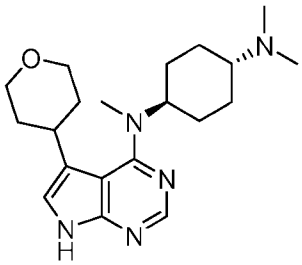

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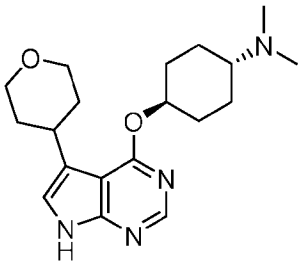

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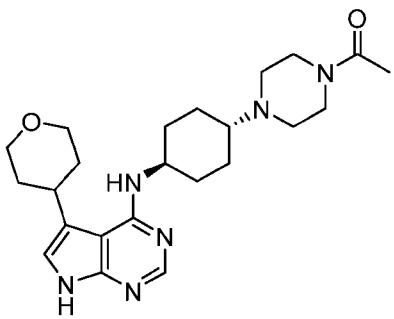

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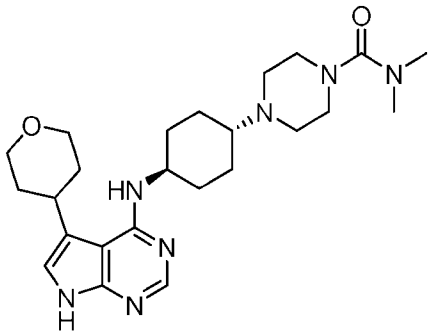

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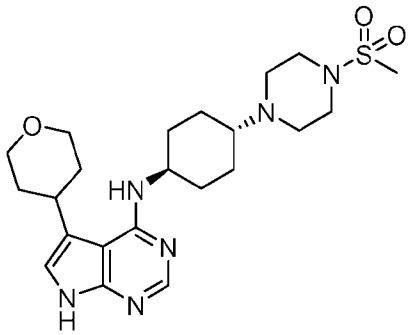

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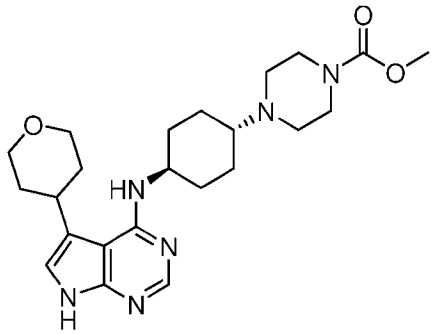

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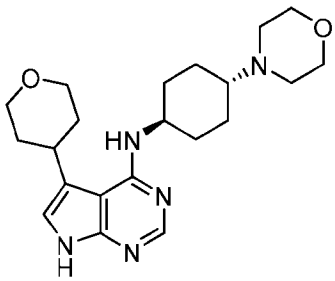

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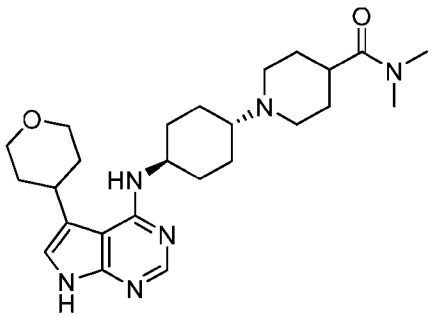

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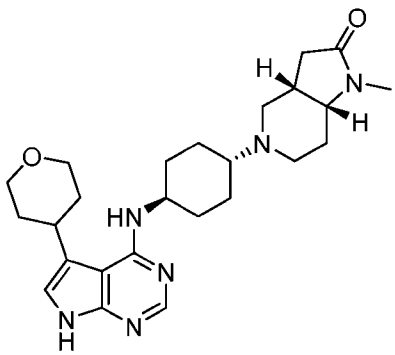

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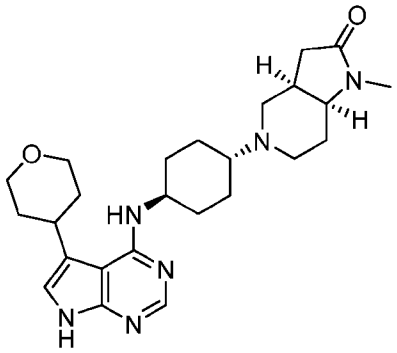

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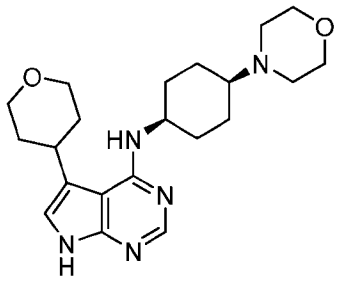

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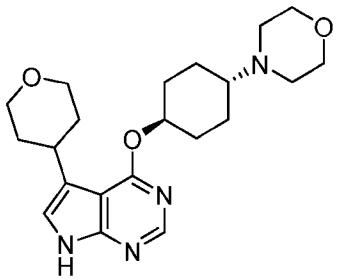

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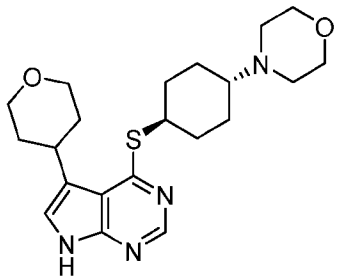

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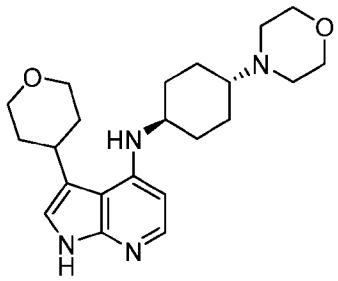
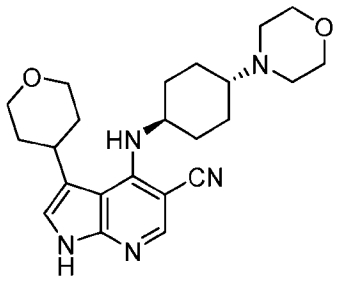


Cmp 35

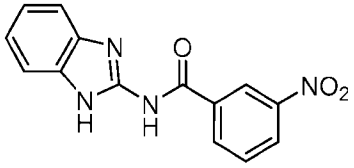
, and



Cmp 36

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00466] In some embodiments, IRAK is selected from a moiety recited in Powers, J.P. *et al.*, *Discovery and initial SAR of inhibitors of interleukin-1 receptor-associated kinase-4*, Bioorg. Med Chem Lett. (2006) 16(11): 2842-45, such as, for example:



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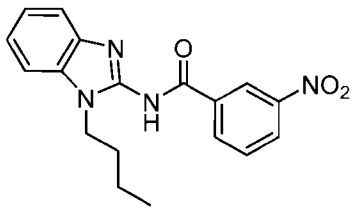

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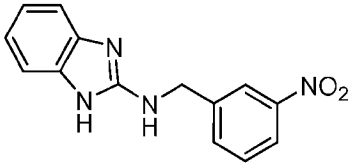

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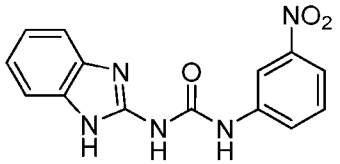

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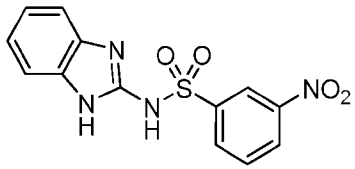

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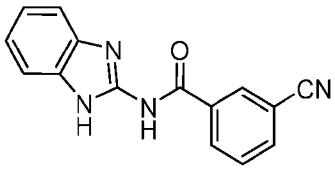

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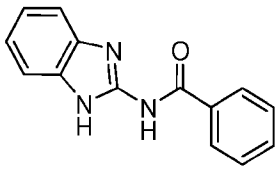

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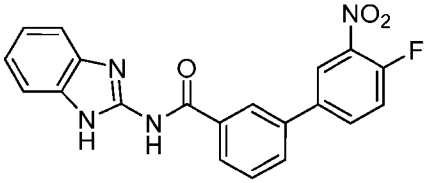

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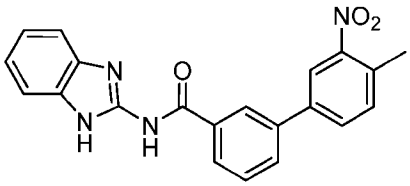

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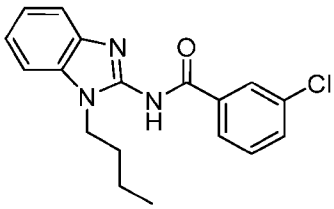

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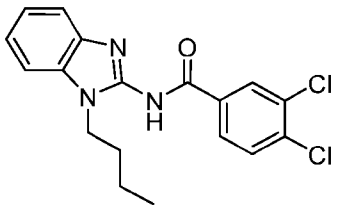

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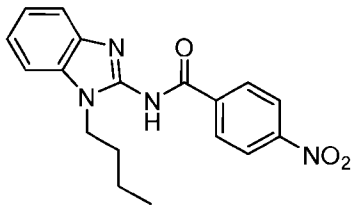

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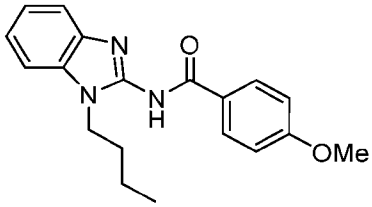

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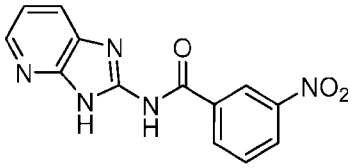

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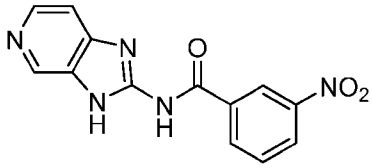

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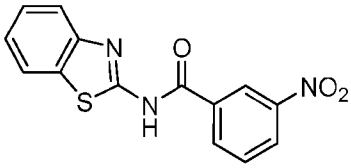

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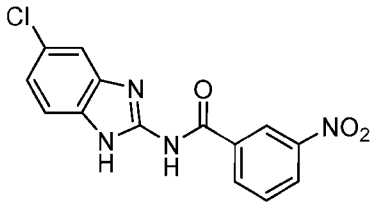

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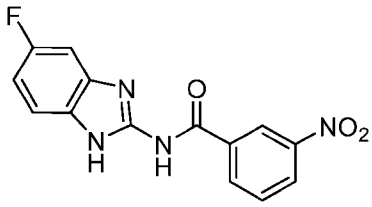

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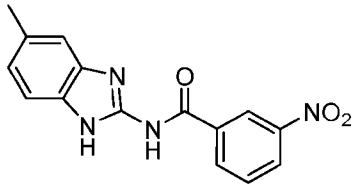

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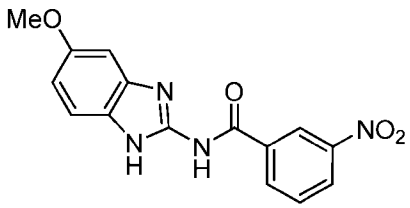

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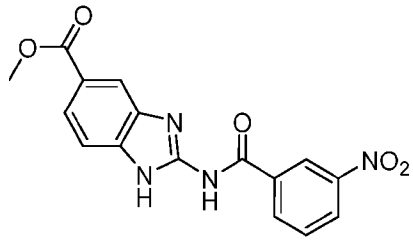

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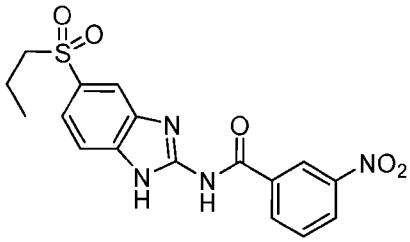

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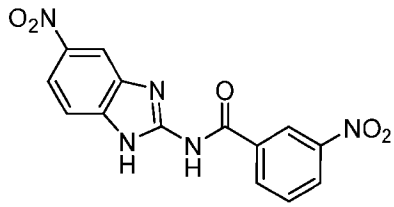

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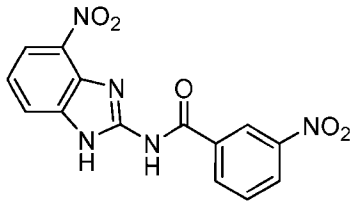

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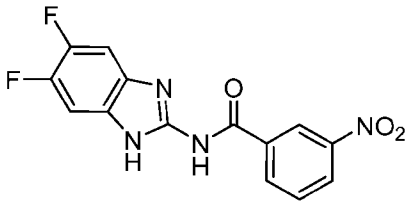

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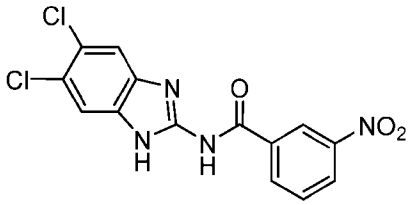

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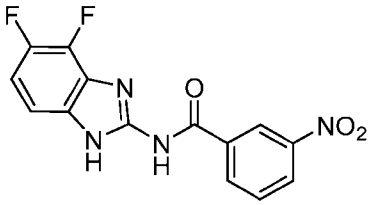

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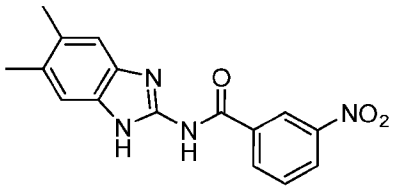

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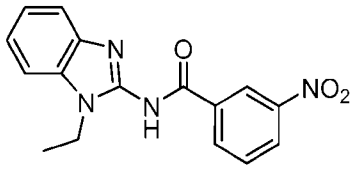

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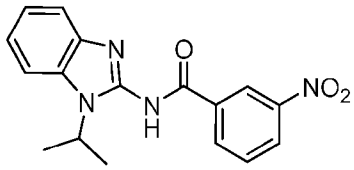

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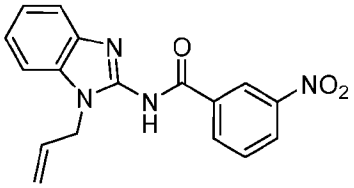
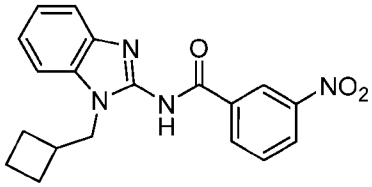
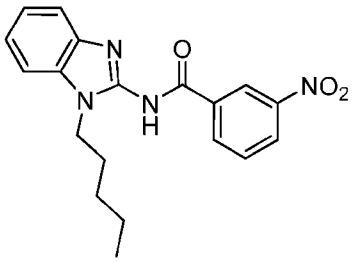


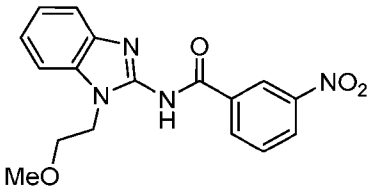
Compound 31



Compound 32



Compound 33



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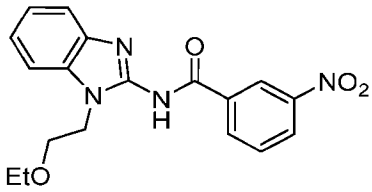
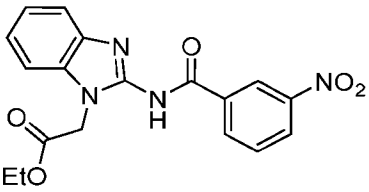


Compound 35



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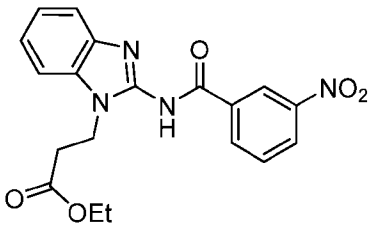

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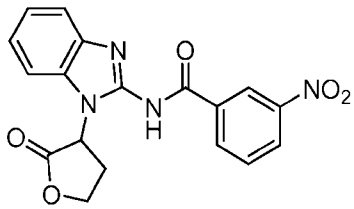

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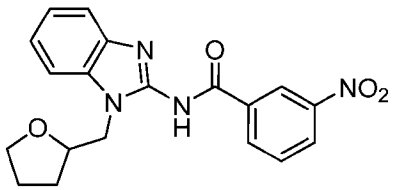

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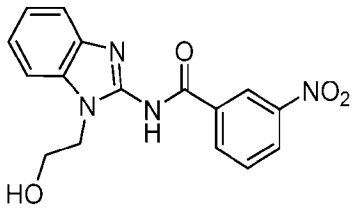

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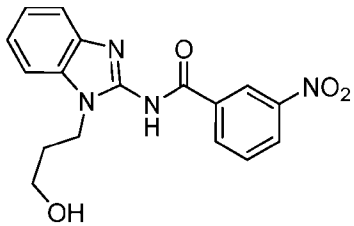
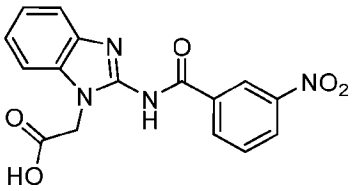


Compound 41



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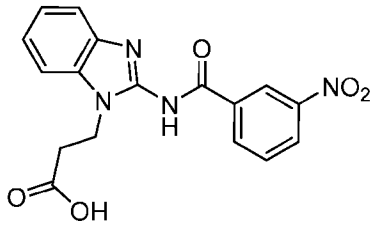

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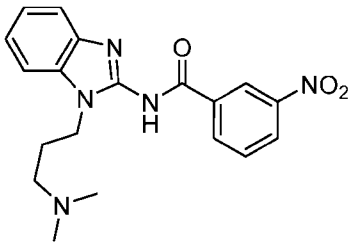
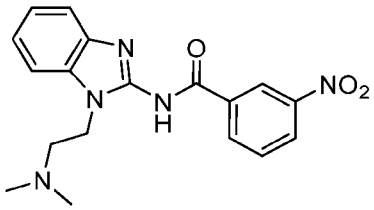
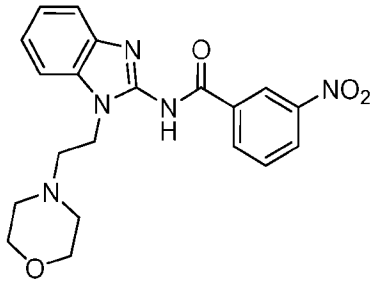


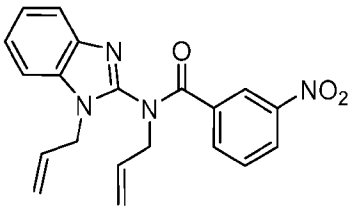
Compound 44



Compound 45

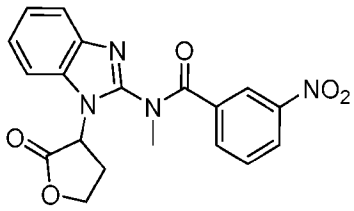


Compound 46



Compound 47

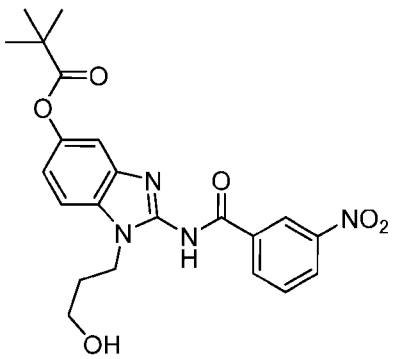
, and



Compound 48

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

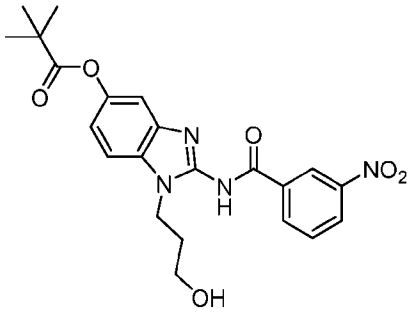
[00467] In some embodiments, IRAK is selected from a moiety recited in Wang, *et al.*, *Crystal Structure of IRAK-4 Kinase in Complex with Inhibitors: Serine/Threonine Kinase with Tyrosine as a Gatekeeper*, Structure, 2006, 14(12): 1835-44, such as, for example:



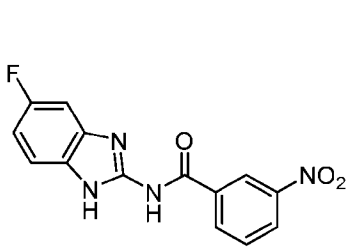
Compound 1

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

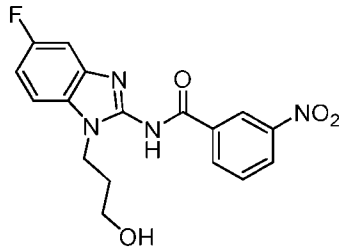
[00468] In some embodiments, IRAK is selected from a moiety recited in Wang, Z. *et al.*, *Discovery of potent, selective, and orally bioavailable inhibitors of interleukin-1 receptor-associated kinase 4*, Bioorg. Med. Chem Lett., 2015, 25(23): 5546-50, such as, for example:



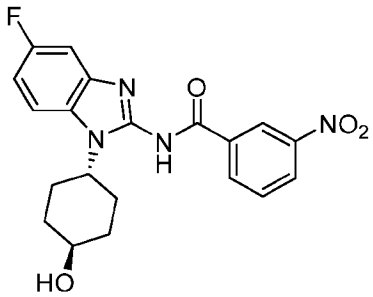
Compound 1



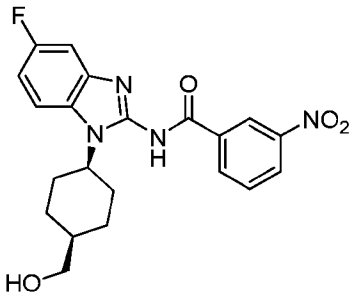
Compound 2



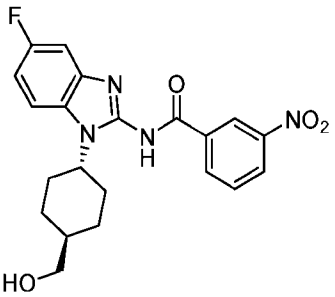
Compound 3



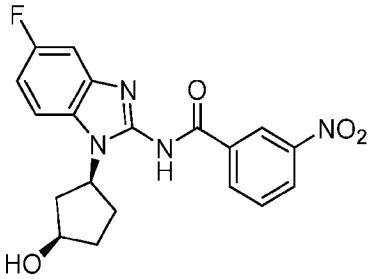
Compound 4



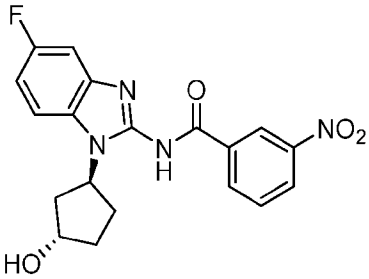
Compound 5



Compound 6



Compound 7



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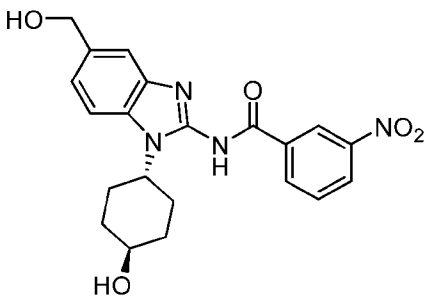
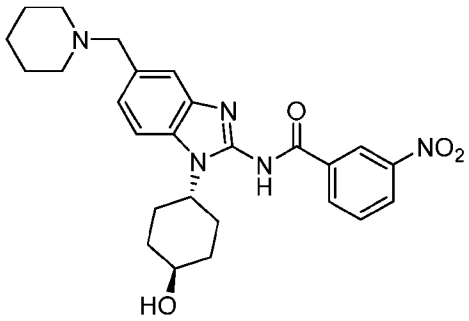


Compound 9



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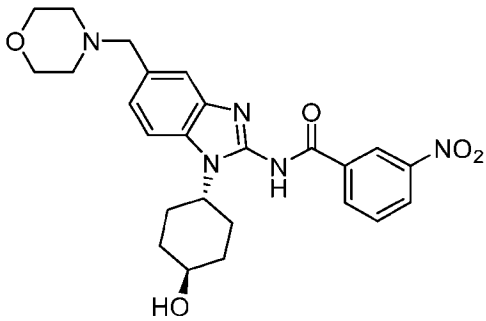

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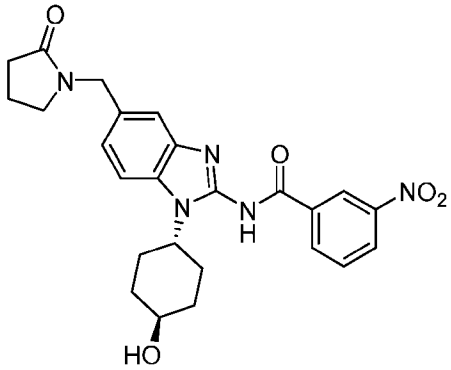
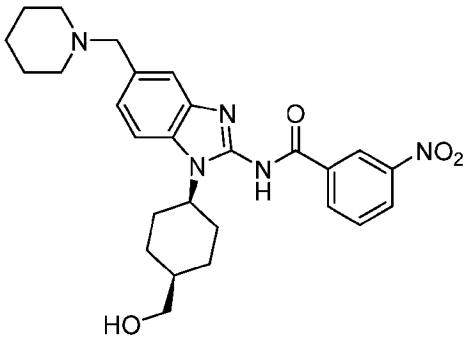


Compound 12



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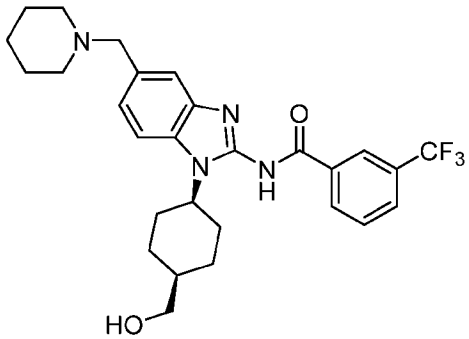
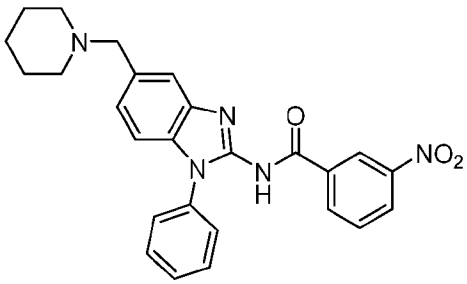
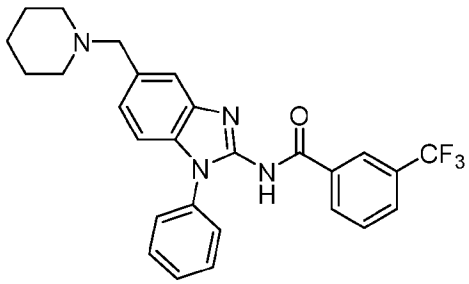
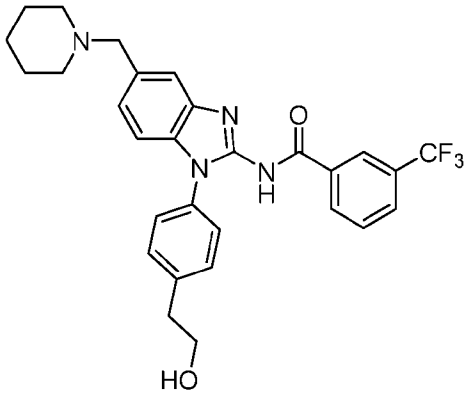


Compound 14

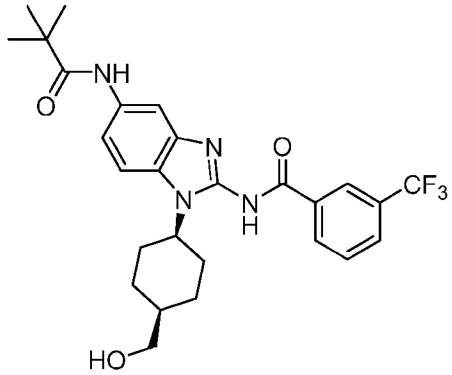




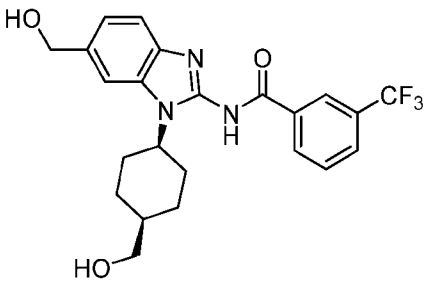
Compound 15



Compound 16



Compound 17



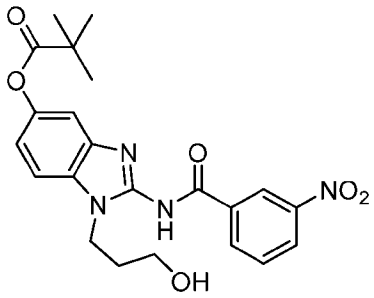
Compound 18

, and

Compound 19

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00469] In some embodiments, IRAK is selected from a moiety recited in Chaudhary, D. *et al.*, *Recent Advances in the Discovery of Small Molecule Inhibitors of Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) as a Therapeutic Target for Inflammation and Oncology Disorders*, J. Med Chem., 2015, 58(1): 96-110, such as, for example:



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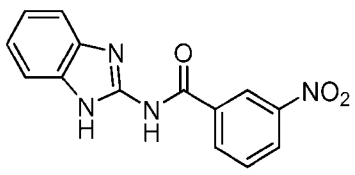

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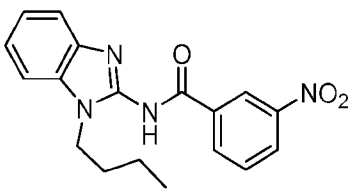

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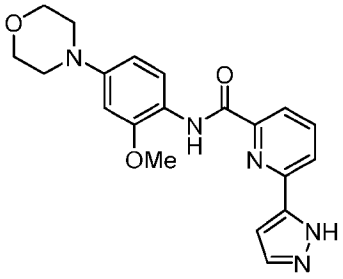

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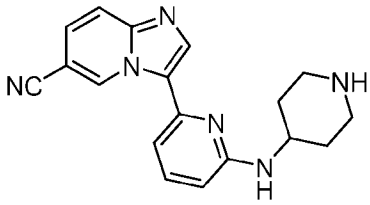

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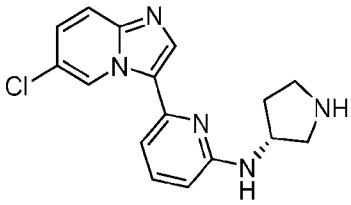

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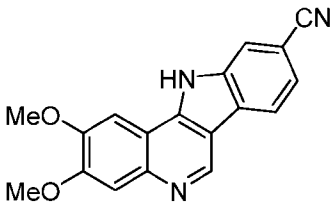

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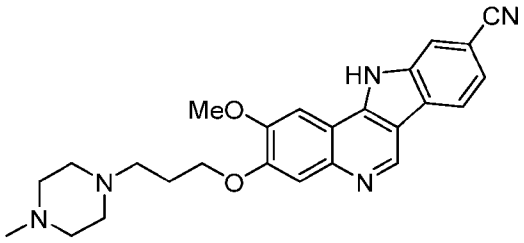

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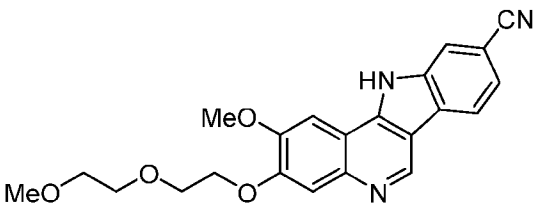

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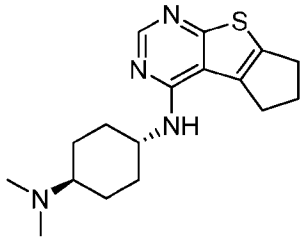

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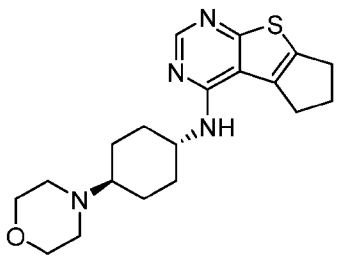

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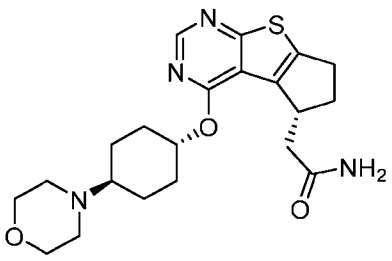

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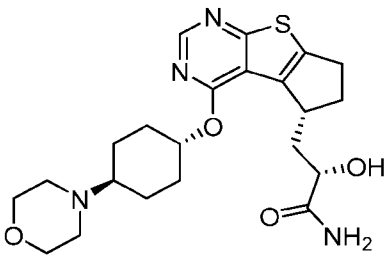

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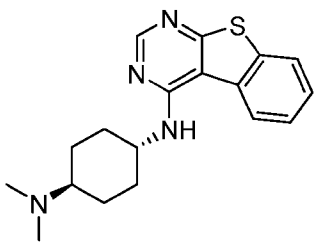

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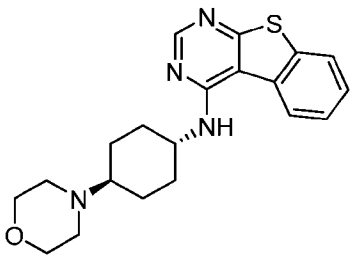

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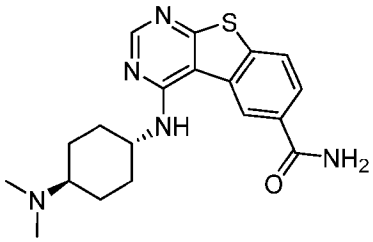

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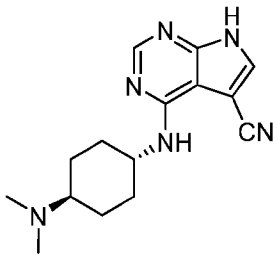

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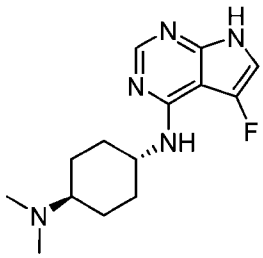

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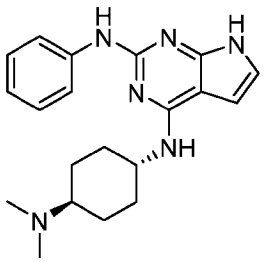

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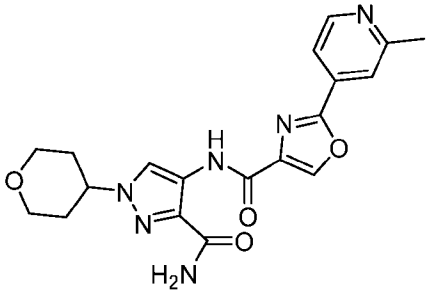
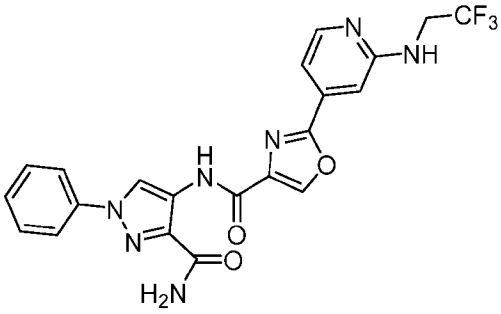


20 (AS2444697)



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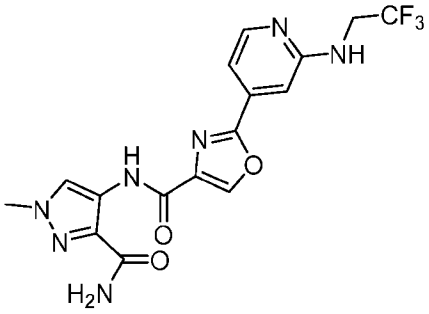

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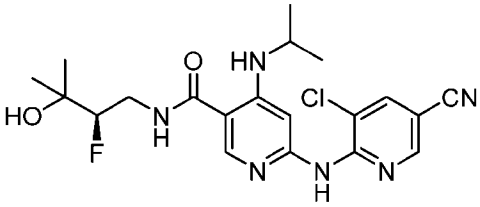

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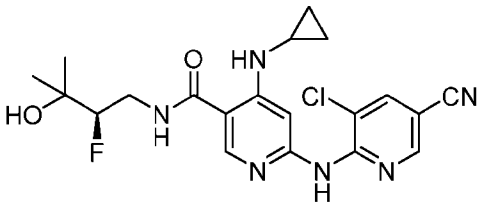

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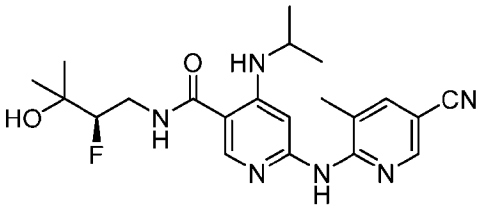

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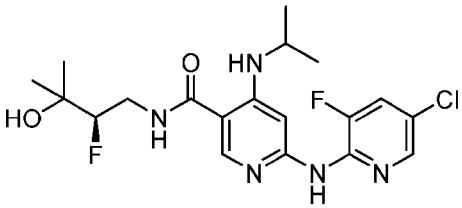

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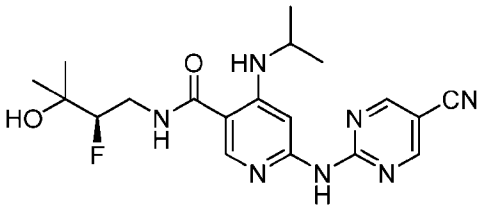

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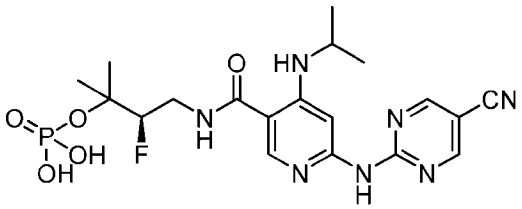

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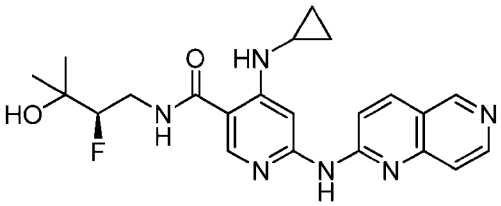

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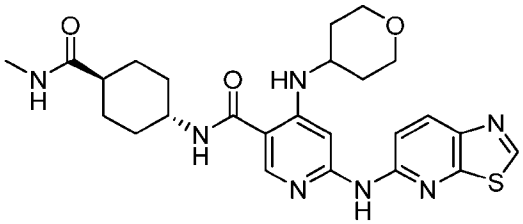

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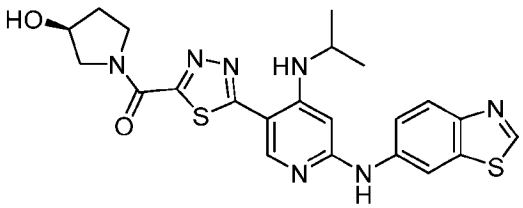

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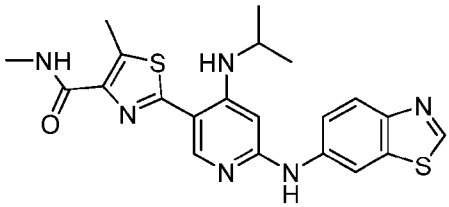

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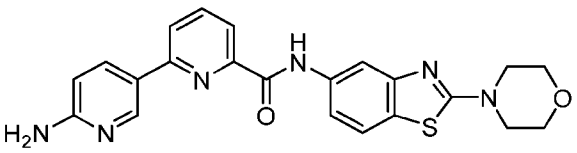

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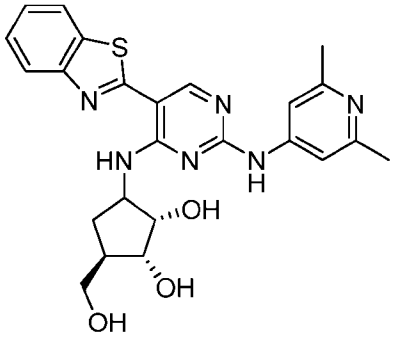

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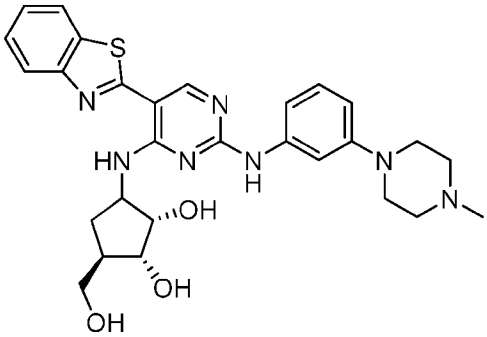

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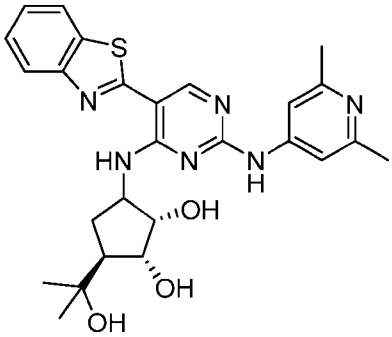

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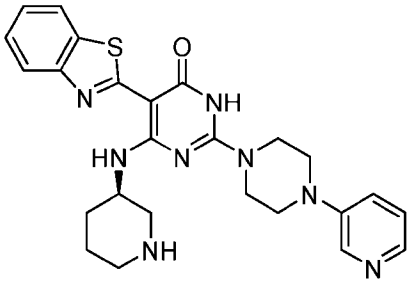

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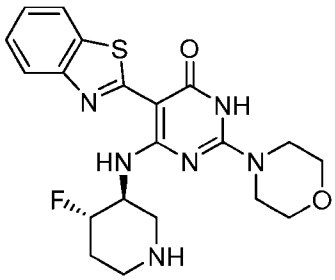

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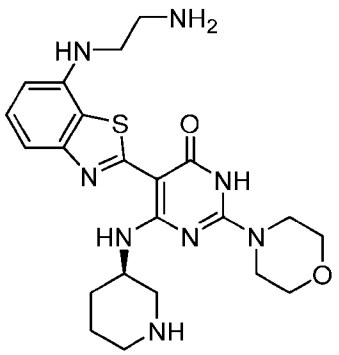

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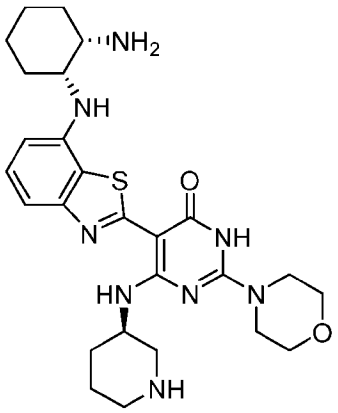

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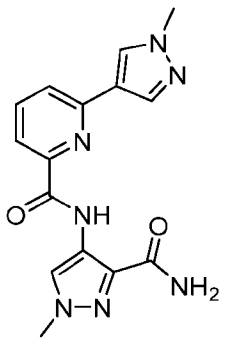

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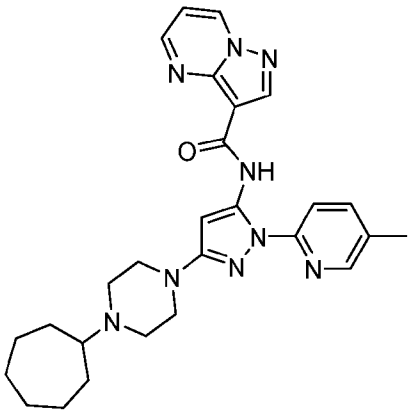

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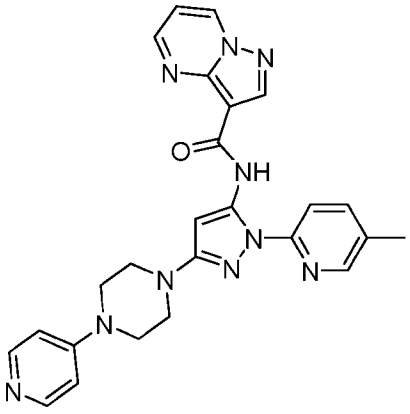

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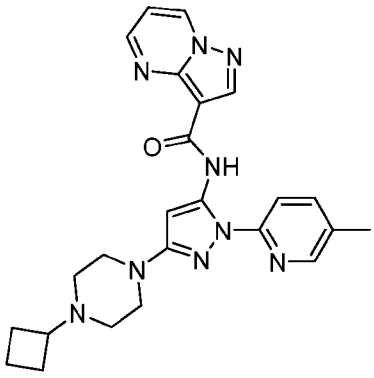

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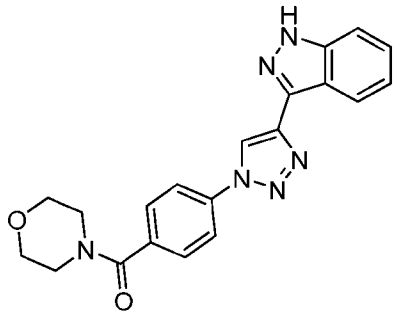

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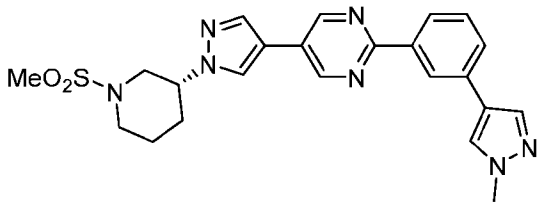

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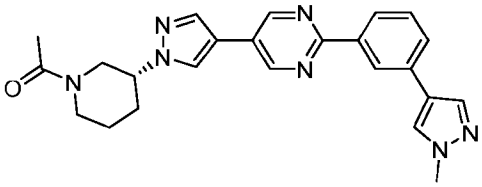

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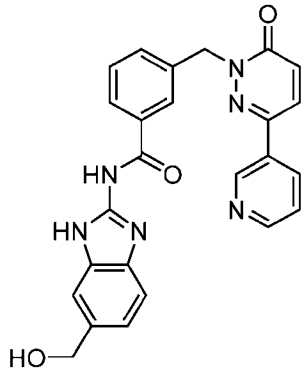

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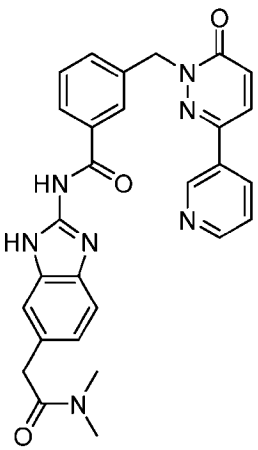

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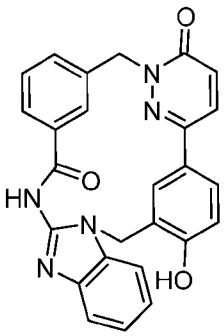

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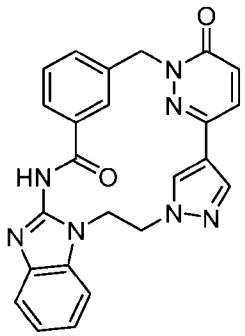

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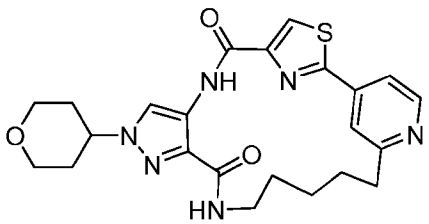

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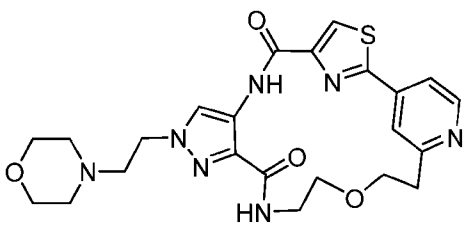

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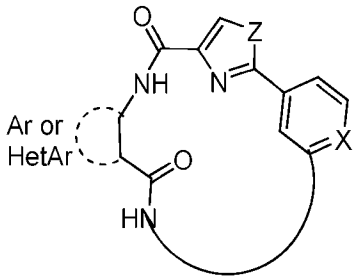

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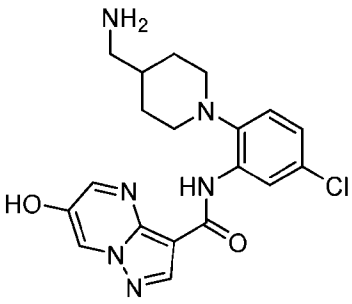

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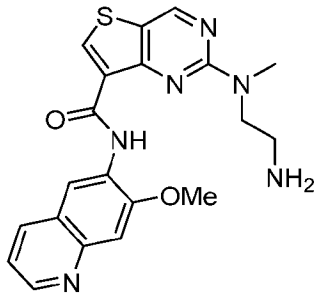
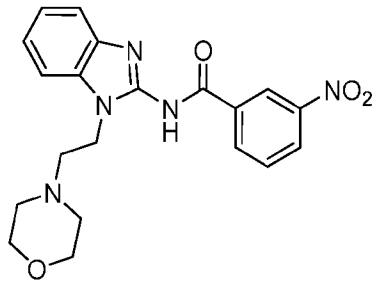


55

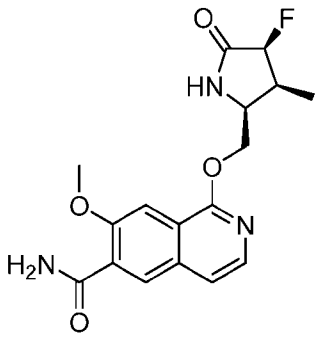
wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00470] In some embodiments, IRAK is selected from a moiety recited in Zhang, D. *et al.*, *Constitutive IRAK4 Activation Underlies Poor Prognosis and Chemoresistance in Pancreatic Ductal Adenocarcinoma*, Clin. Can. Res., 2017, 23(7): 1748-59, such as, for example:



wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

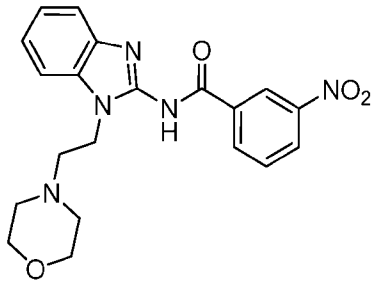
[00471] In some embodiments, IRAK is selected from a moiety recited in Cushing, L. *et al.*, *IRAK4 kinase controls Toll-like receptor induced inflammation through the transcription factor IRF5 in primary human monocytes*, J. Bio. Chem., 2017, 292(45): 18689-698, such as, for example:



PF-06426779

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00472] In some embodiments, IRAK is selected from a moiety recited in Li, N. *et al.*, *Targeting interleukin-1 receptor-associated kinase for human hepatocellular carcinoma*, J. Ex. Clin. Can. Res., 2016, 35(1): 140-50, such as, for example:

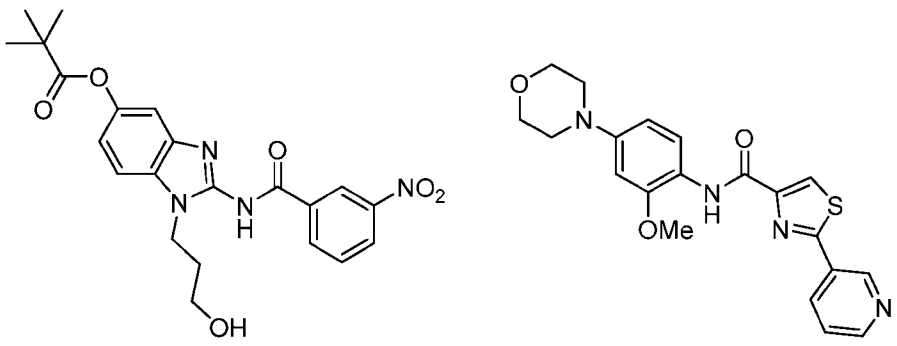


I-5409 (Sigma)

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00473] In some embodiments, IRAK is selected from a moiety recited in Dudhgaonkar, S. *et al.*, *Selective IRAK4 Inhibition Attenuates Disease in Murine Lupus Models and Demonstrates Steroid Sparing Activity*, J. of Immun., 2017, 198(3): 1308-19, such as, for example BMS-986126, wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00474] In some embodiments, IRAK is selected from a moiety recited in Wang, Z. *et al.*, *IRAK-4 Inhibitors for Inflammation*, Cur. Top. Med. Chem., 2009, 9(8): 724-37, such as, for example:



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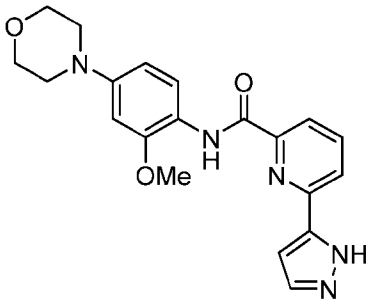

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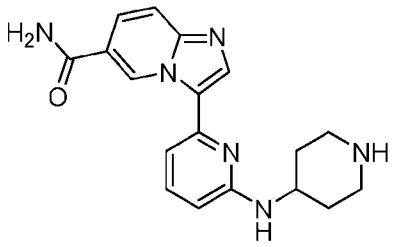

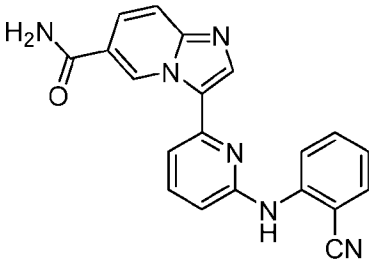

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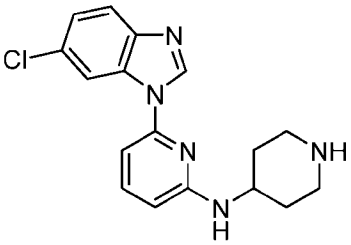

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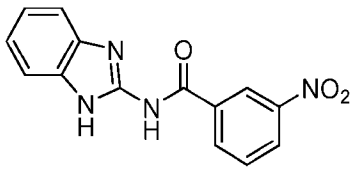

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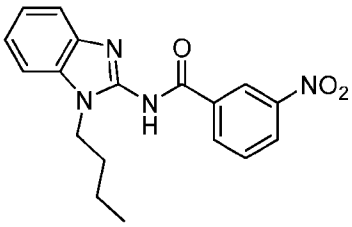

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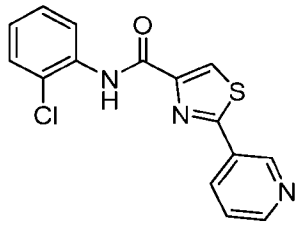

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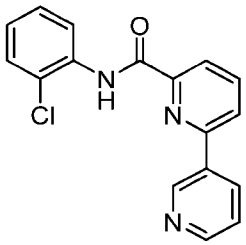

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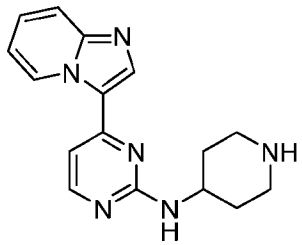

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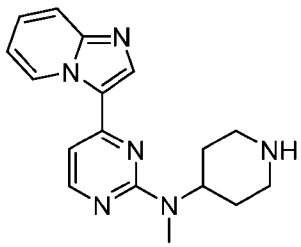

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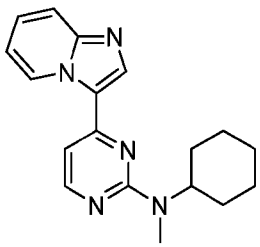

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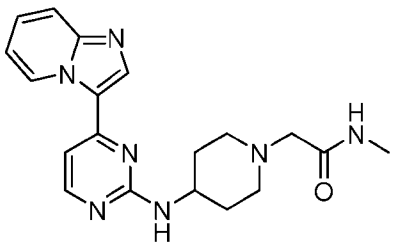

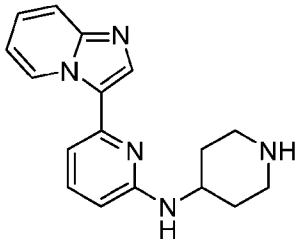

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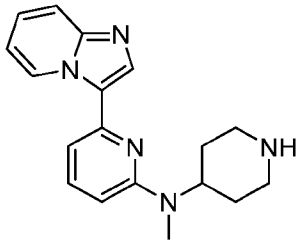

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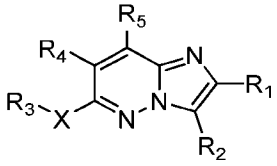

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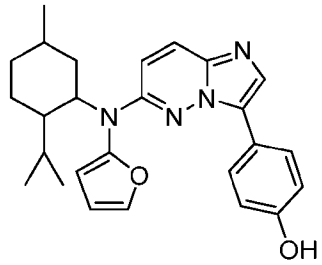

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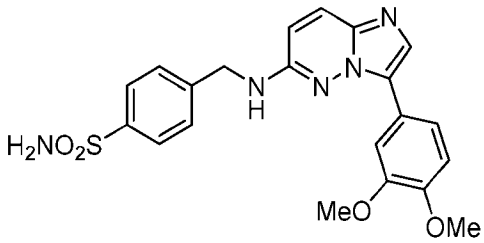

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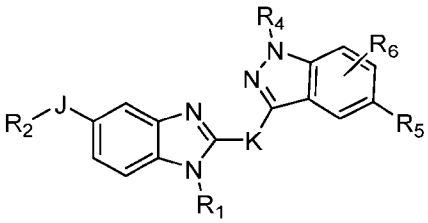

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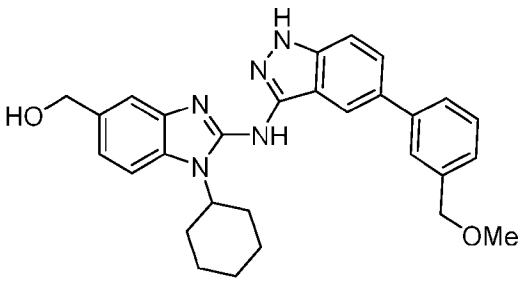

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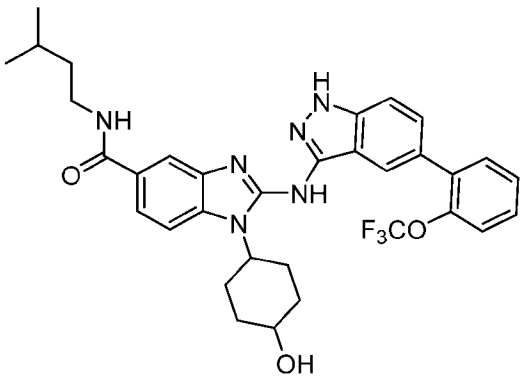
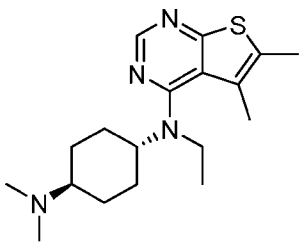


, and

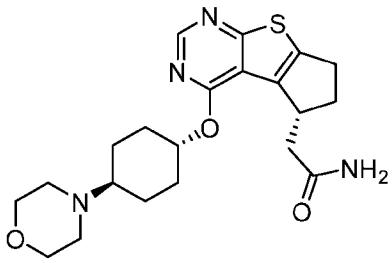
22

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

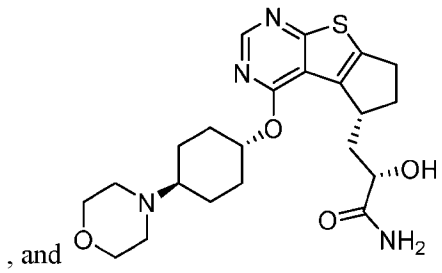
[00475] In some embodiments, IRAK is selected from a moiety recited in Kelly, P.N. *et al.*, *Selective interleukin-1 receptor-associated kinase 4 inhibitors for the treatment of autoimmune disorders and lymphoid malignancy*, J. Exp. Med., 2015, 212(13): 2189-201, such as, for example:



ND-1659



ND-2110

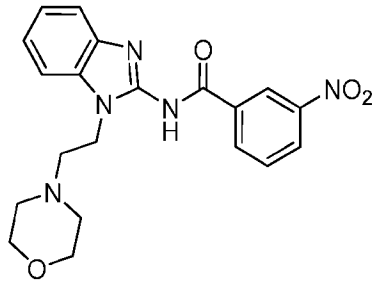


, and

ND-2158

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

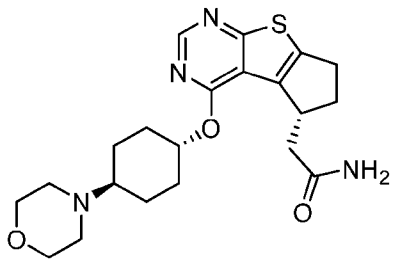
[00476] In some embodiments, IRAK is selected from a moiety recited in Dunne, A. *et al.*, *IRAK1 and IRAK4 Promote Phosphorylation, Ubiquitation, and Degradation of MyD88 Adaptor-like (Mal)*, J. Bio. Chem., 2010, 285(24): 18276-82, such as, for example:



IRAK1/4 inhibitor

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00477] In some embodiments, IRAK is selected from a moiety recited in Küppers, R., *IRAK inhibition to shut down TLR signaling in autoimmunity and MyD88-dependent lymphomas*, J. Exp. Med, 2015, 212(13): 2184, such as, for example:



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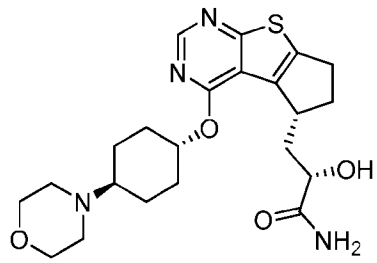
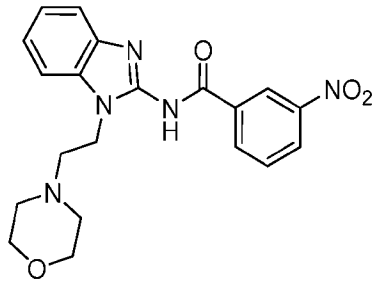


ND-2110 ND-2158

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

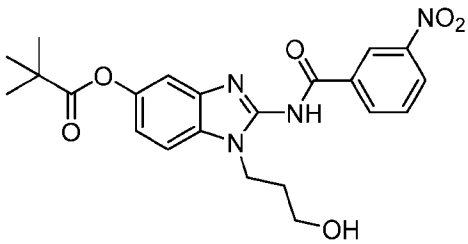
[00478] In some embodiments, IRAK is selected from a moiety recited in Chiang, E.Y. *et al.*, *Immune Complex-Mediated Cell Activation from Systemic Lupus Erythematosus and Rheumatoid Arthritis Patients Elaborate Different Requirements for IRAK1/4 Kinase Activity across human Cell Types*, J. Immunol., 2011, 186(2): 1279-88, such as, for example:



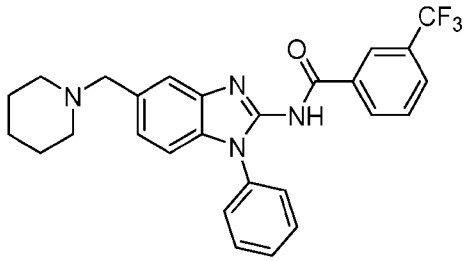
IRAK1/4 inhibitor

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00479] In some embodiments, IRAK is selected from a moiety recited in Lee, K.L. *et al.*, *Discovery of Clinical Candidate 1-{[2S,3S,4S)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoine-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 9IRAK4), by Fragment-Based Drug Design*, J. Med. Chem., 2017, 60(13): 5521-42, such as, for example:



Amgen 1



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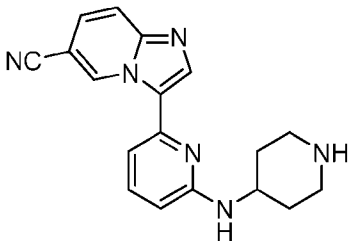

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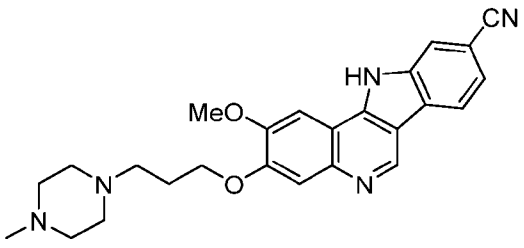

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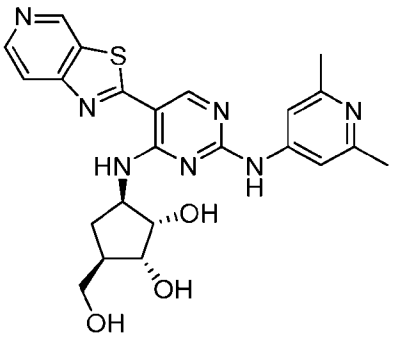

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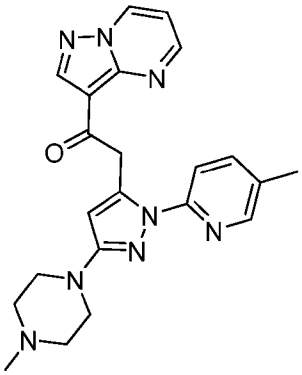

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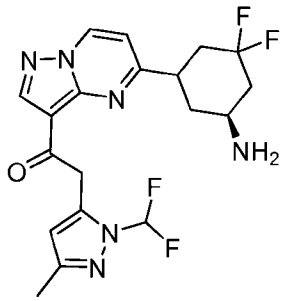

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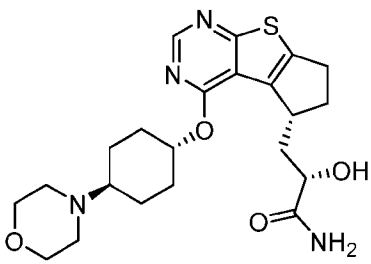
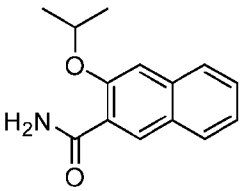


Nimbus 8



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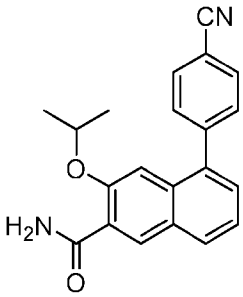

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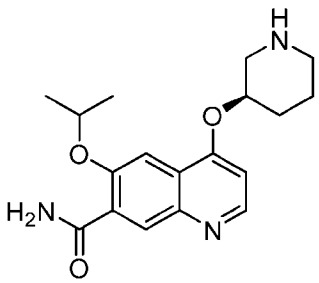

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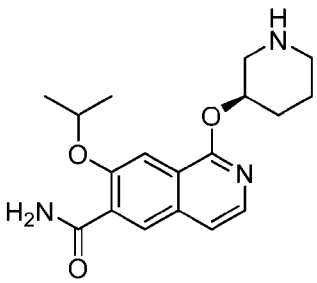

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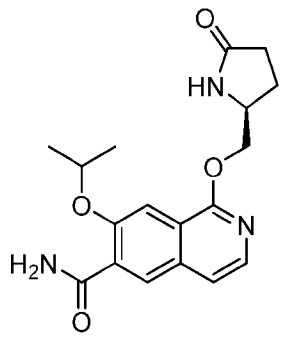

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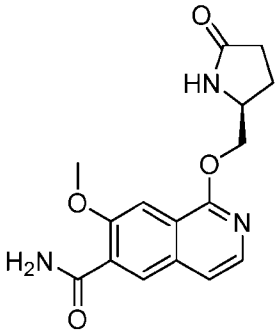

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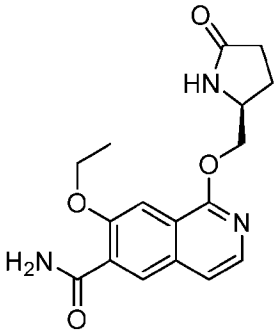

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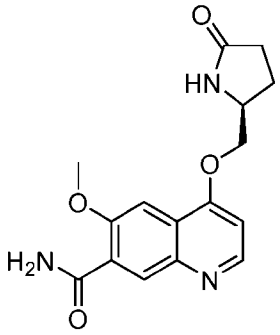

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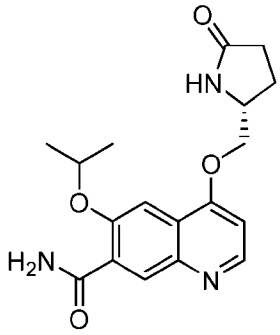

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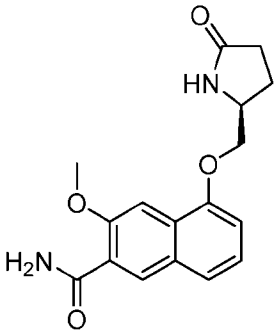

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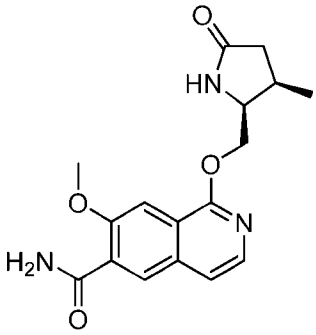

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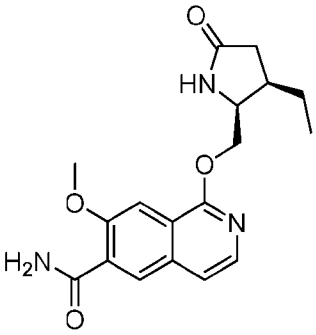

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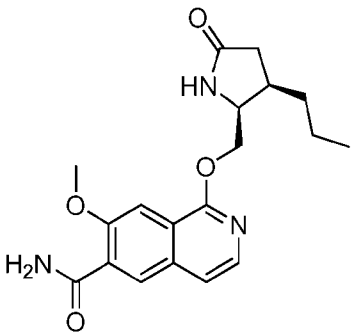

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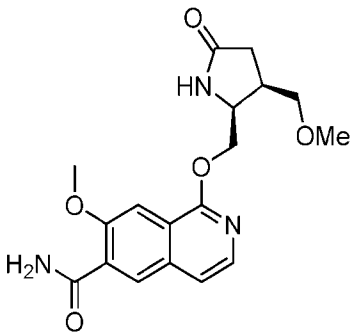

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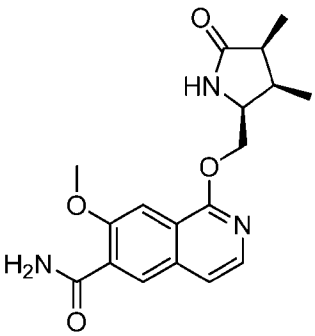

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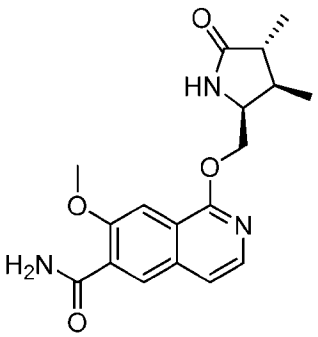

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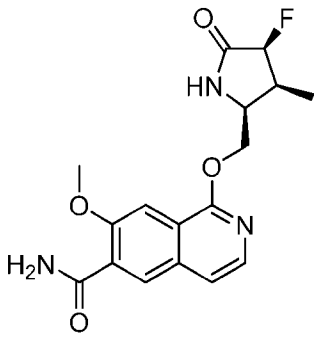

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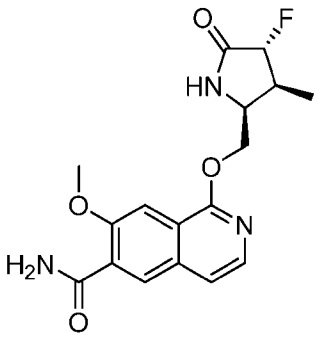

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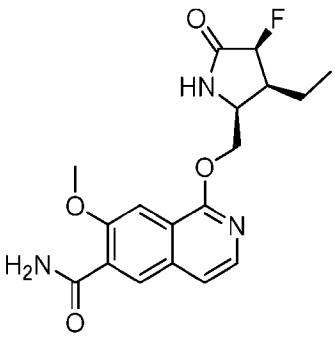

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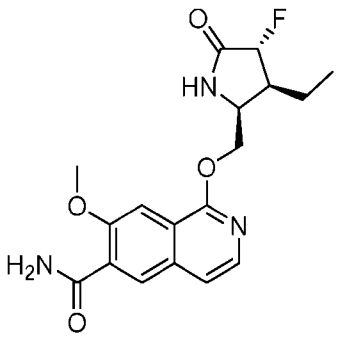

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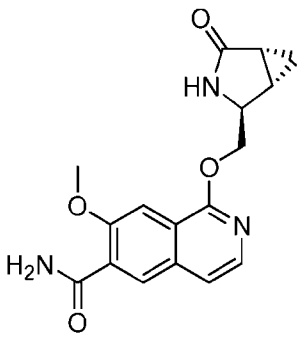

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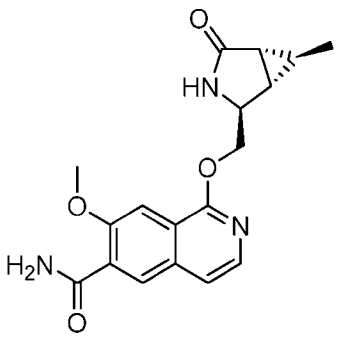

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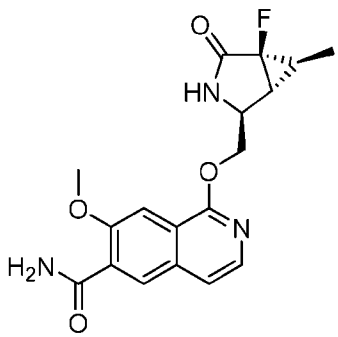
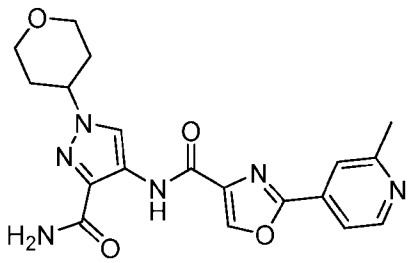


50

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00480] In some embodiments, IRAK is selected from a moiety recited in Kondo, M. *et al.*, *Renoprotective effects of novel interleukin-1 receptor-associated kinase 4 inhibitor AS2444697 through anti-inflammatory action in 5/6 nephrectomized rats*, Naunyn-Schmiedeberg's Arch Pharmacol., 2014, 387(10): 909-19, such as, for example:



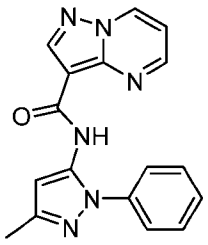
AS2444697

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00481] In some embodiments, IRAK is selected from a moiety recited in Song, K.W. *et al.*, *The Kinase activities of interleukin-1 receptor associated kinase (IRAK)-1 and 4 are redundant in the control of inflammatory cytokine expression in human cells*, Mol. Immunol., 2009, 46(7): 1458-66, such as, for example: RO0884, RO1679, or RO6245, wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00482] In some embodiments, IRAK is selected from a moiety recited in Vollmer, S. *et al.*, *The mechanism of activation of IRAK1 and IRAK4 by interleukin-1 and Toll-like receptor agonists*, Biochem. J., 2017, 474(12): 2027-38, such as, for example: IRAK-IN-1A, JNK-IN-7, and JNK-IN-8, wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00483] In some embodiments, an IRAK ligand is selected from moiety recited in McElroy, W.T., *et al.*, *Potent and Selective Amidopyrazole Inhibitors of IRAK4 That Are Efficacious in a Rodent Model of Inflammation*, Med. Chem. Lett., 2015, 6(6): 677-82, such as, for example:



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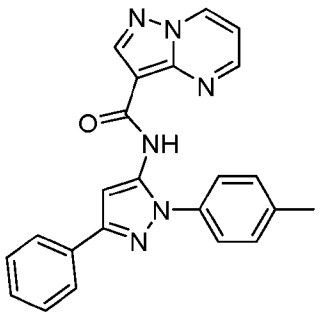

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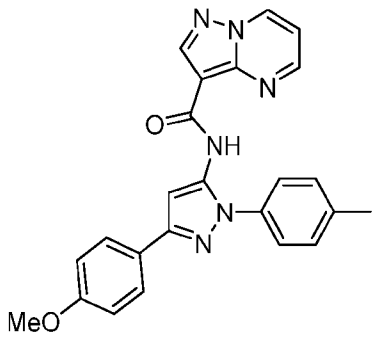

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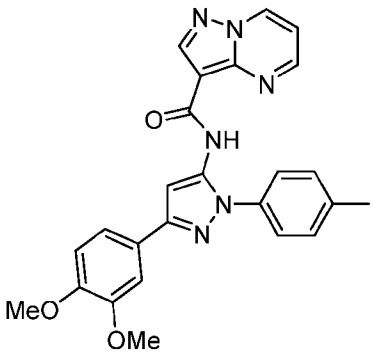

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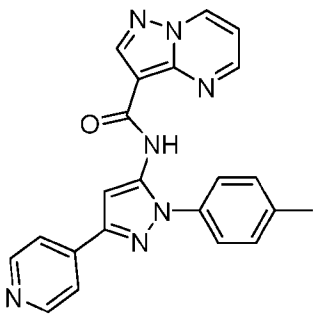

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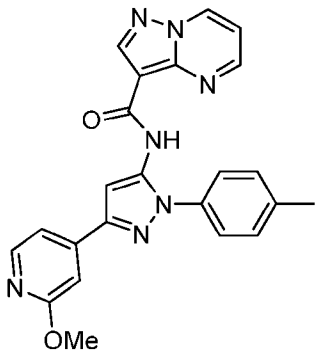

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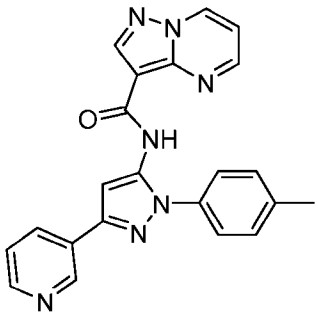

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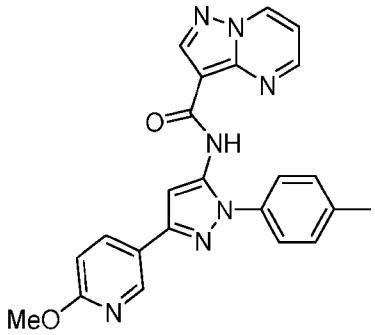

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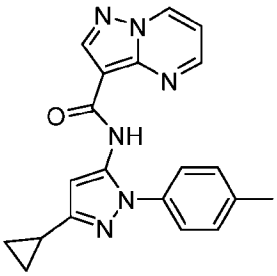

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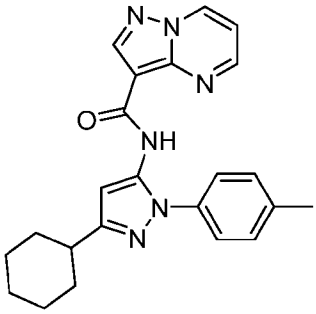

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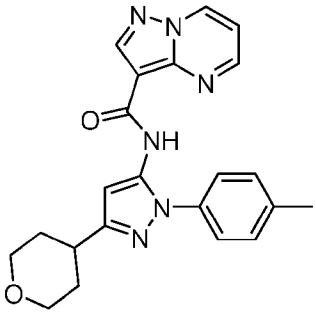

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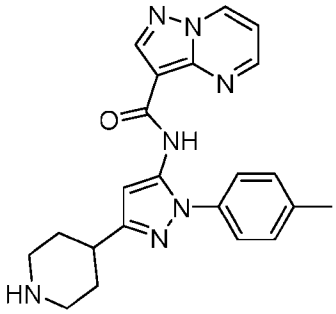

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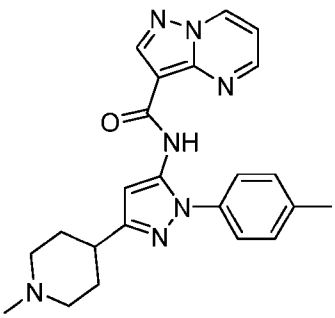

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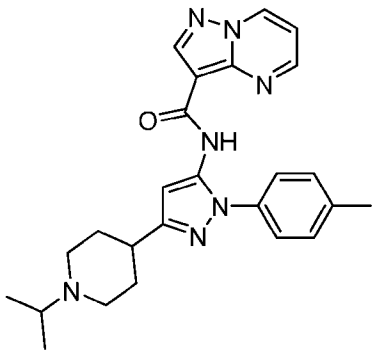

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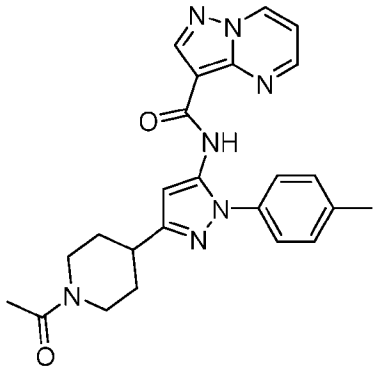

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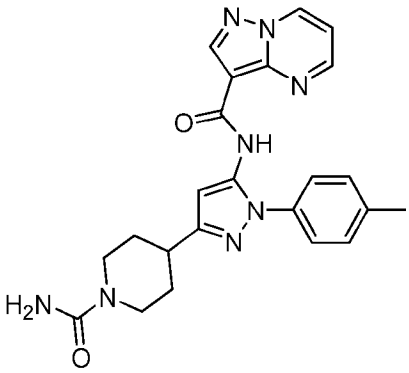

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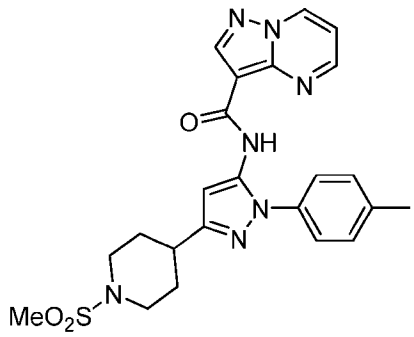

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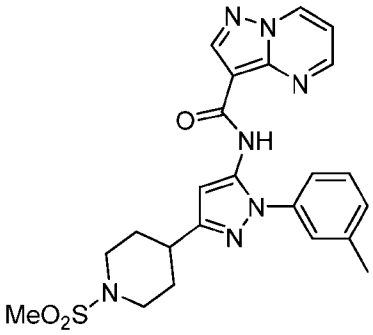

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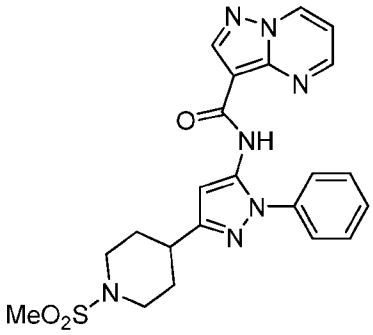

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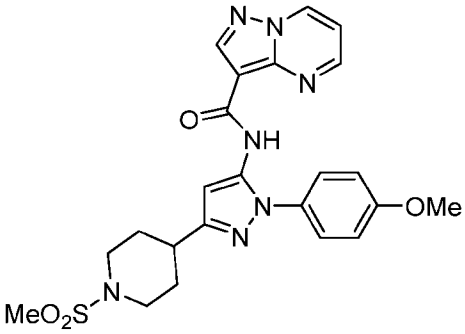

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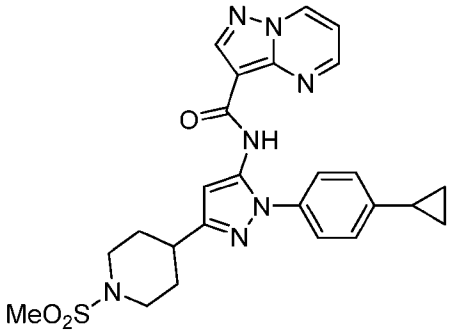

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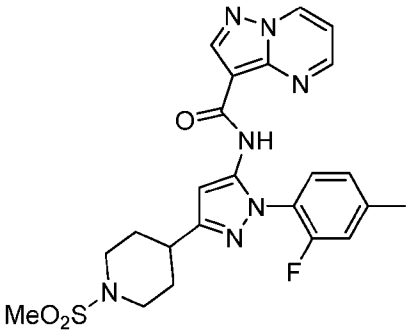

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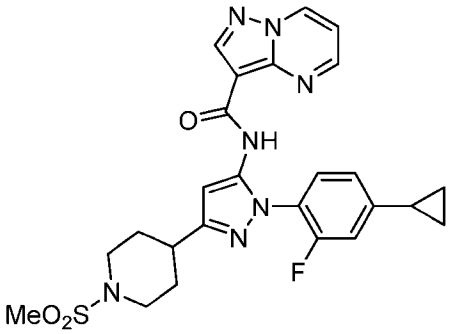

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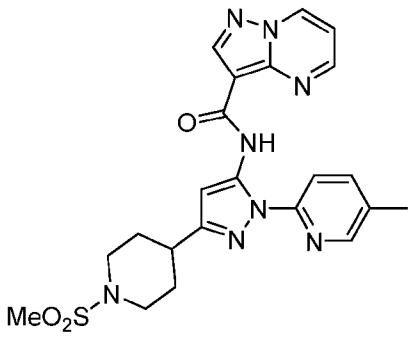

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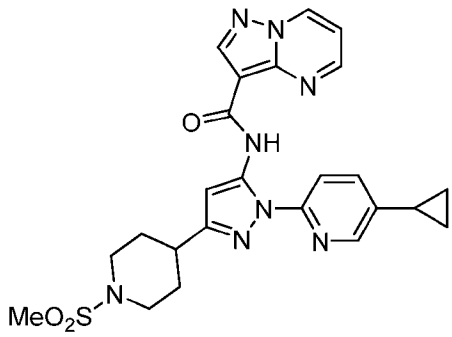

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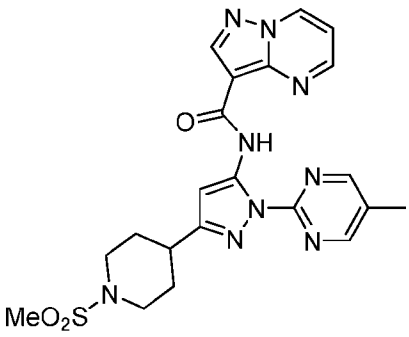

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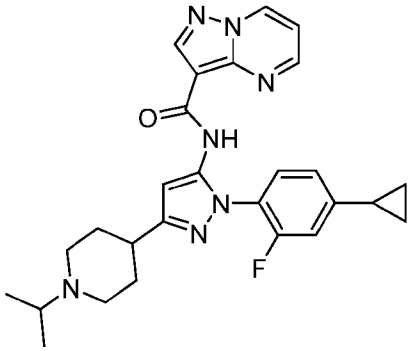

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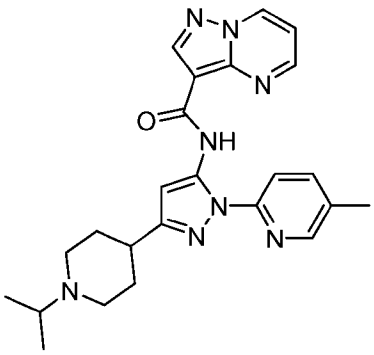

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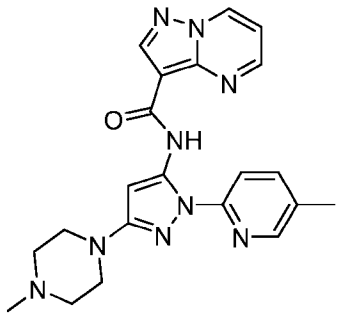

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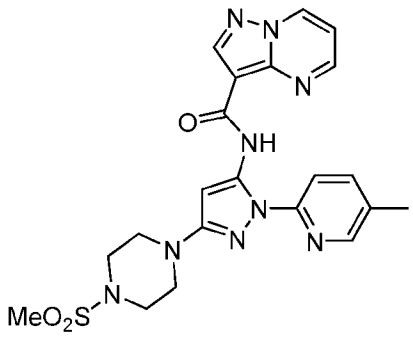

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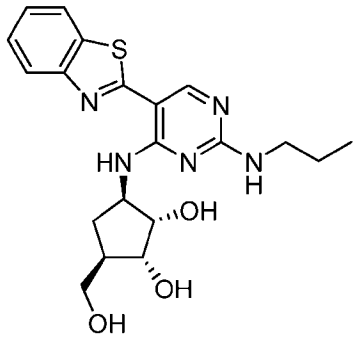
wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00484] In some embodiments, an IRAK ligand is selected from moiety recited in Seganish, W.M., *et al*., *Discovery and Structure Enabled Synthesis of 2,6-diaminopyrimidine-4-one IRAK4 Inhibitors*, Med. Chem. Lett., 2015, 6(8): 942-47, such as, for example:



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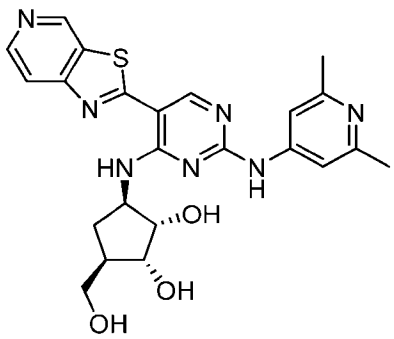

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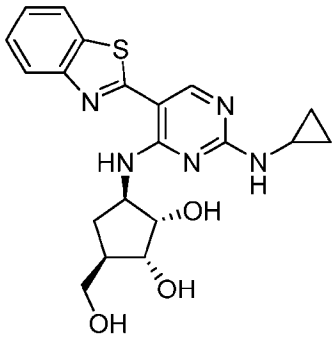

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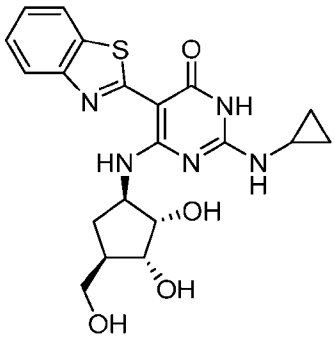

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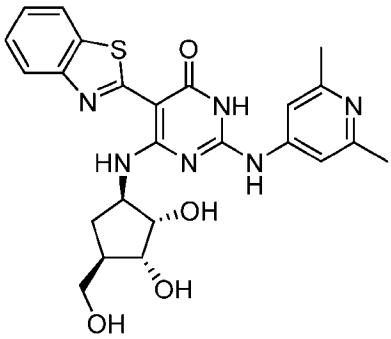

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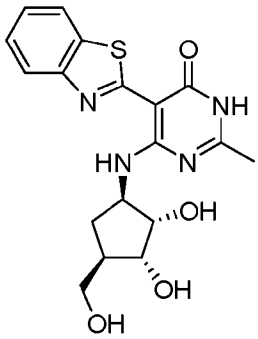

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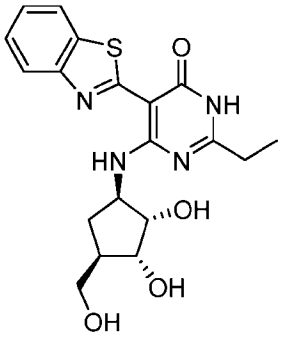

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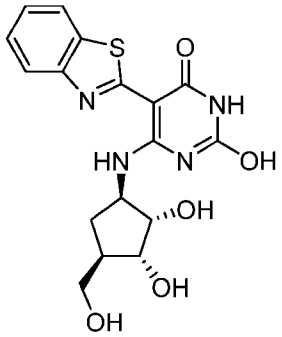

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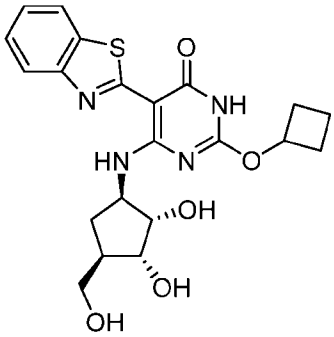

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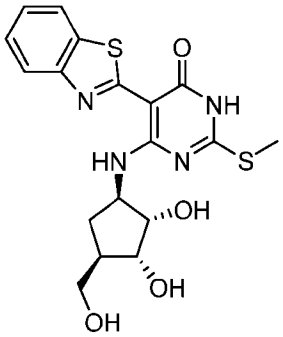

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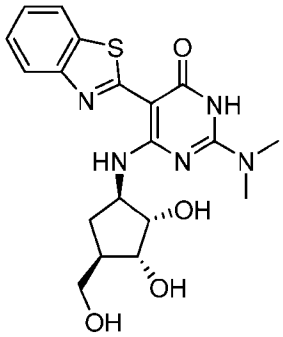

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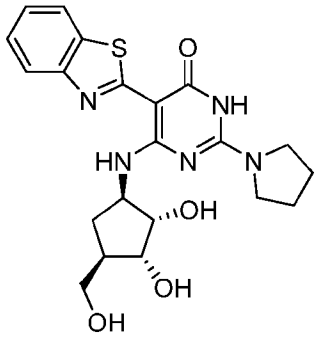

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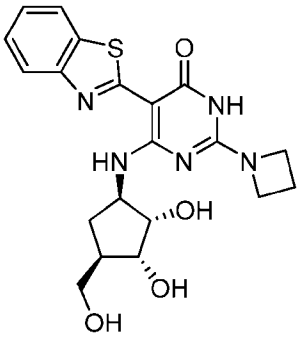

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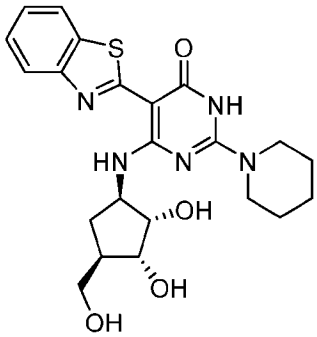

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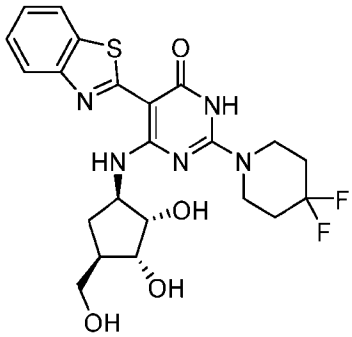

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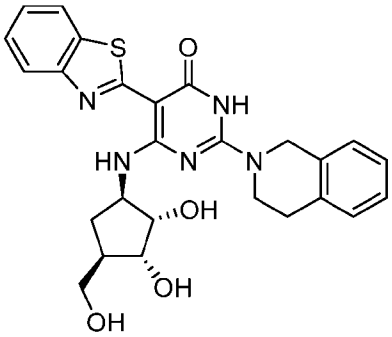

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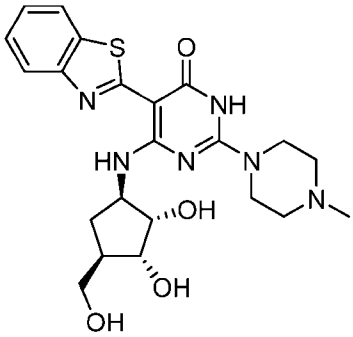

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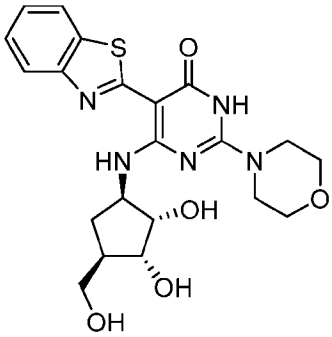

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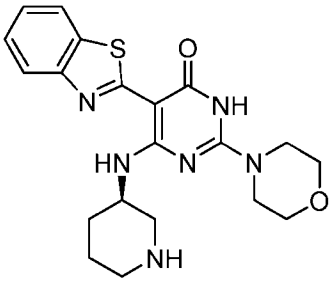

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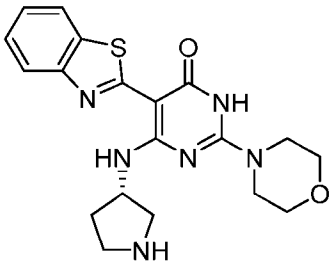

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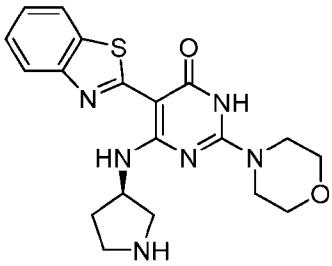

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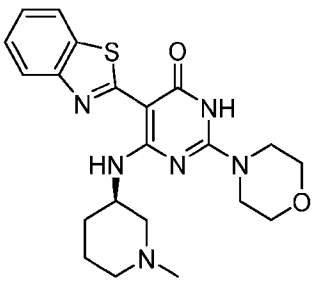

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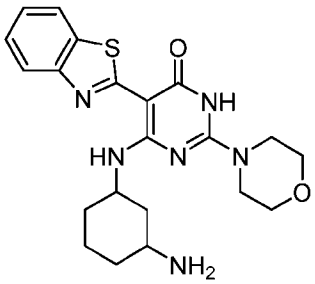

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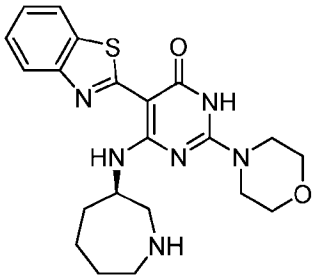

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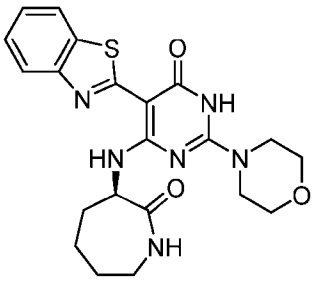

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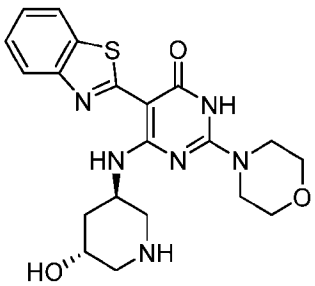

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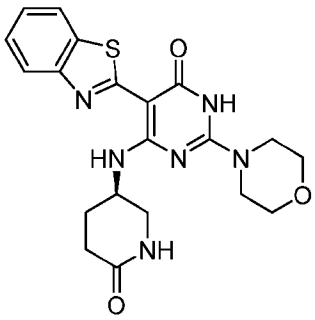

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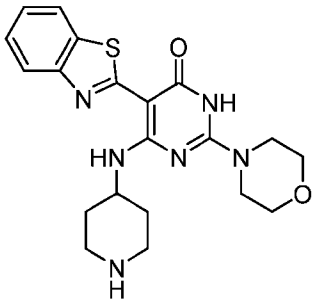

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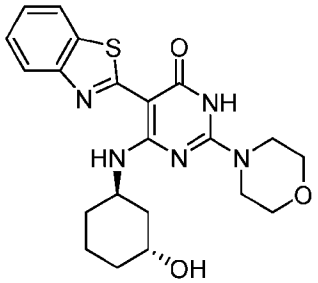

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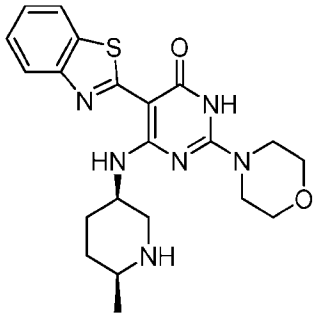

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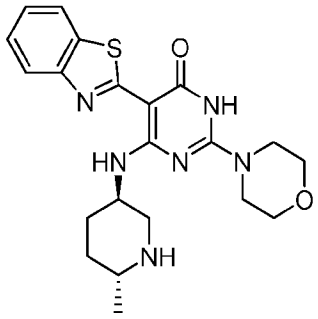

, and

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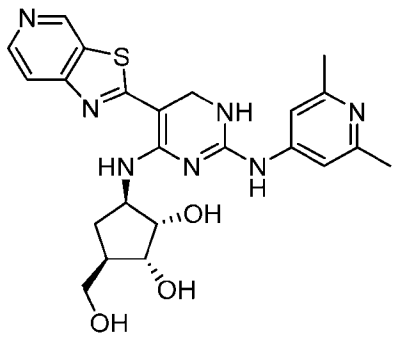
wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00485] In some embodiments, an IRAK ligand is selected from moiety recited in Seganish, W.M., *et al*., *Initial optimization and series evolution of diaminopyrimidine inhibitors of interleukin-1 receptor associated kinase 4*, Bioorg. Med. Chem. Lett., 2015, 25(16): 3203-207, such as, for example:



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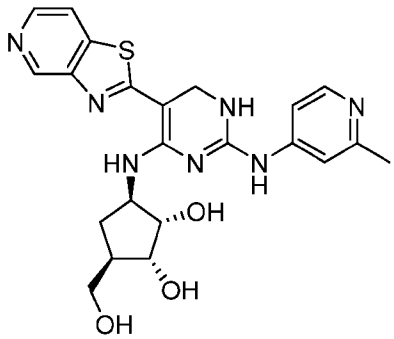

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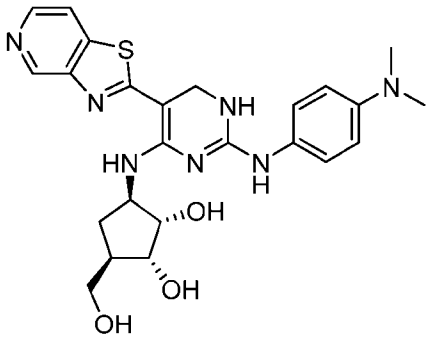

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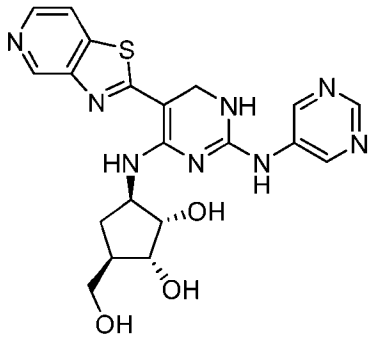

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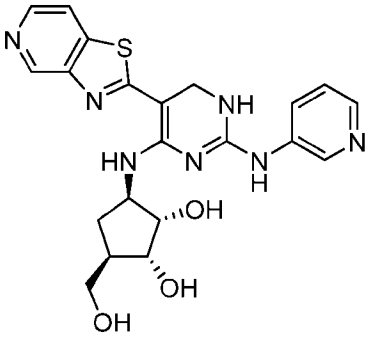

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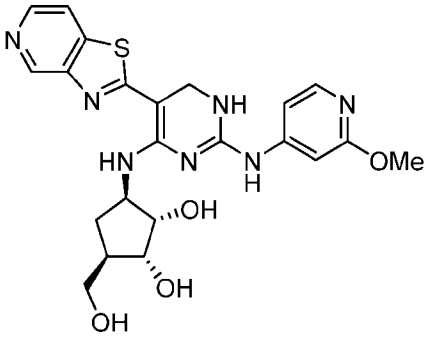

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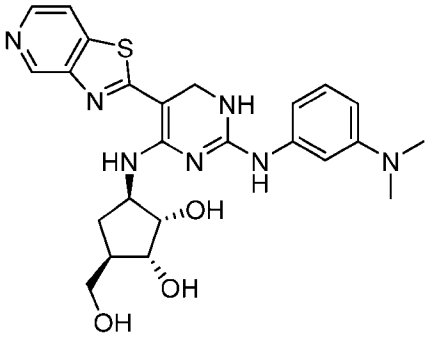

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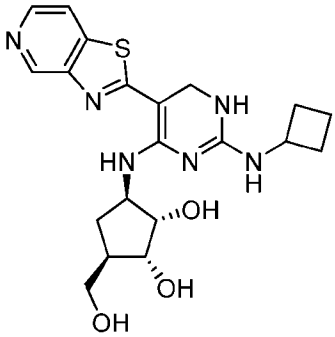

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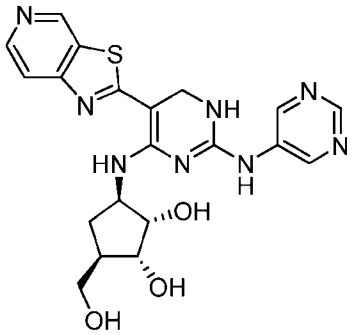

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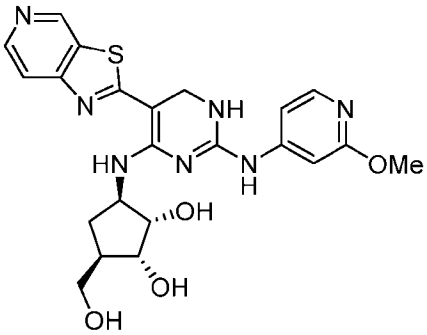

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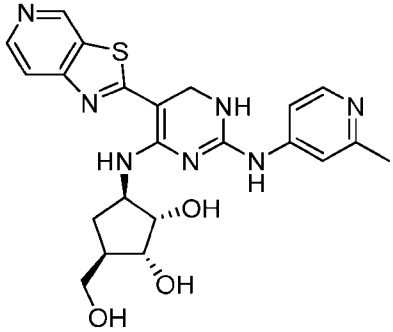

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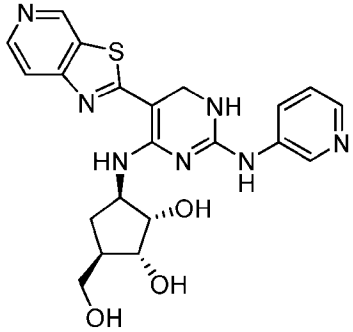

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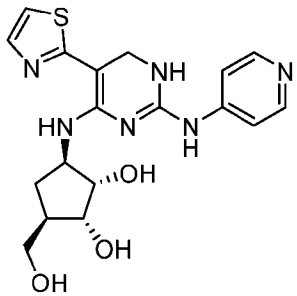

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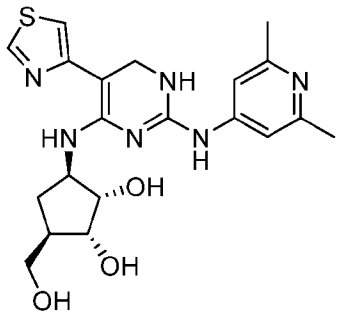

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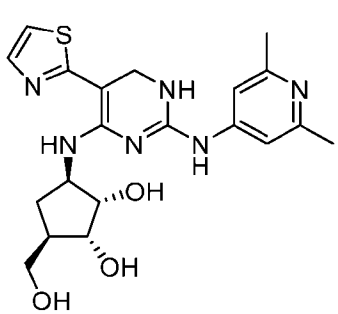

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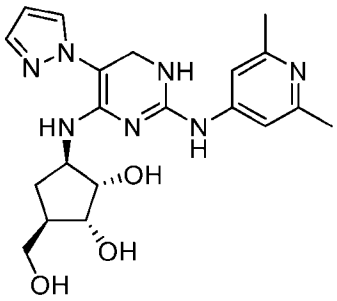

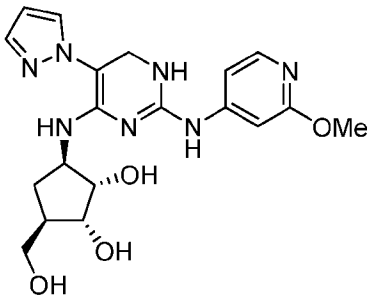

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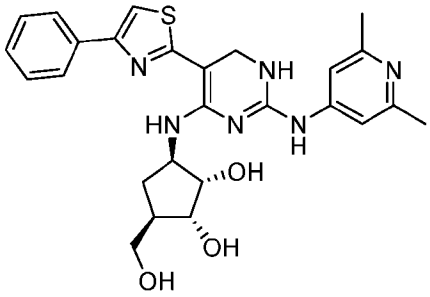

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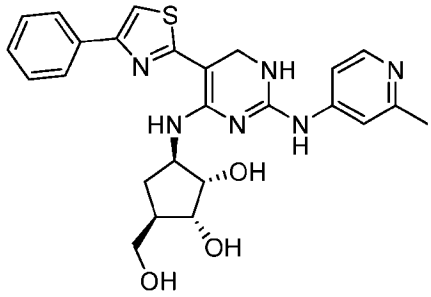

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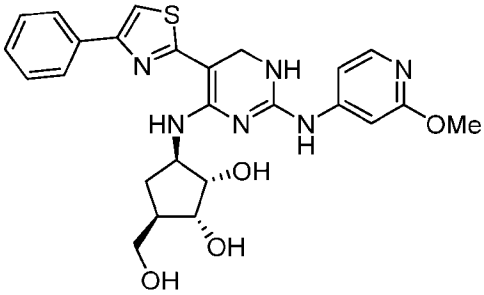

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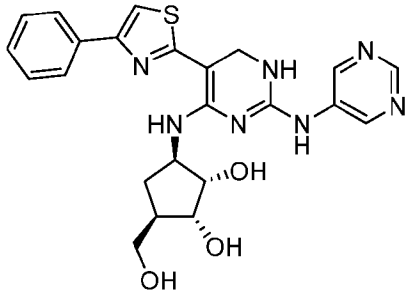

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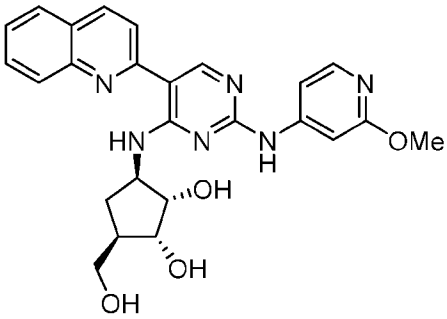

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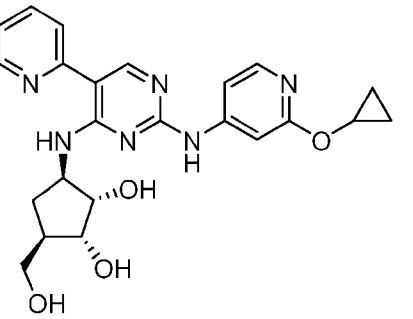

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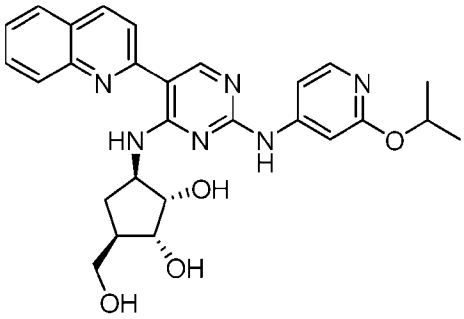

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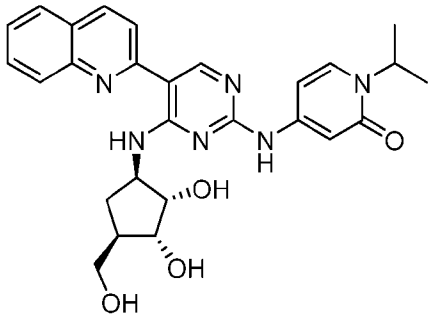

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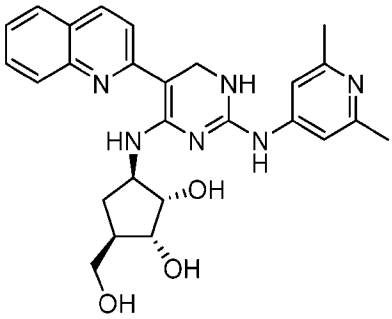

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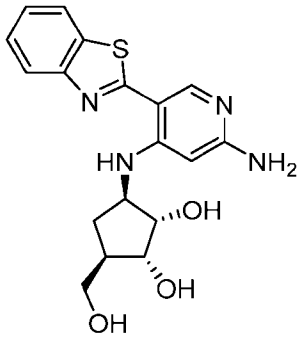

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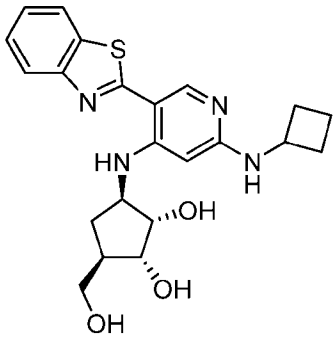

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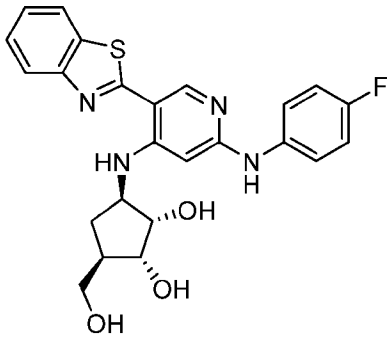

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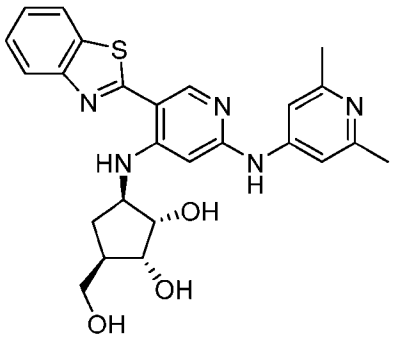

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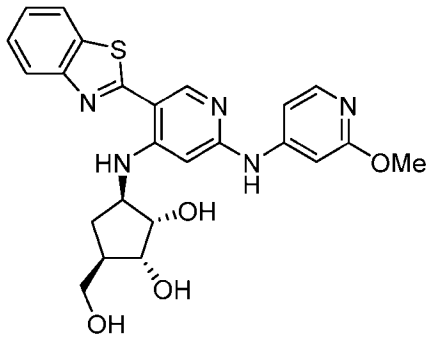

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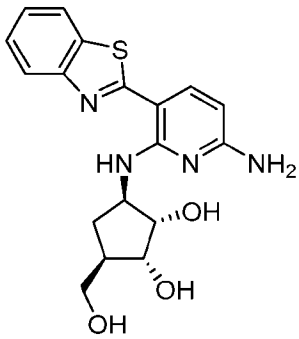

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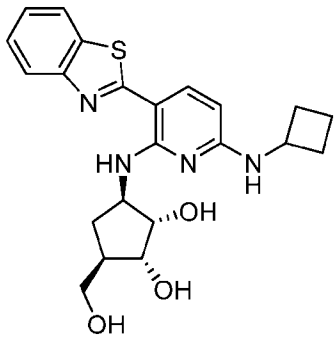
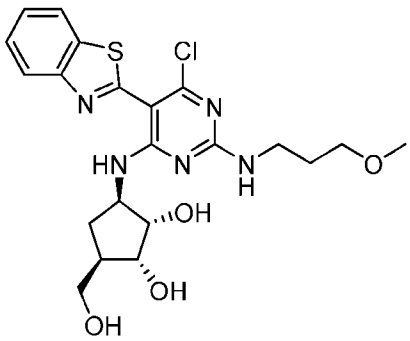


33

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00486] In some IRAK ligand is selected from moiety recited in McElroy, W.T., *et al*., *Discovery and hit-to-lead optimization of 2,6-diaminopyrimidine Inhibitors of interleukin-1 receptor-associated kinase 4*, Bioorg. Med. Chem. Lett., 2015, 25(9): 1836-41, such as, for example:



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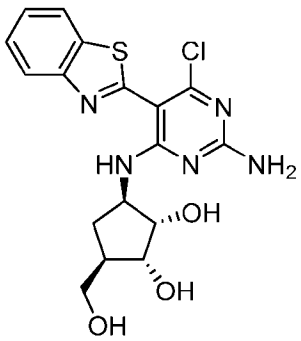

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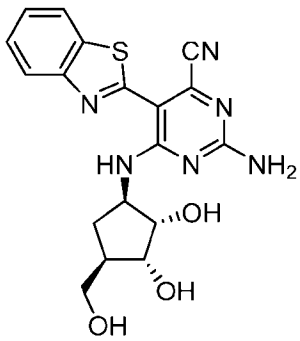

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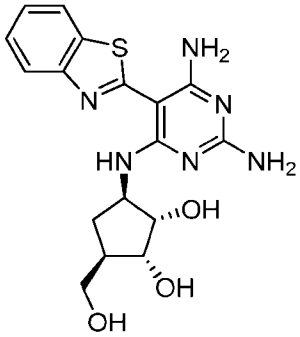

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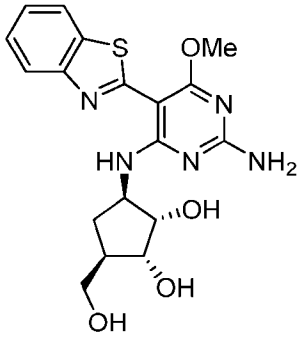

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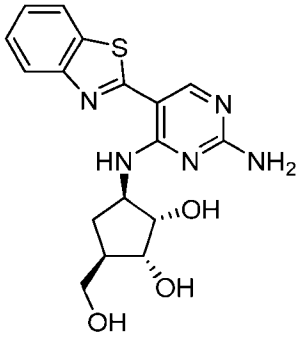

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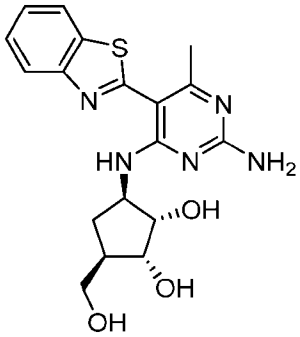

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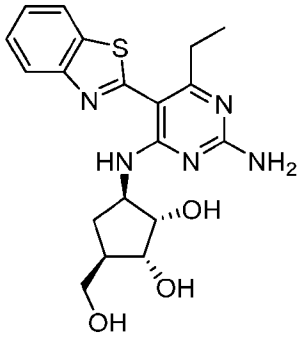

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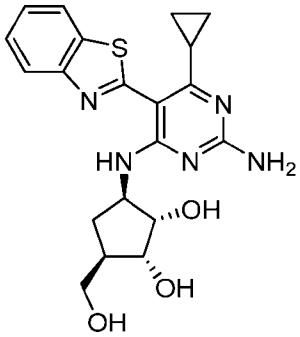

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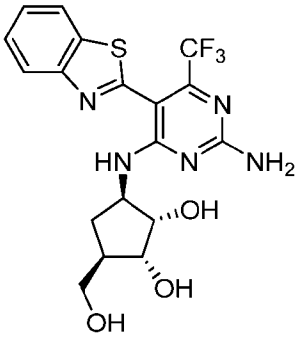

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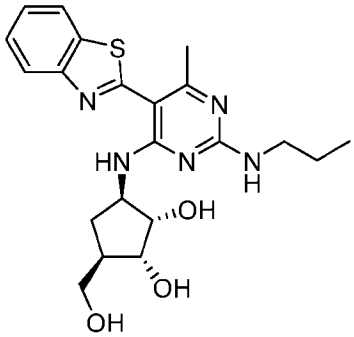

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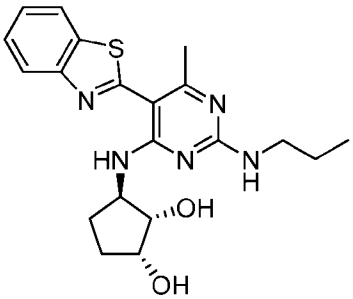

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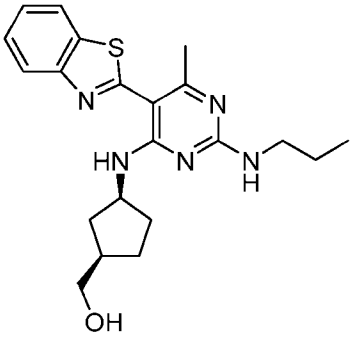

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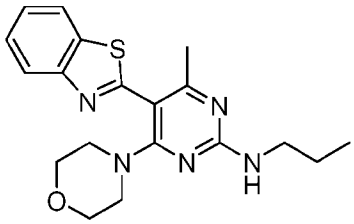

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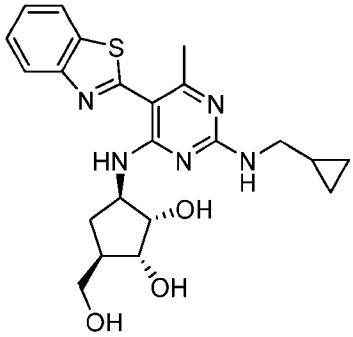

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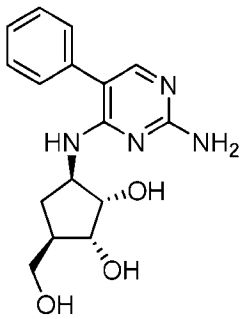

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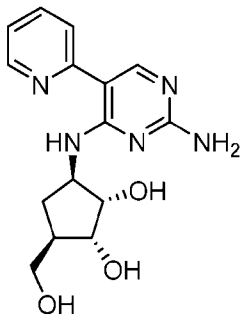

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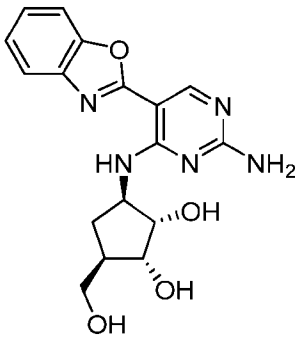

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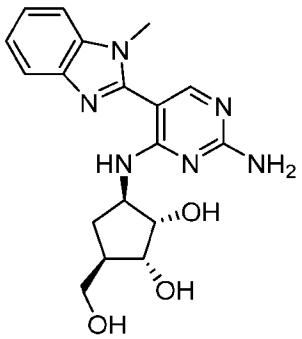

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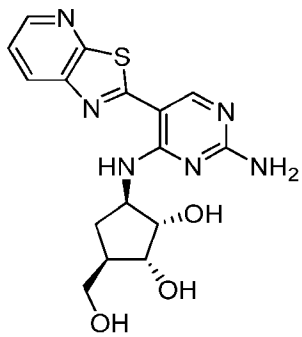

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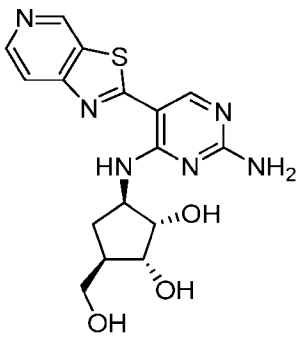

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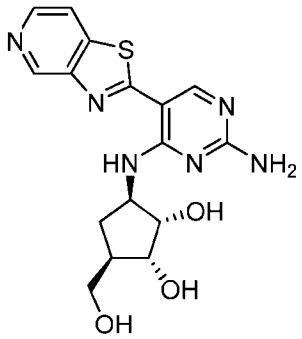
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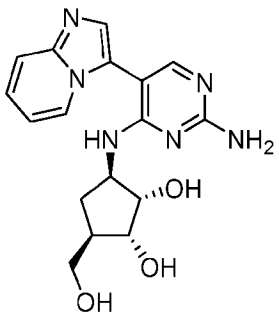
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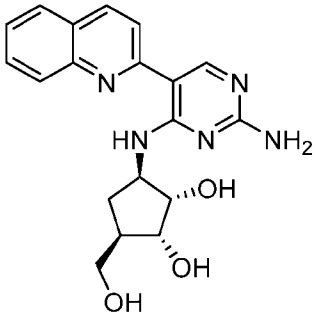
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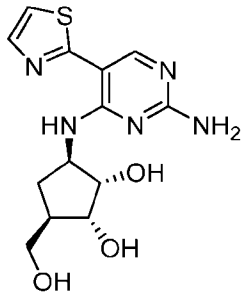
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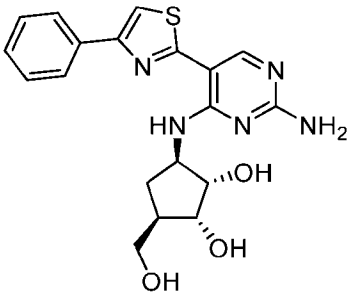
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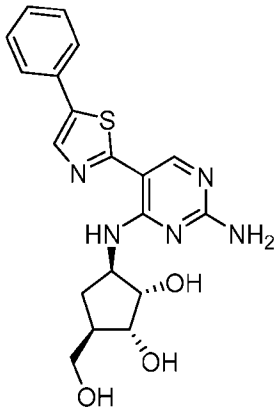
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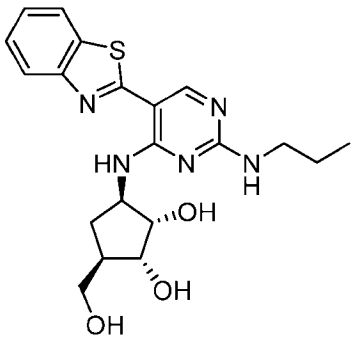
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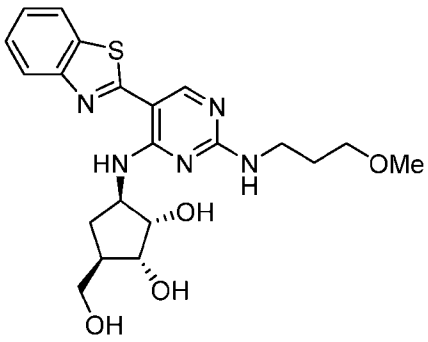
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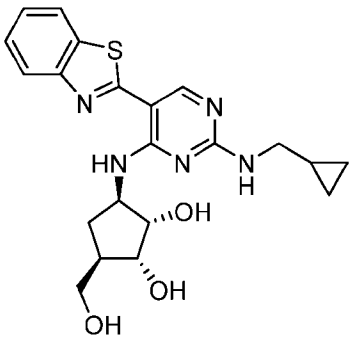
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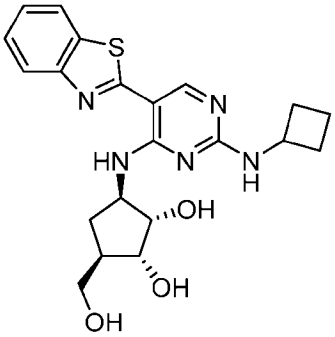

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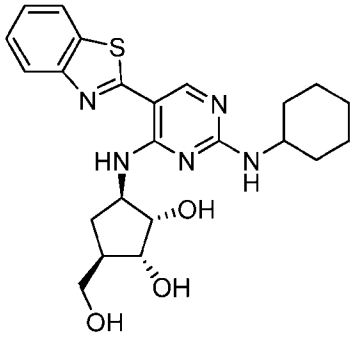

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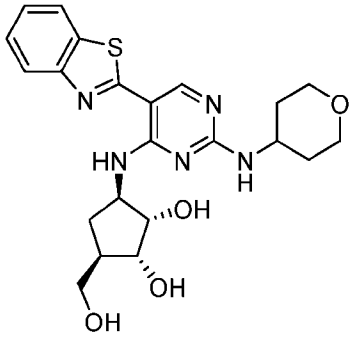

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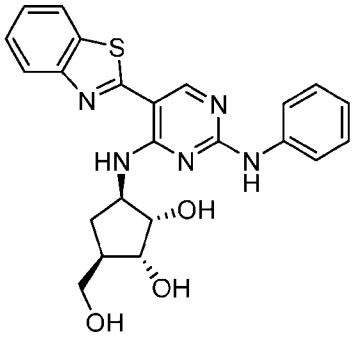

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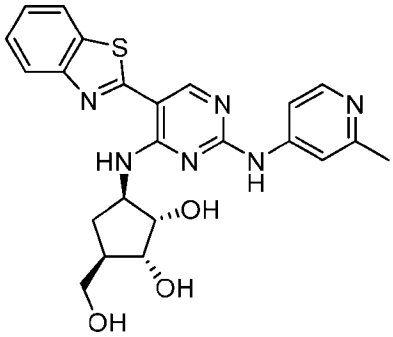

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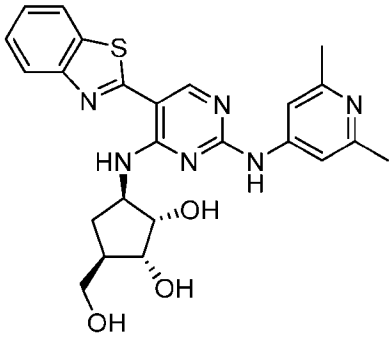

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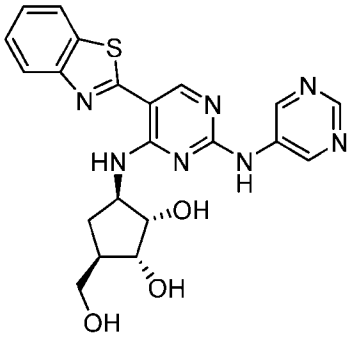

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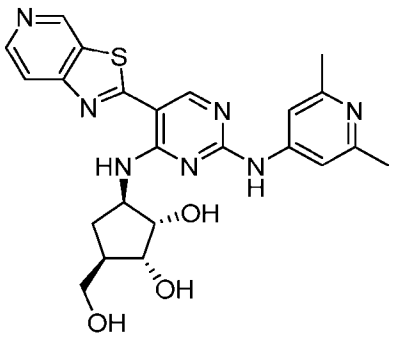
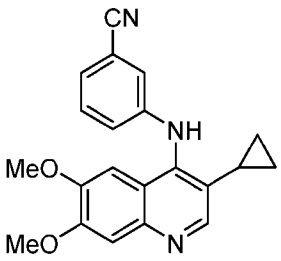


, and

38

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00487] In some embodiments, an IRAK ligand is selected from moiety recited in Tumey, L.N., *et al.*, *Identification and optimization of indolo[2,3-c]quinoline inhibitors of IRAK4*, Bioorg. Med. Chem. Lett., 2014, 24(9): 2066-72, such as, for example:



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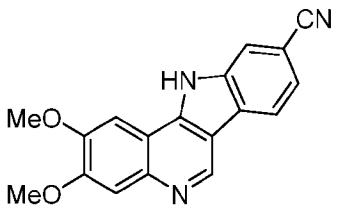

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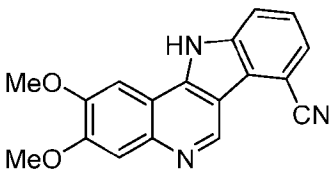

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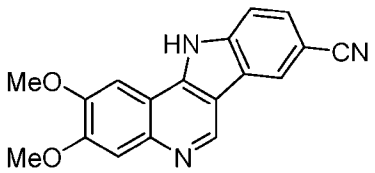

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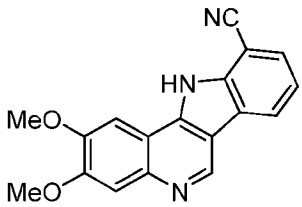

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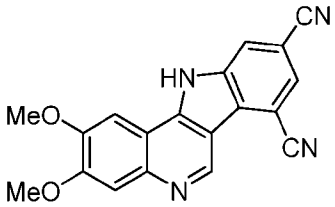

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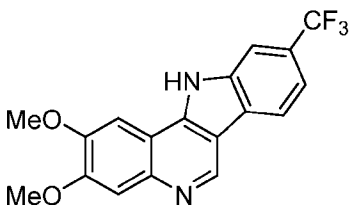

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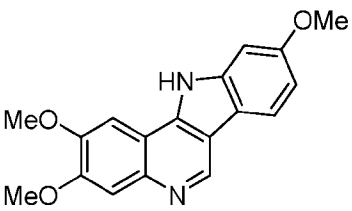

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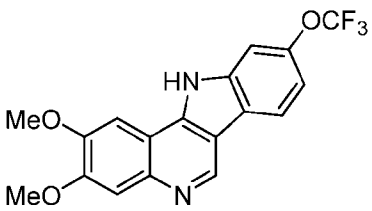

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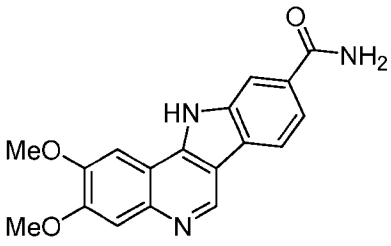

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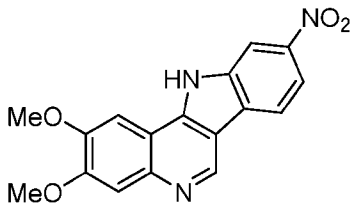

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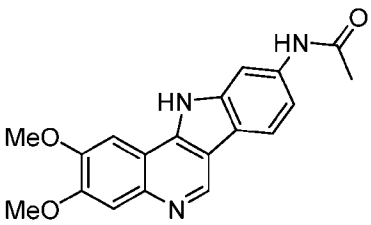

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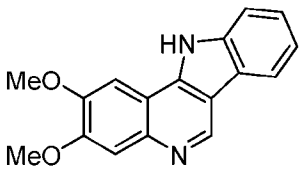

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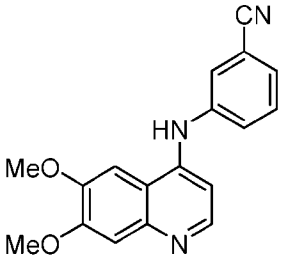

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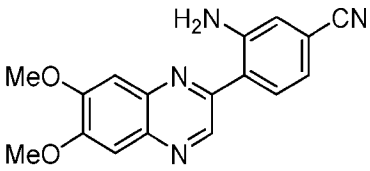

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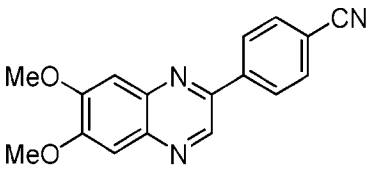

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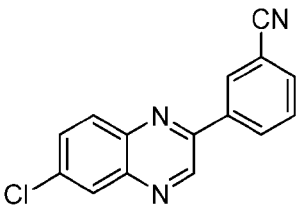

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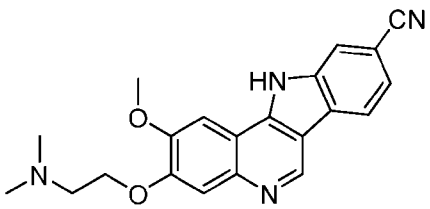

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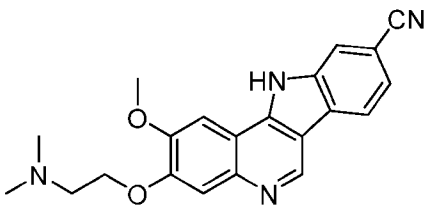

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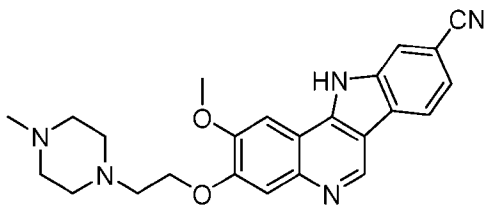

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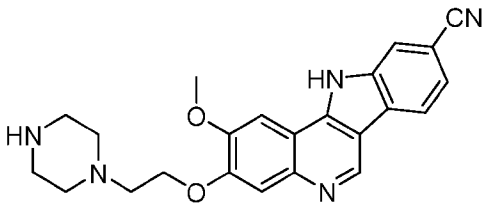

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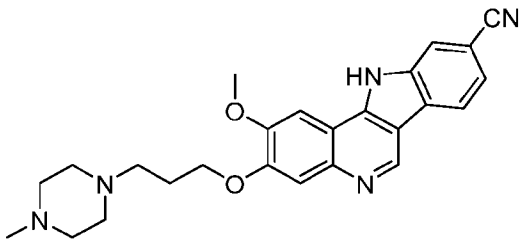

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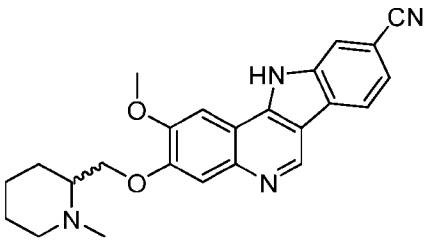

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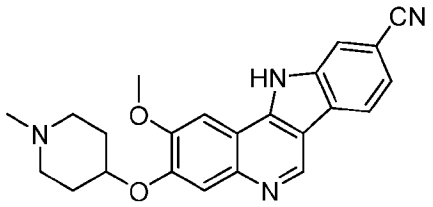

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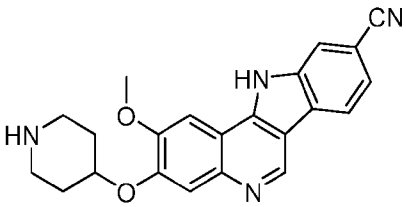

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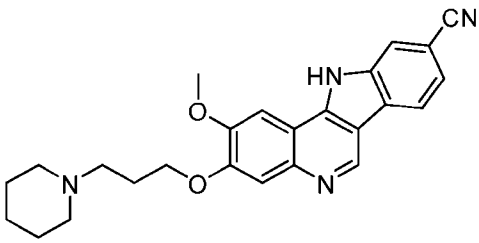
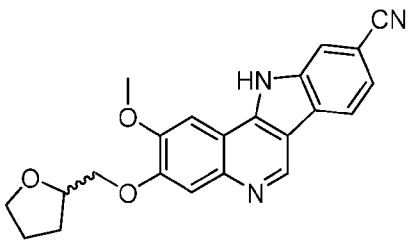
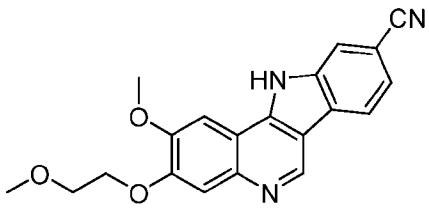


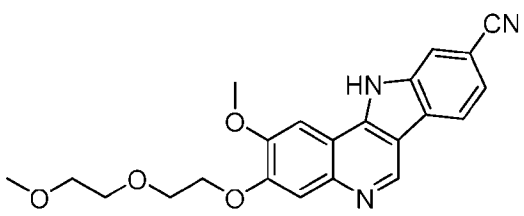
29 (sic)



30 (sic)

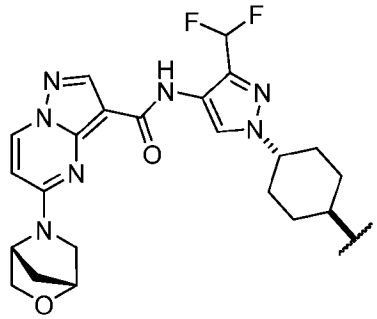
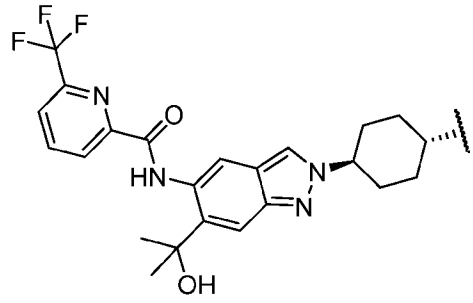
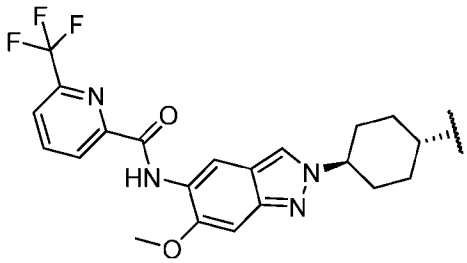
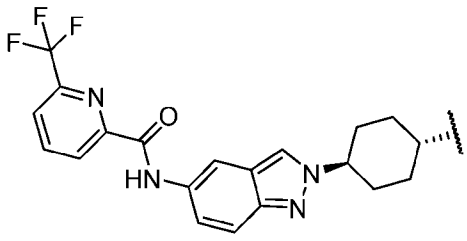
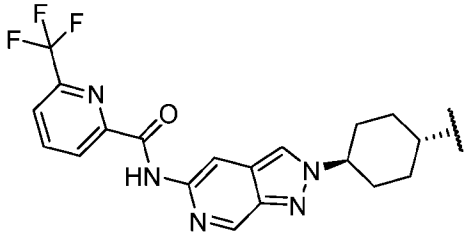
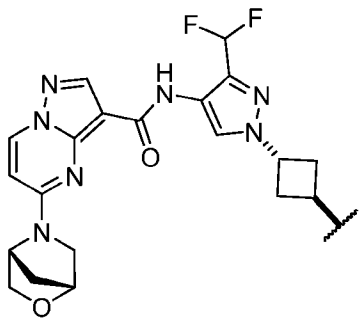


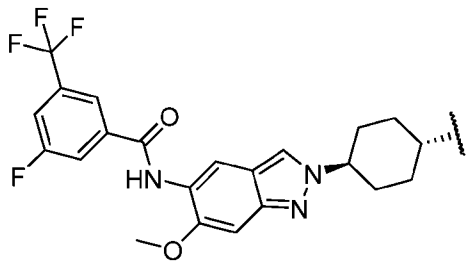
31 (sic)

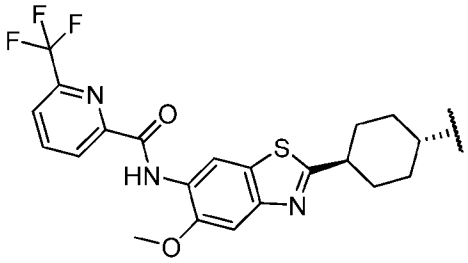
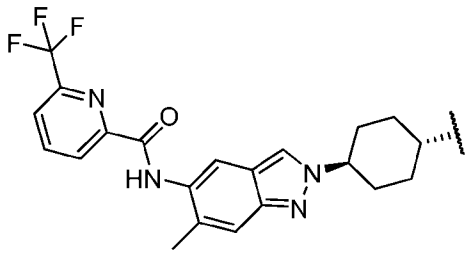
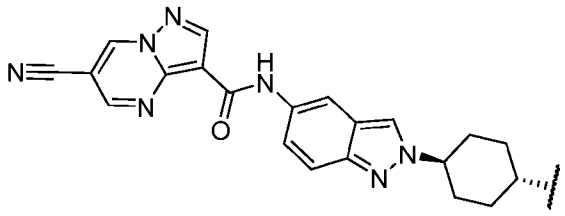
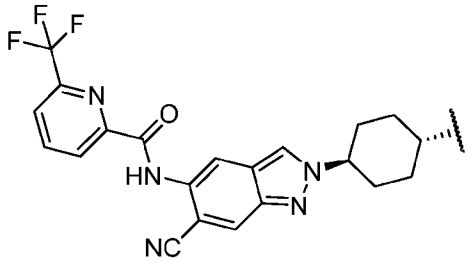
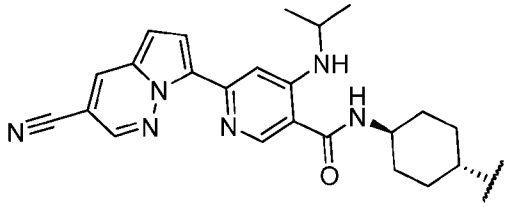
, and 

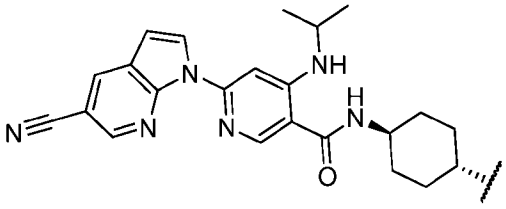
32 (sic)

wherein -L-DBM is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

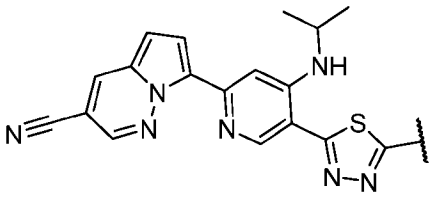
[00488] In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  .



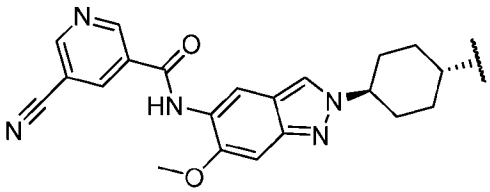
. In some embodiments, IRAK is . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is



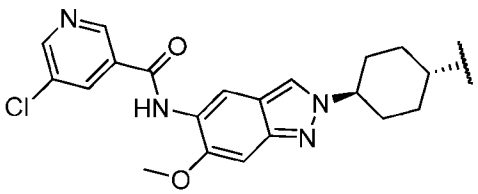
. In some embodiments, IRAK is



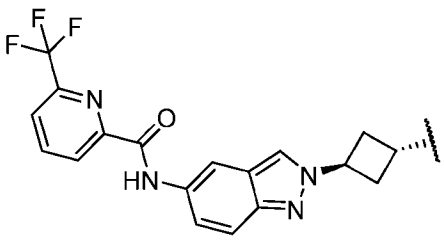
. In some embodiments, IRAK is



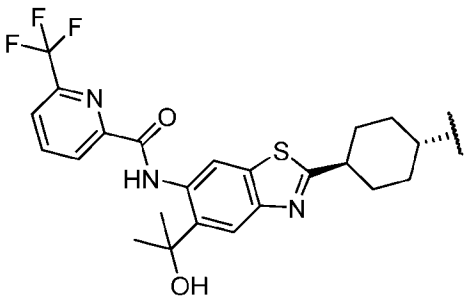
. In some embodiments, IRAK is



. In some embodiments, IRAK is



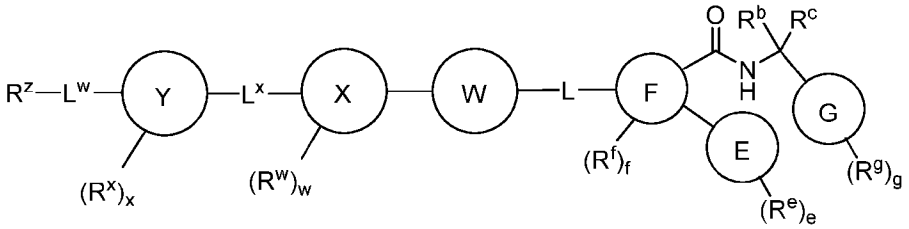
. In some embodiments, IRAK is



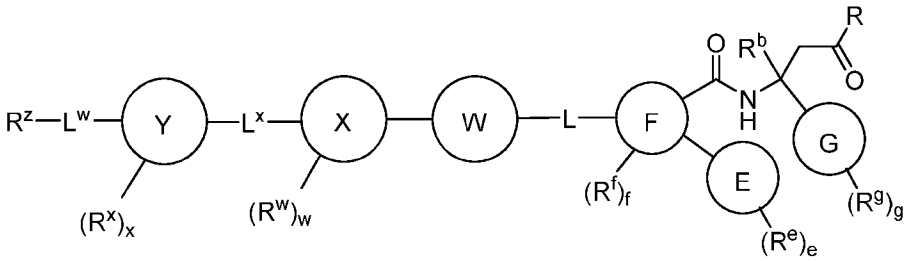
.

[00489] In some embodiments, IRAK is selected from those depicted in **Table 1**, below.

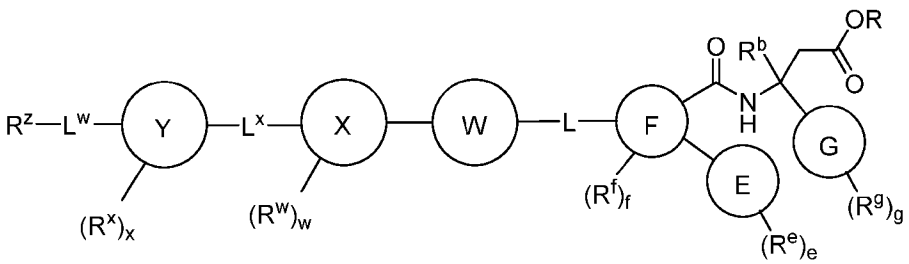
[00490] In some embodiments, the present invention provides a compound of any one of the following formulae:



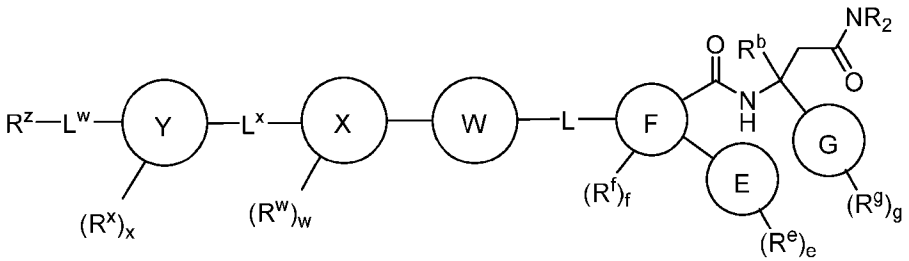
I-aa-10



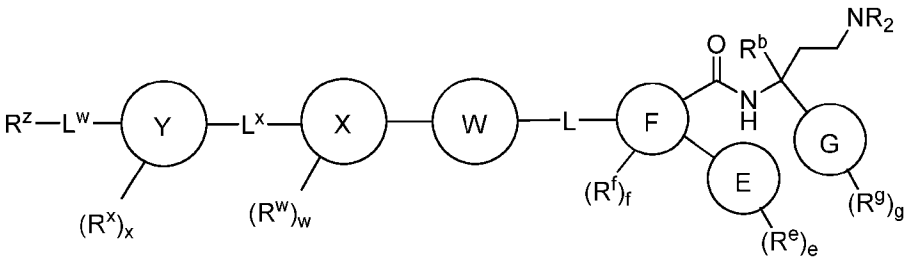
I-aa-11



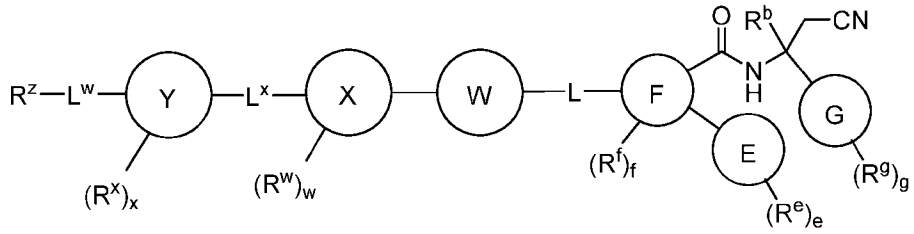
I-aa-12



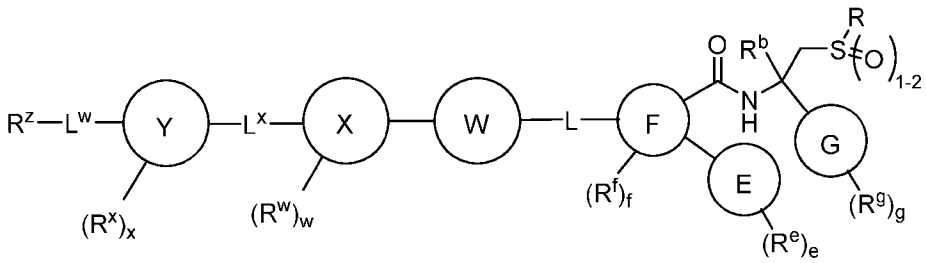
I-aa-13



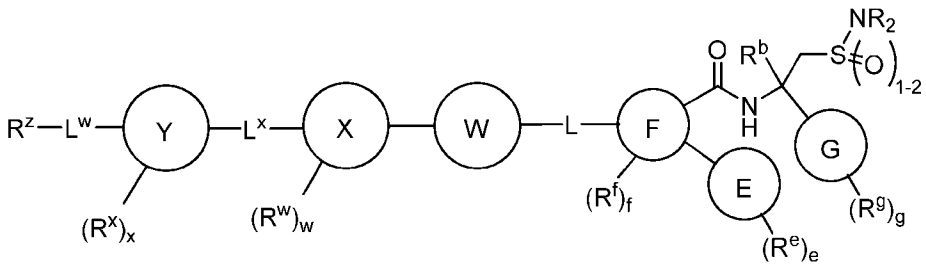
I-aa-14



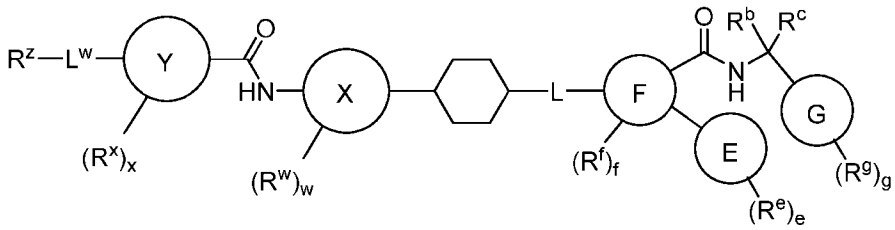
I-aa-15



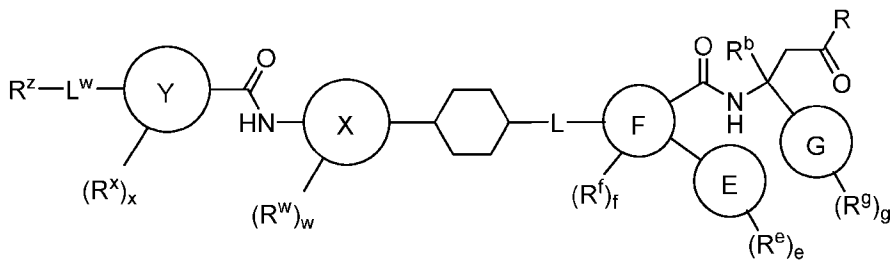
I-aa-16



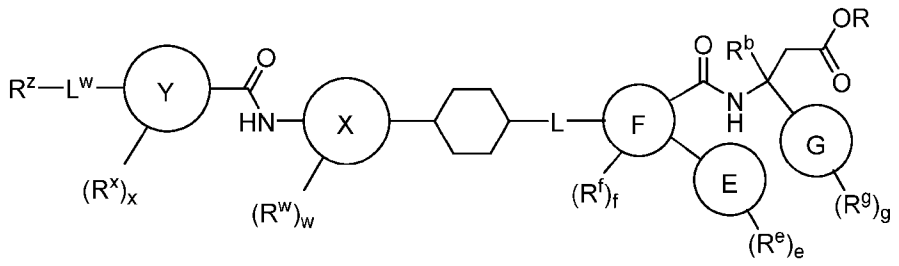
I-aa-17



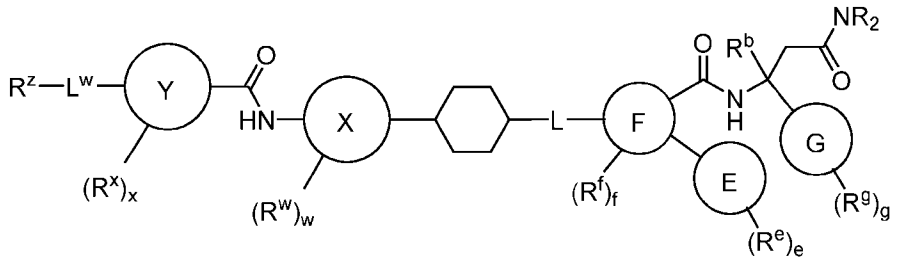
I-aa-18



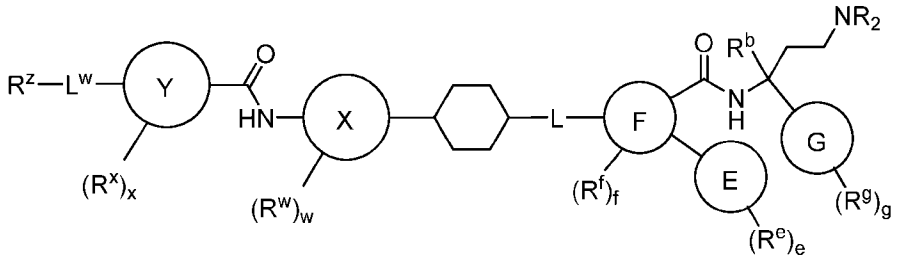
I-aa-19



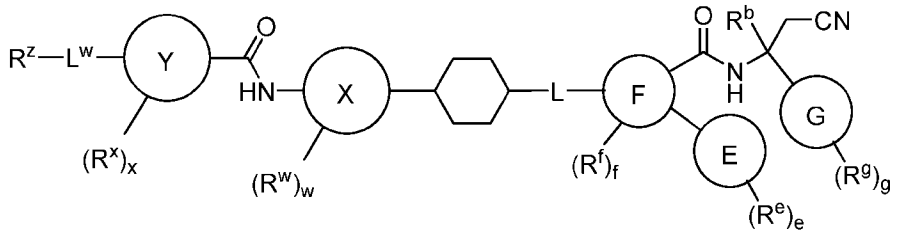
I-aa-20



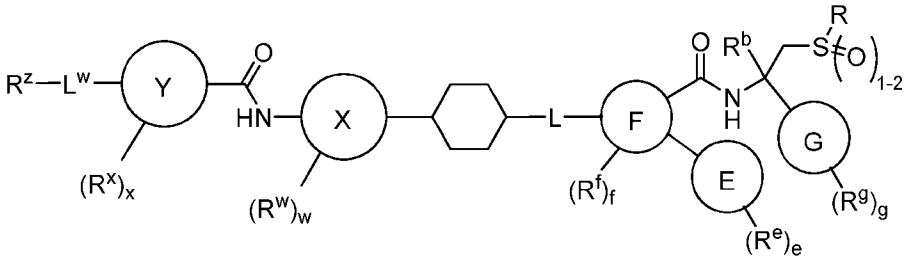
I-aa-21



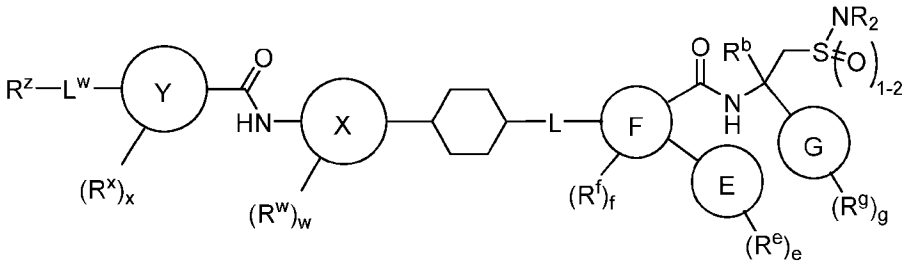
I-aa-22



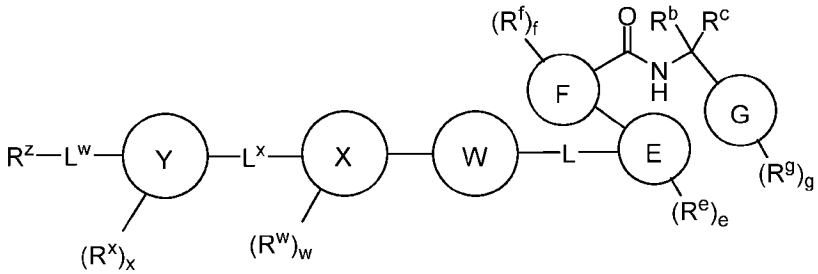
I-aa-23



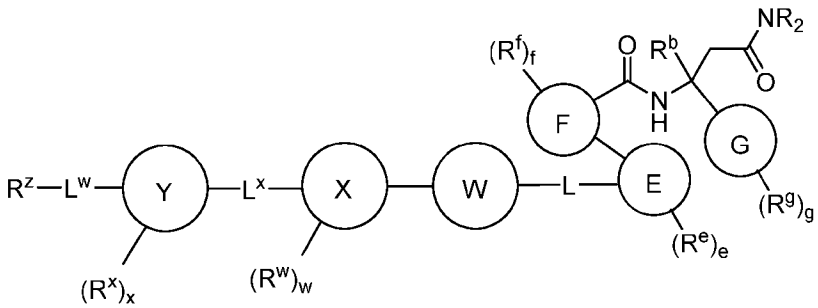
I-aa-24



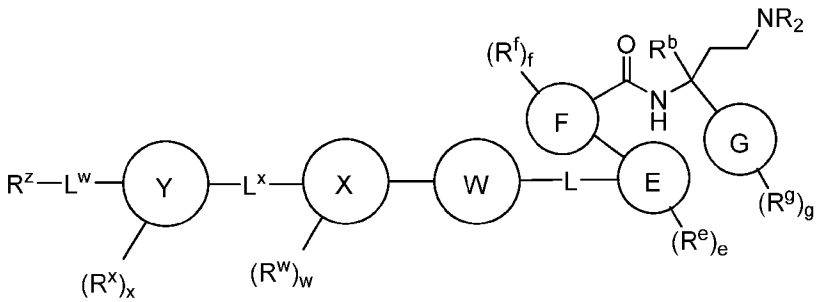
I-aa-25



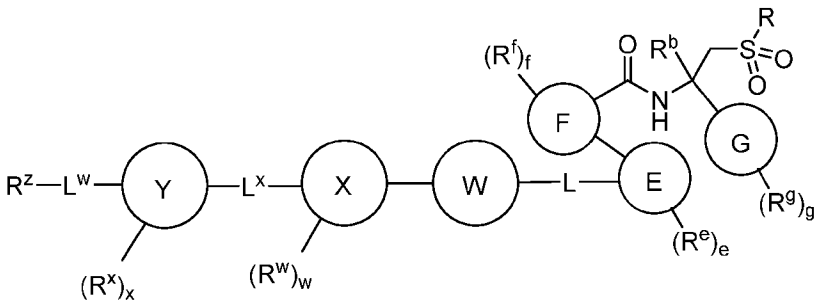
I-aa-26



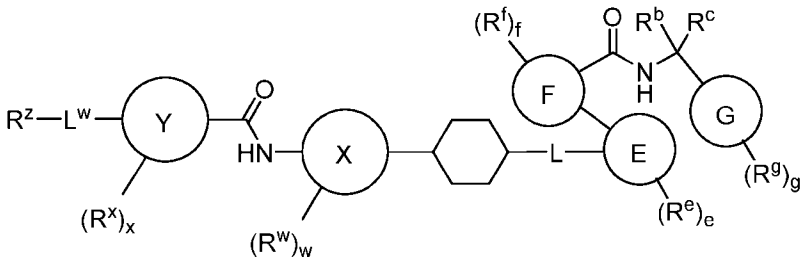
I-aa-27



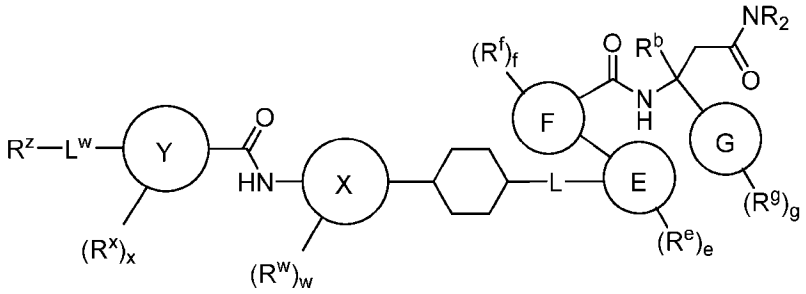
I-aa-28



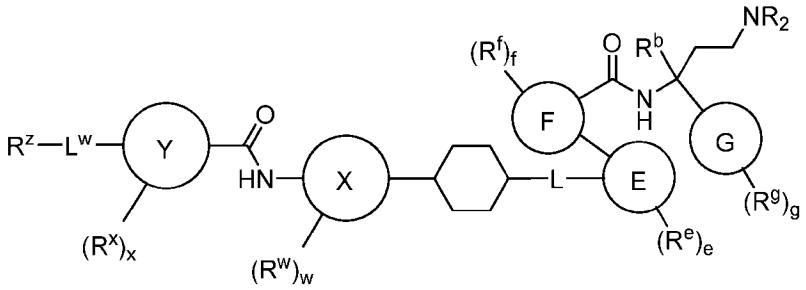
I-aa-29



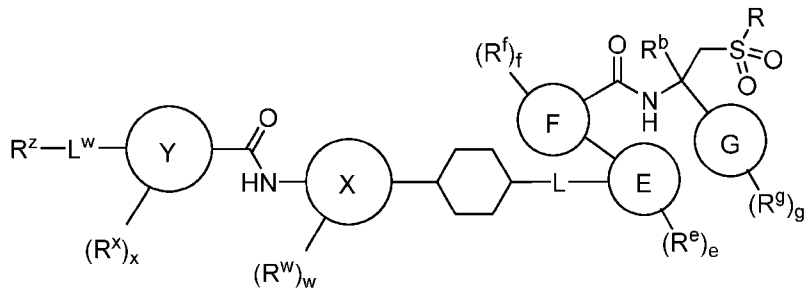
I-aa-30



I-aa-31



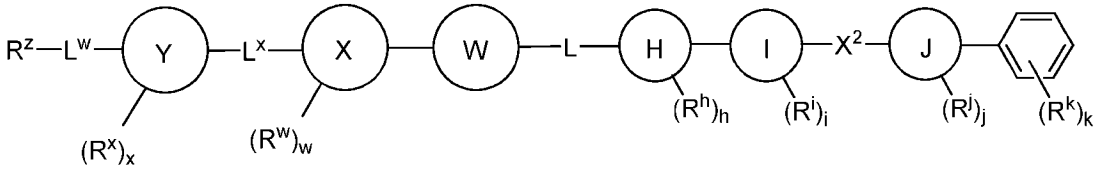
I-aa-32



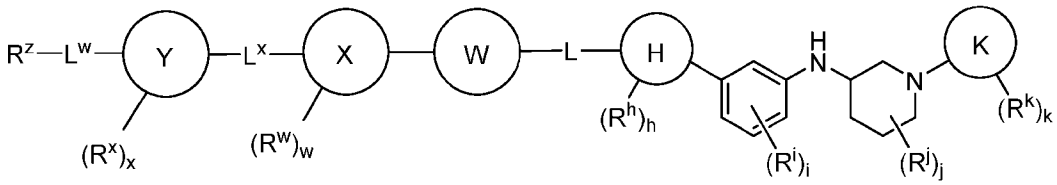
I-aa-33

or a pharmaceutically acceptable salt thereof, wherein each of the variables is as defined in formulae **I-a'** and **I-aa'** above and described in embodiments herein, both singly and in combination.

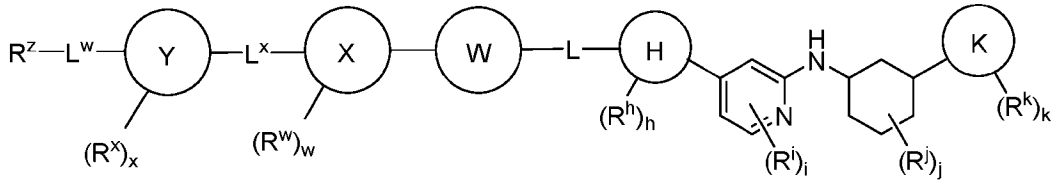
[00491] In some embodiments, the present invention provides a compound of any one of the following formulae:



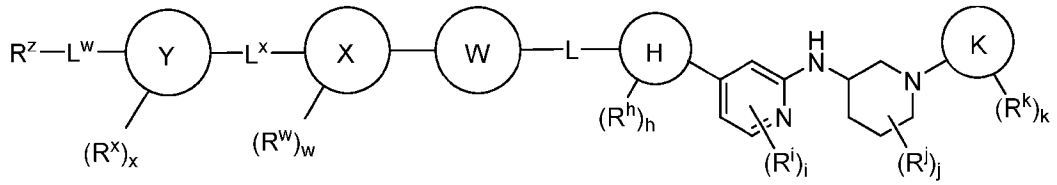
I-bb-10



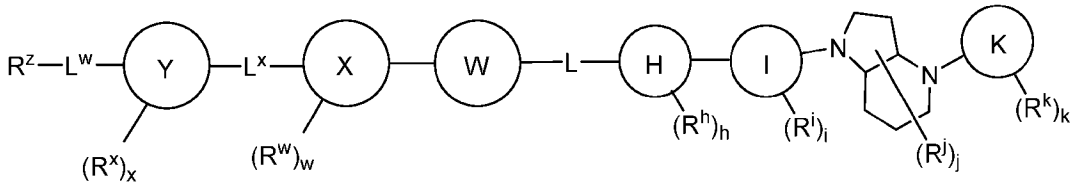
I-bb-11



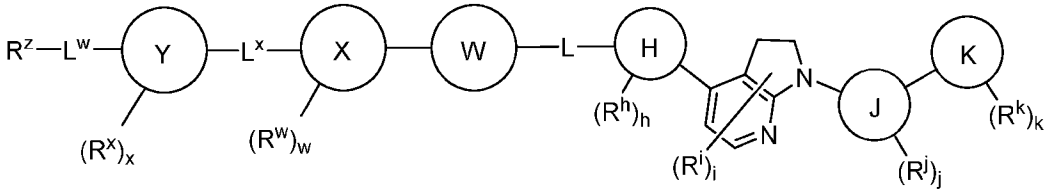
I-bb-12



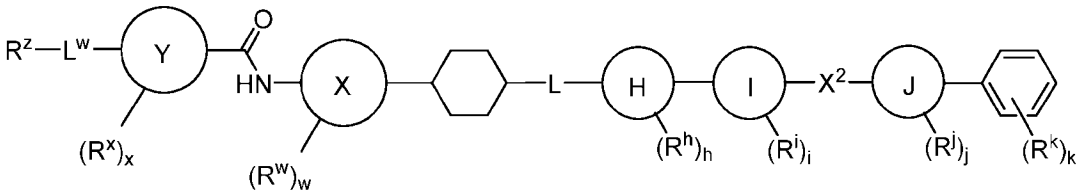
I-bb-13



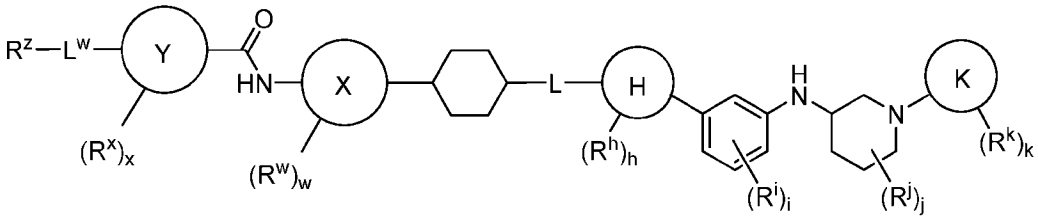
I-bb-14



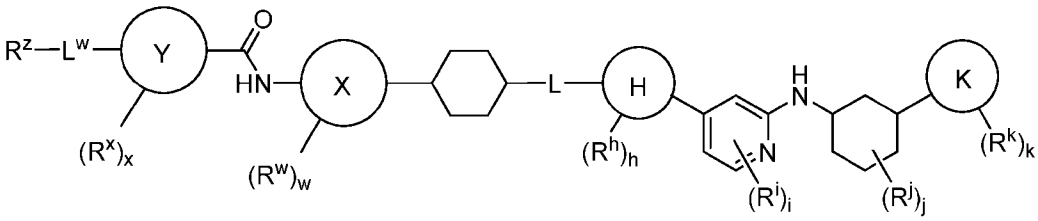
I-bb-15



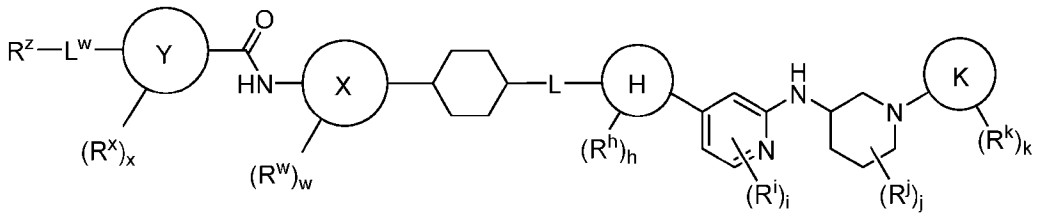
I-bb-16



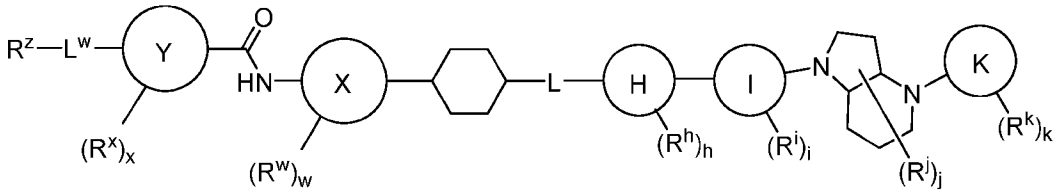
I-bb-17



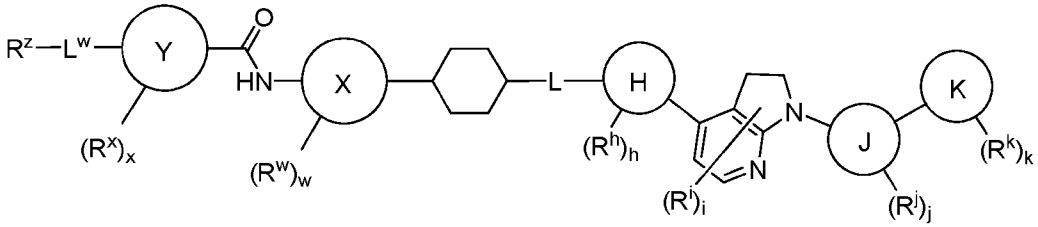
I-bb-18



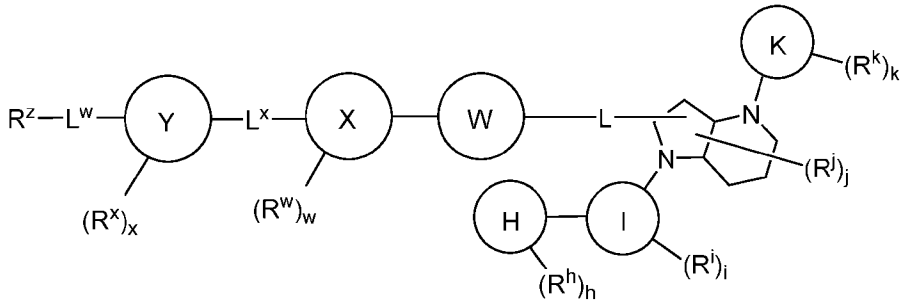
I-bb-19



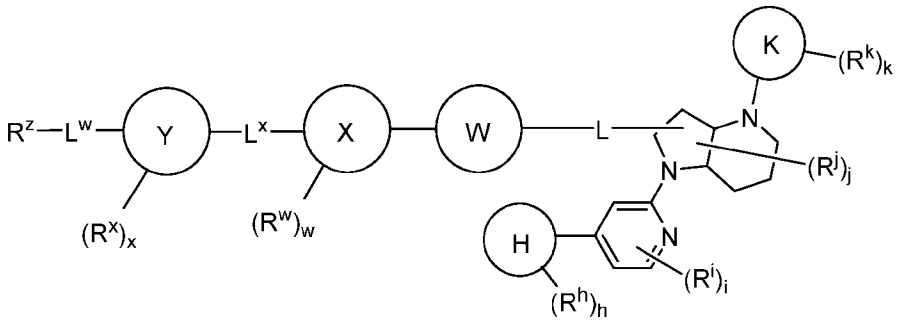
I-bb-20



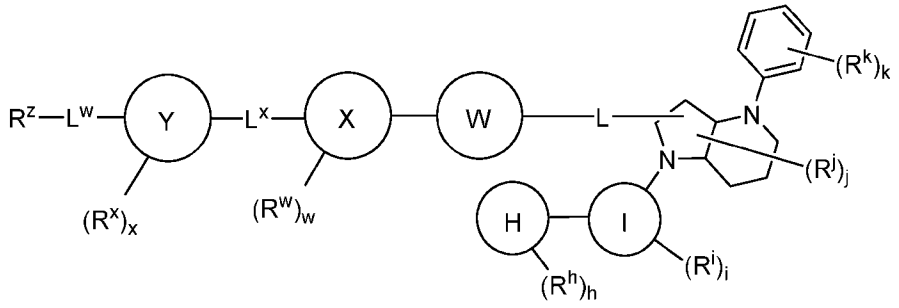
I-bb-21



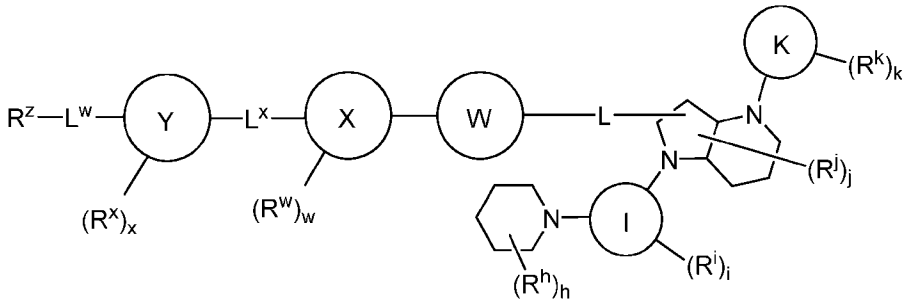
I-bb-22



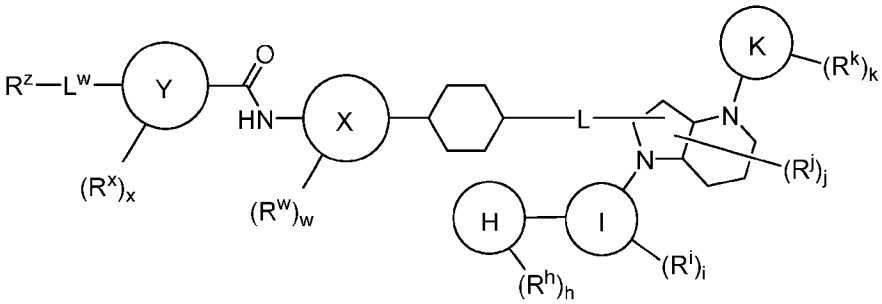
I-bb-23



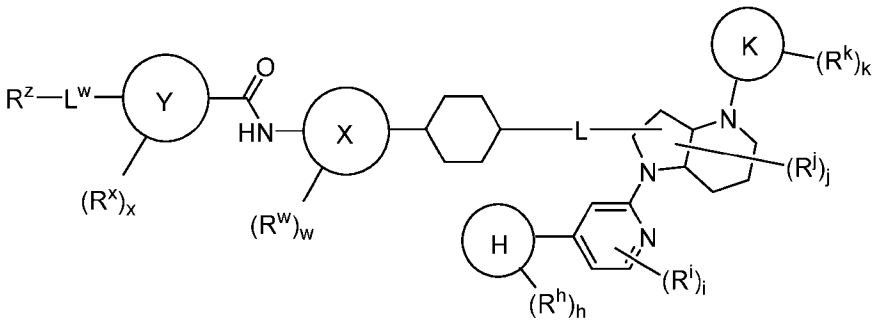
I-bb-24



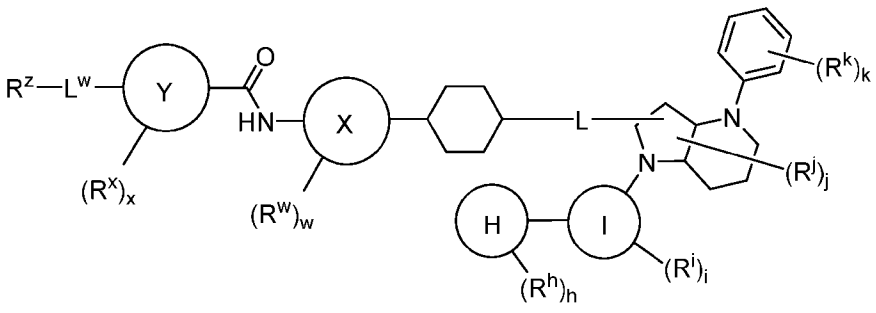
I-bb-25



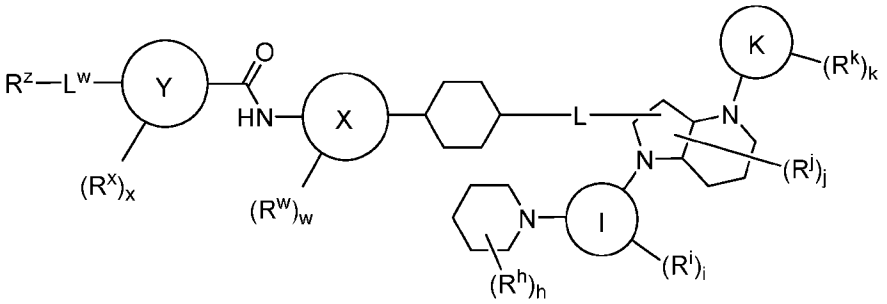
I-bb-26



I-bb-27



I-bb-28



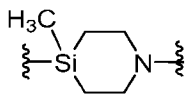
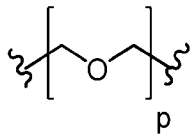
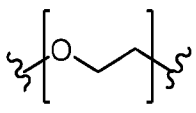
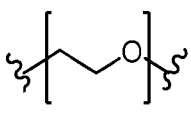
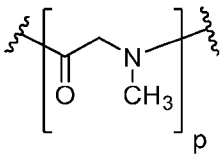
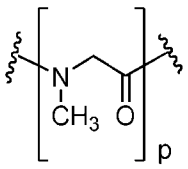
I-bb-29

or a pharmaceutically acceptable salt thereof, wherein each of the variables is as defined in formulae **I-b'** and **I-aa'** above and described in embodiments herein, both singly and in combination.

Linker (L)

[00492] As defined above and described herein, L is a bivalent moiety that connects IRAK to DBM.

[00493] In some embodiments, L is a bivalent moiety that connects IRAK to DBM.

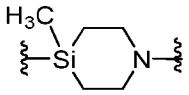
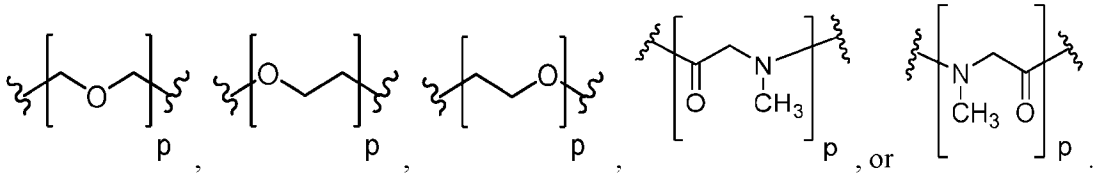
[00494] As defined above and described herein, L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -CRF-, -CF_2-, -Cy-, -O-, -N(R)-, -$Si(R)_2$-, -Si(OH)(R)-, -$Si(OH)_2$-, -P(O)(OR)-, -P(O)(R)-, -$P(O)(NR_2)$-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-,  ,  ,  ,  ,  ,  , wherein:

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected

from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R is as defined and described herein; and

each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

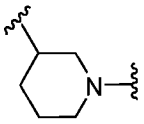
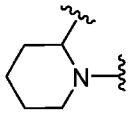
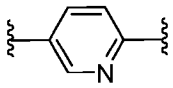
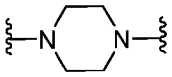
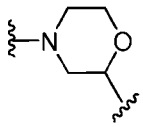
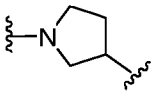
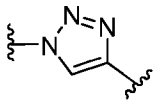
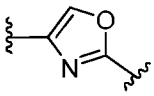
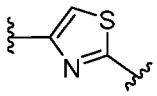
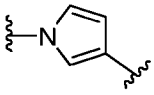
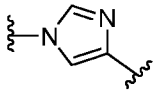
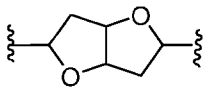
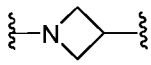
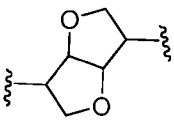
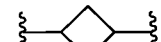
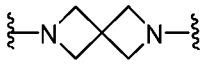
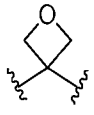
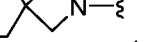
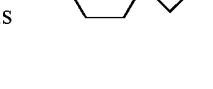
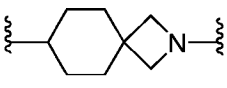
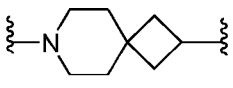
[00495] In some embodiments, L is a covalent bond. In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-50}, C_{1-40}, C_{1-30}, C_{1-20}, or C_{1-10} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, $-CF_2-$, -O-, -N(R)-, $-Si(R)_2-$, -Si(OH)(R)-, $-Si(OH)_2-$, -P(O)(OR)-, -P(O)(R)-, $-P(O)(NR_2)-$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-,  ,  , or .

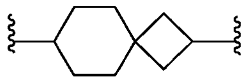
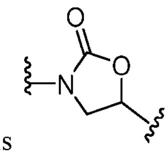
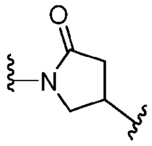
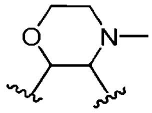
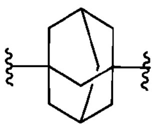
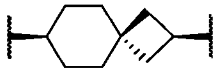
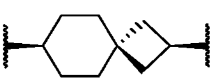
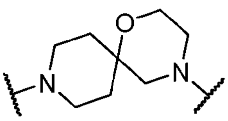
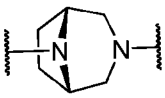
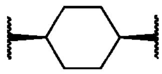
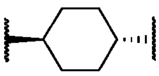
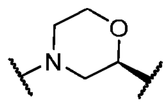
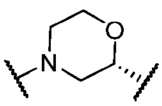
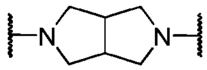
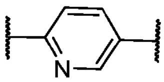
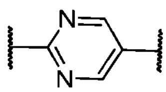
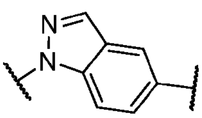
[00496] In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, $-CF_2-$, -O-, -N(R)-, $-Si(R)_2-$, -Si(OH)(R)-, $-Si(OH)_2-$, -P(O)(OR)-, -P(O)(R)-, $-P(O)(NR_2)-$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, or -N(R)C(O)O-.

[00497] In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, $-CF_2-$, -O-, -N(R)-, -S-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, -N(R)C(O)-, or -N(R)C(O)O-.

[00498] In some embodiments, each –Cy– is independently an optionally substituted bivalent phenylenyl. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic arylenyl. In some embodiments, each –Cy– is independently an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclylenyl. In some embodiments, each –Cy– is independently an optionally substituted 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl. In some embodiments, each –Cy– is independently an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic saturated

or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00499] In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In

some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  .

[00500] In some embodiments, -Cy- is selected from those depicted in **Table 1**, below.

[00501] In some embodiments, r is 0. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4. In some embodiments, r is 5. In some embodiments, r is 6. In some embodiments, r is 7. In some embodiments, r is 8. In some embodiments, r is 9. In some embodiments, r is 10.

[00502] In some embodiments, r is selected from those depicted in **Table 1**, below.

[00503] In some embodiments, L is -NR-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-NR-(C_{1-10}aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-NR-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-NR-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NR-. In

some embodiments, L is -Cy-(C_{1-10} aliphatic)-NR-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-NR-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-NR-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-NR-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-NR-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NR-Cy-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-NR-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NR-Cy-(C_{1-10} aliphatic)-.

[00504] In some embodiments, L is -CONR-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-CONR-(C_{1-10}aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-CONR-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-CONR-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-CONR-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-CONR-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-CONR-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-CONR-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-CONR-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-CONR-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-CONR-Cy-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-CONR-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-CONR-Cy-(C_{1-10} aliphatic)-.

[00505] In some embodiments, L is -NRCO-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-NRCO-(C_{1-10}aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-NRCO-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-NRCO-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NRCO-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NRCO-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-NRCO-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-NRCO-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-NRCO-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-NRCO-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NRCO-Cy-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-NRCO-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-NRCO-Cy-(C_{1-10} aliphatic)-.

[00506] In some embodiments, L is -O-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-O-(C_{1-10}aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-O-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-O-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-O-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-O-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-O-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-O-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-O-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-O-.In some embodiments, L is -Cy-(C_{1-10} aliphatic)-O-Cy-.In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-O-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-O-Cy-(C_{1-10} aliphatic)-.

[00507] In some embodiments, L is -Cy-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-. In some embodiments, L is -Cy-(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-Cy-. In some embodiments, L is -(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-Cy-(C_{1-10} aliphatic)-.

[00508] In some embodiments, L is -NR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-NR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-NR-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-NR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NR-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-NR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-NR-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-NR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-NR-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NR-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-NR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NR-Cy-$(CH_2)_{1-10}$-.

[00509] In some embodiments, L is -CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-CONR-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-CONR-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-CONR-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-Cy-$(CH_2)_{1-10}$-.

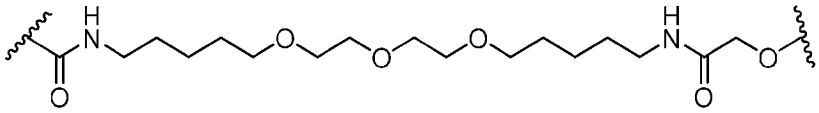
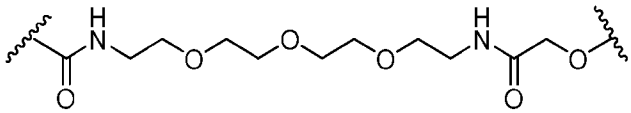
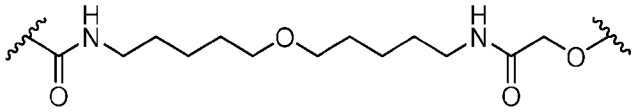
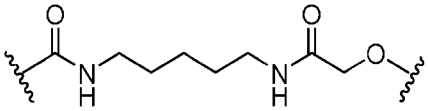
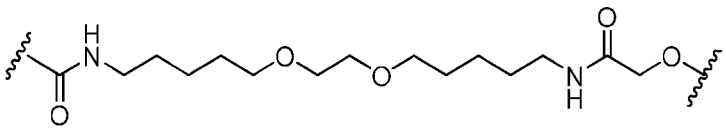
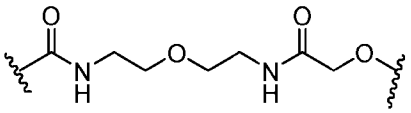
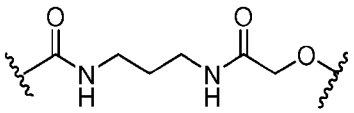
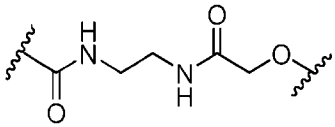
[00510] In some embodiments, L is -NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-NRCO-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NRCO-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-NRCO-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-NRCO-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NRCO-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NRCO-Cy-$(CH_2)_{1-10}$-.

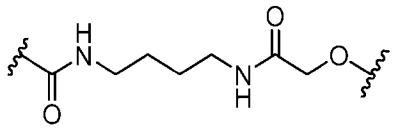
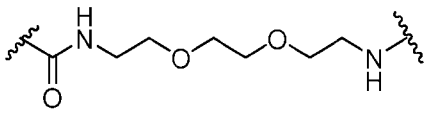
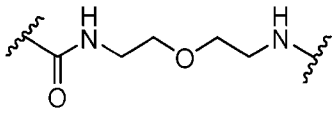
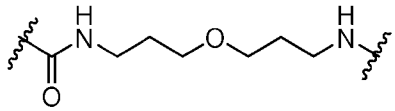
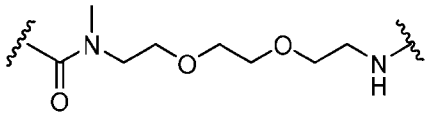
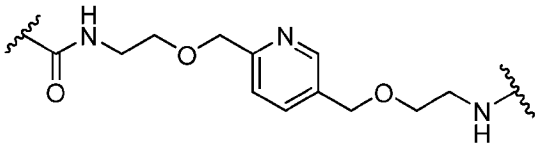
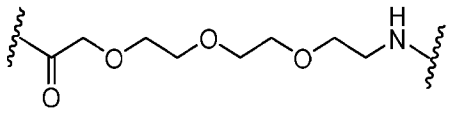
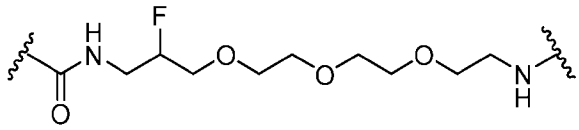
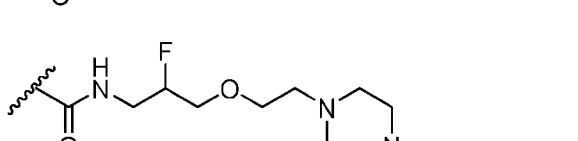
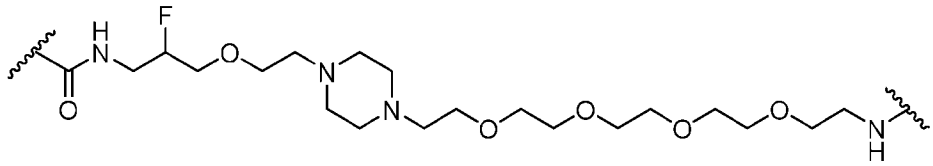
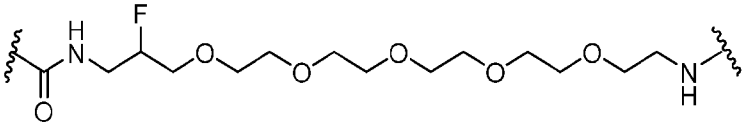
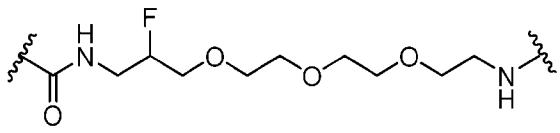
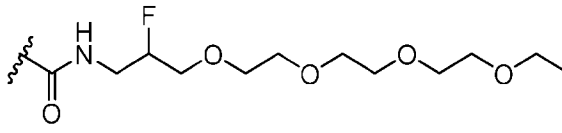
[00511] In some embodiments, L is -O-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-O-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-O-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-O-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-O-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-O-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-O-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-O-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-O-$(CH_2)_{1-10}$-. In some embodiments,

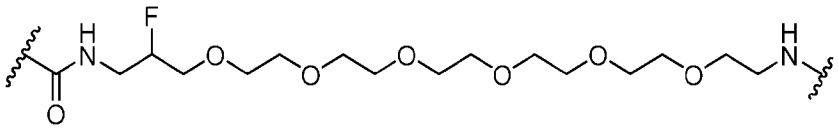
L is -Cy-$(CH_2)_{1-10}$-Cy-O-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-O-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-O-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-O-Cy-$(CH_2)_{1-10}$-.

[00512] In some embodiments, L is -Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-Cy-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-.

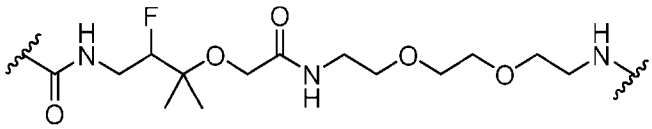
[00513] In some embodiments, L is -CO-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -CO-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -CO-Cy-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -CO-Cy-$(CH_2)_{1-10}$-Cy-. In some embodiments, L is -CO-Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -CO-Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-Cy-. In some embodiments, L is -CO-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-Cy-$(CH_2)_{1-10}$-CO-. In some embodiments, L is -Cy-Cy-$(CH_2CH_2O)_{1-10}CH_2$-CO-. In some embodiments, L is -Cy-Cy-$(CH_2CH_2O)_{1-10}CH_2CH_2$-CO-.

[00514] In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

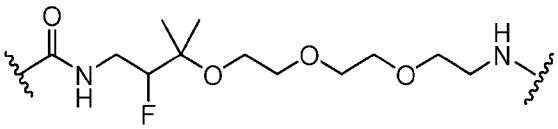
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is



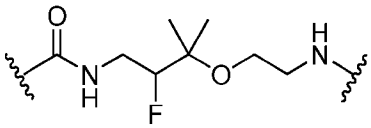
. In some embodiments, L is



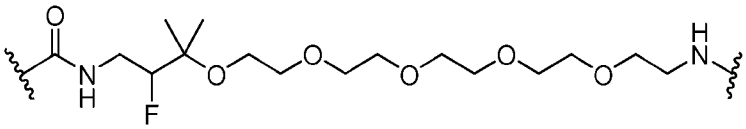
. In some embodiments, L is



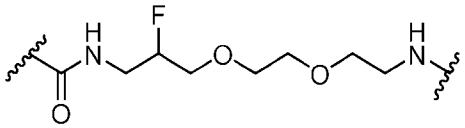
. In some embodiments, L is



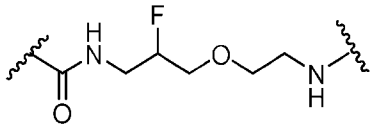
. In some embodiments, L is



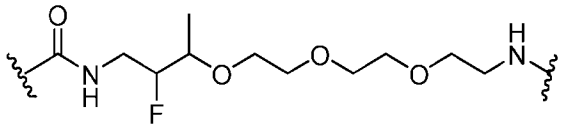
. In some embodiments, L is



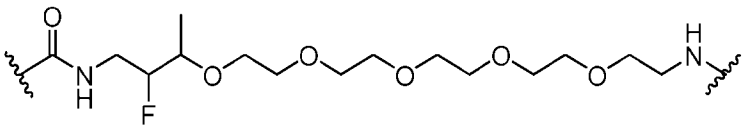
. In some embodiments, L is



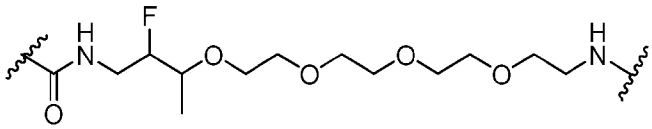
. In some embodiments, L is



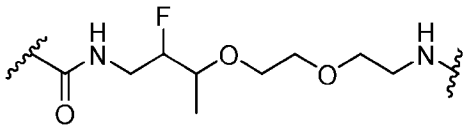
. In some embodiments, L is



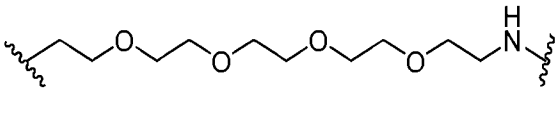
. In some embodiments, L is



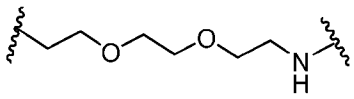
. In some embodiments, L is



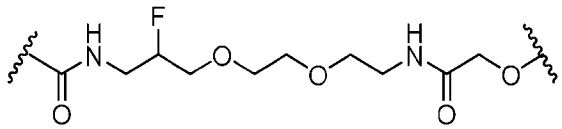
. In some embodiments, L is



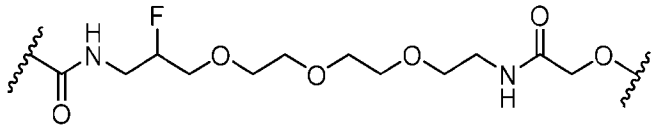
. In some embodiments, L is



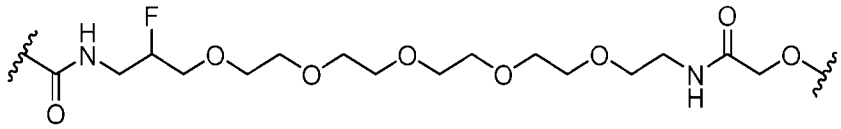
. In some embodiments, L is



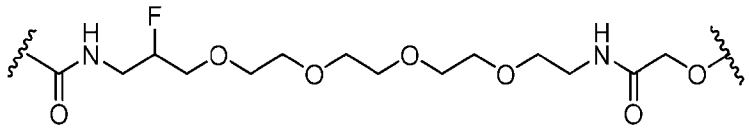
. In some embodiments, L is



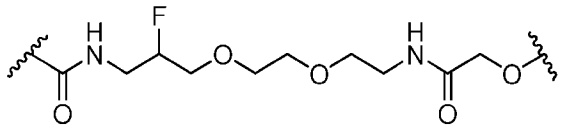
. In some embodiments, L is



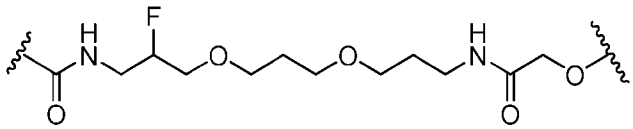
. In some embodiments, L is



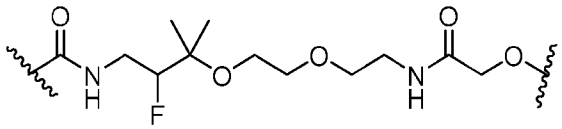
. In some embodiments, L is



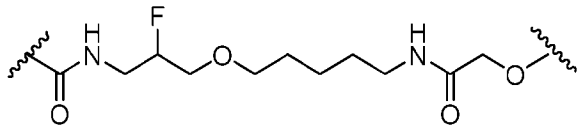
. In some embodiments, L is



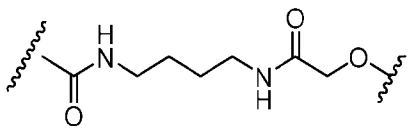
. In some embodiments, L is



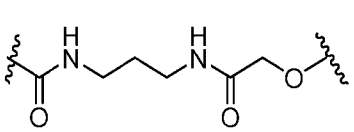
. In some embodiments, L is



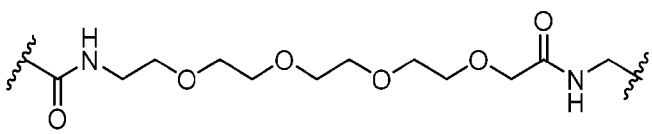
. In some embodiments, L is



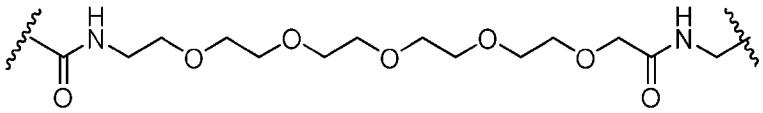
. In some embodiments, L is



. In some embodiments, L is



. In some embodiments, L is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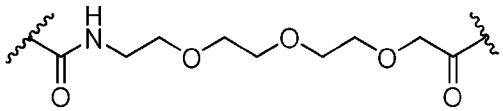
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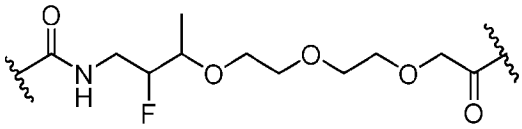
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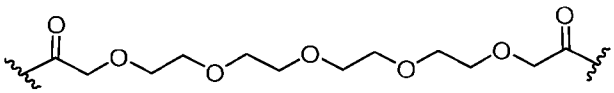
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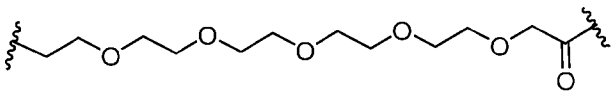
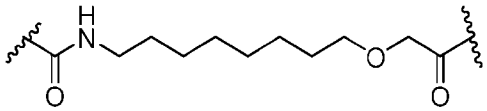
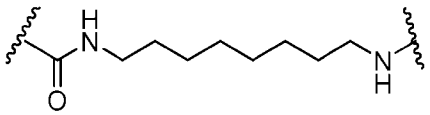

. In some embodiments, L is


. In some embodiments, L is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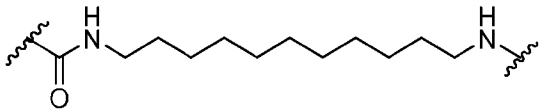
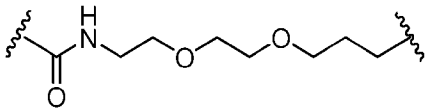
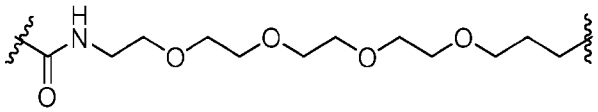
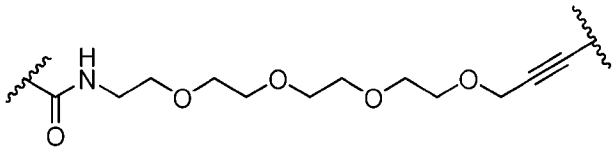
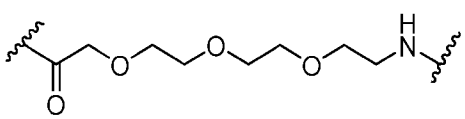
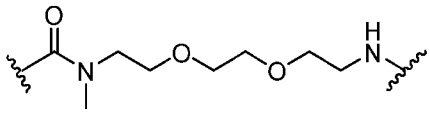
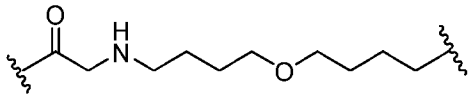
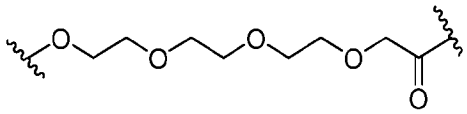
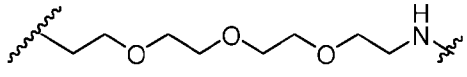
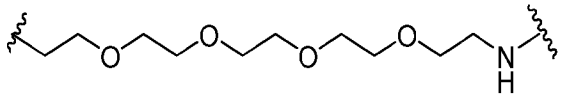
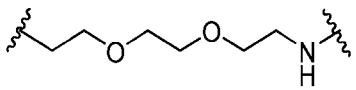
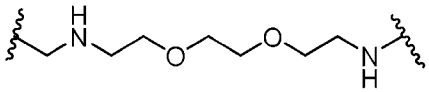
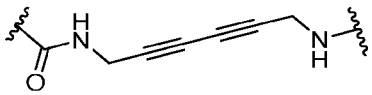
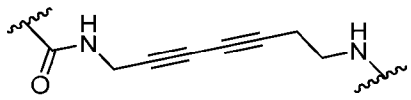
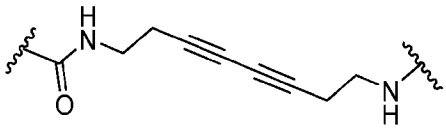
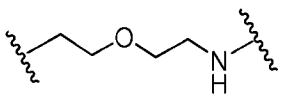
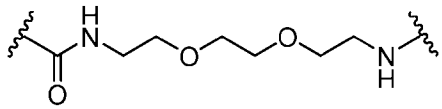
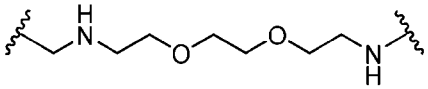
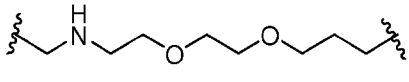
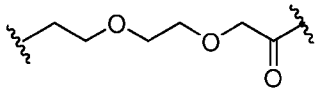
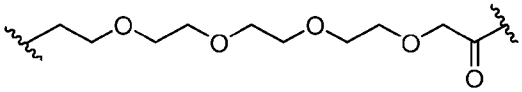
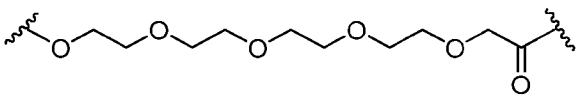

. In some embodiments, L is

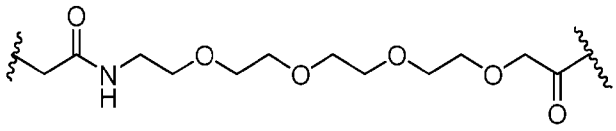
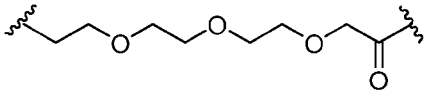
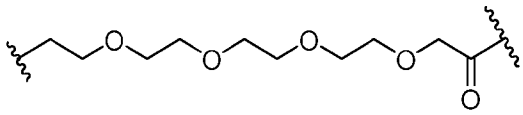
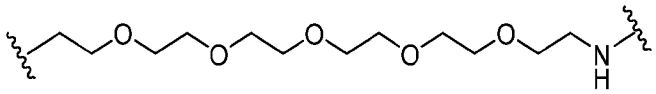
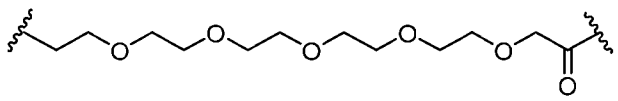
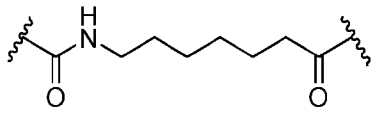
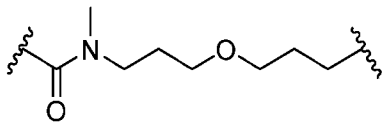
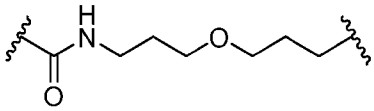
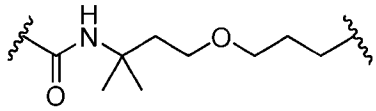
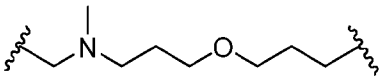
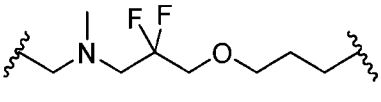
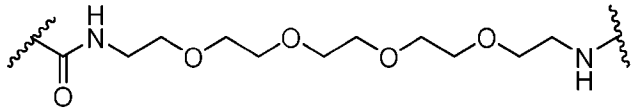
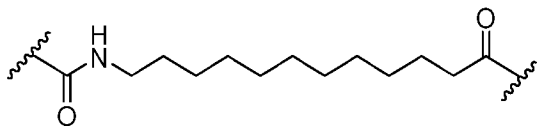
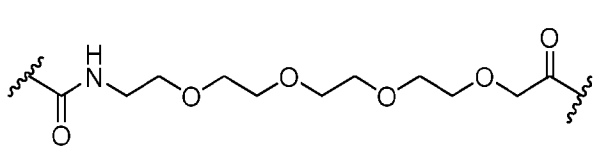

. In some embodiments, L is

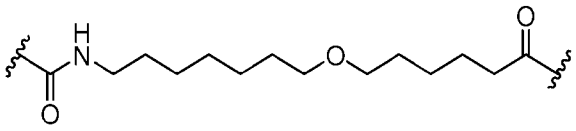
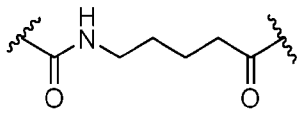

. In some embodiments, L is

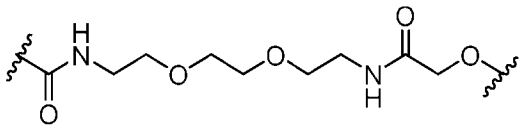

. In some embodiments, L is

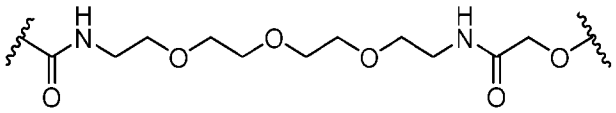

. In some embodiments, L is

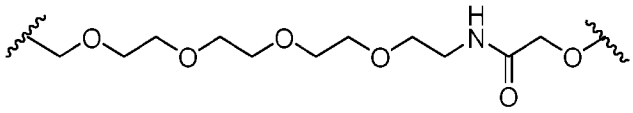
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

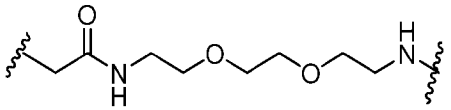
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

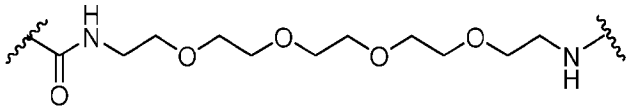

. In some embodiments, L is 

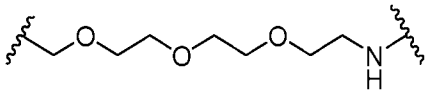
. In some embodiments, L is  . In some embodiments, L is

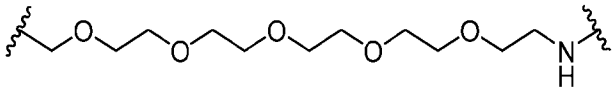
 . In some embodiments, L is

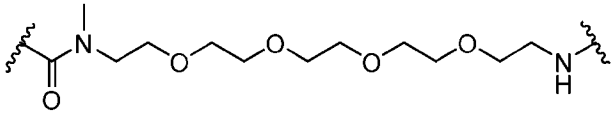
 . In some embodiments, L is

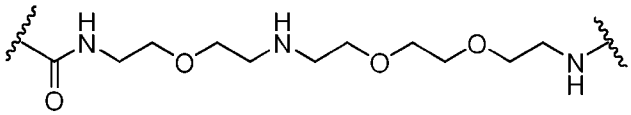
 . In some embodiments, L is

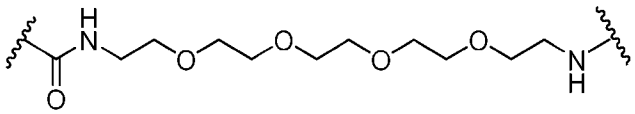
 . In some embodiments, L is

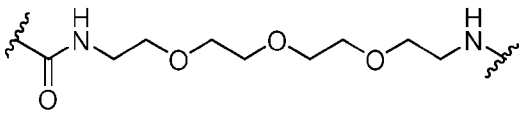
 . In some embodiments, L is

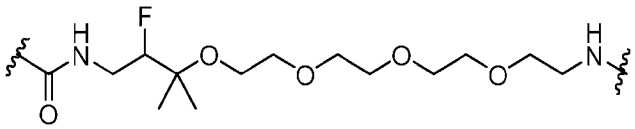
 . In some embodiments, L is

 . In some embodiments, L is

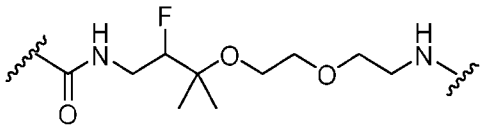
 . In some embodiments, L is

 . In some embodiments, L is

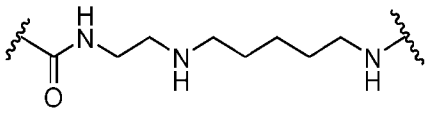
 . In some embodiments, L is



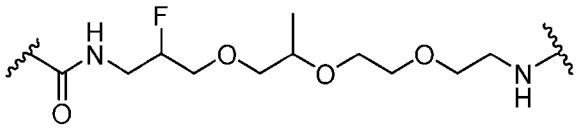
. In some embodiments, L is



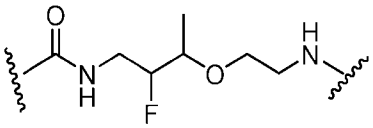
. In some embodiments, L is



. In some embodiments, L is



. In some embodiments, L is



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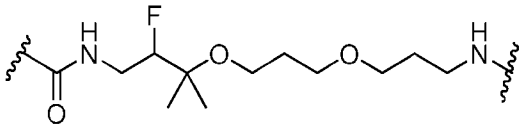
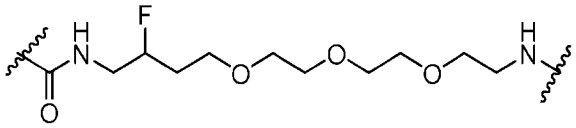
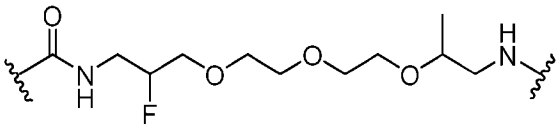


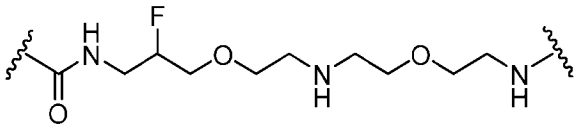
. In some embodiments, L is



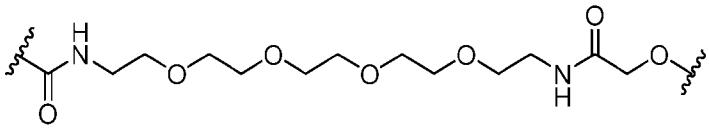
. In some embodiments, L is



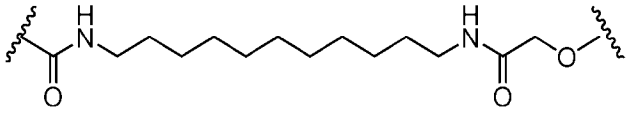
. In some embodiments, L is



. In some embodiments, L is



. In some embodiments, L is



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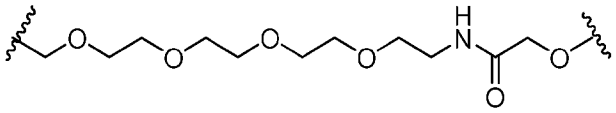

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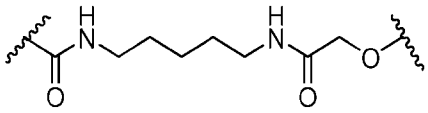
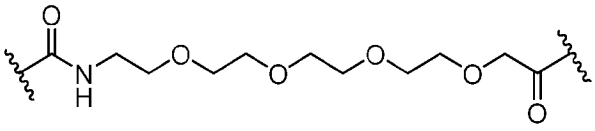


. In some embodiments, L is



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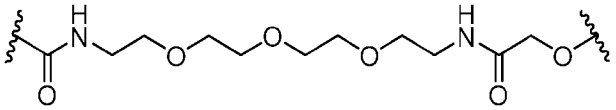

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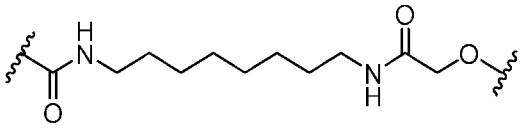

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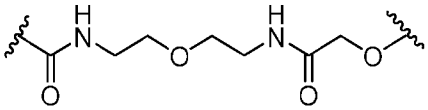

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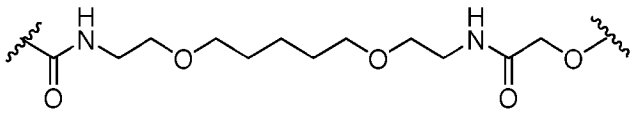

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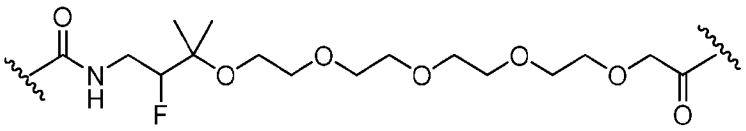
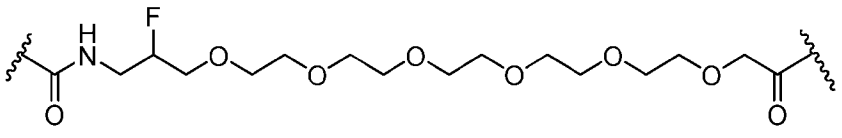
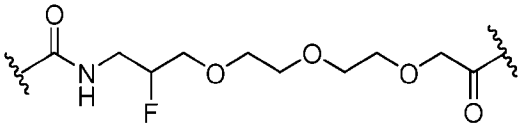


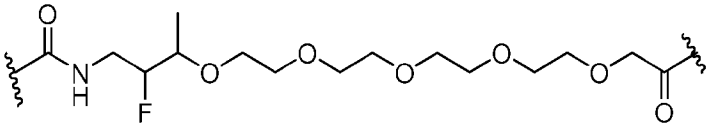
. In some embodiments, L is



. In some embodiments, L is



. In some embodiments, L is



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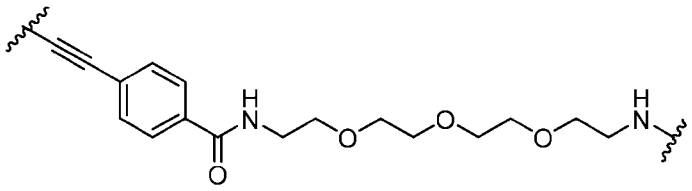
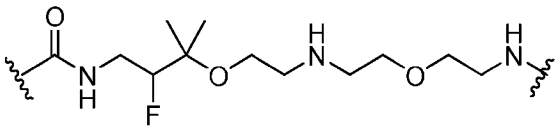


. In some embodiments, L is



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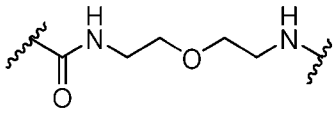
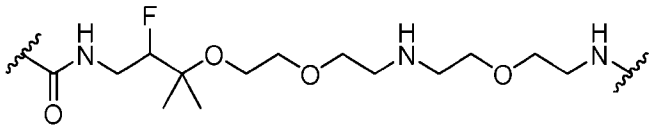


. In some embodiments, L is



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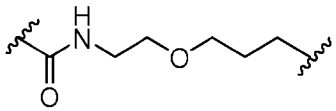
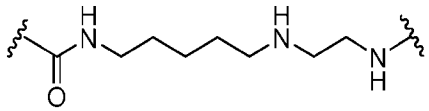
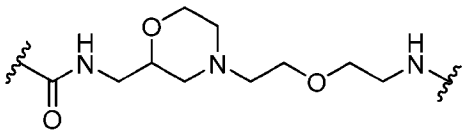


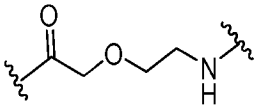
. In some embodiments, L is



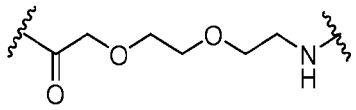
. In some embodiments, L is



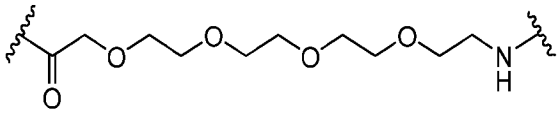
. In some embodiments, L is



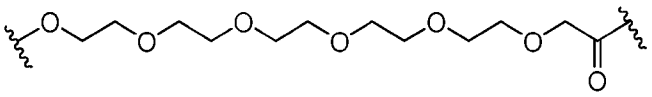
. In some embodiments, L is



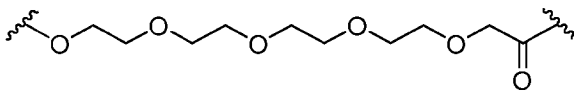
. In some embodiments, L is



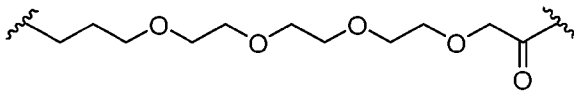
. In some embodiments, L is



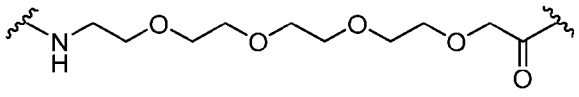
. In some embodiments, L is



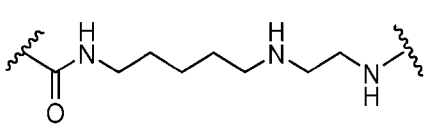
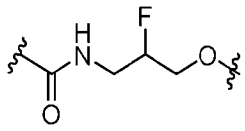
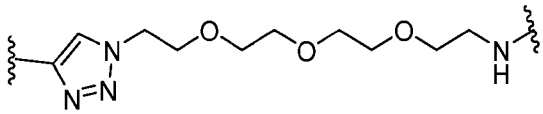
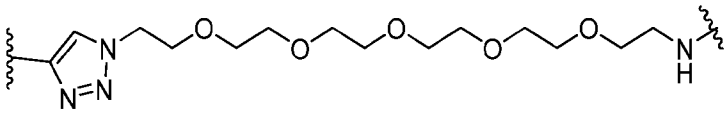
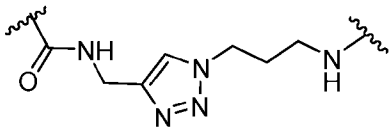
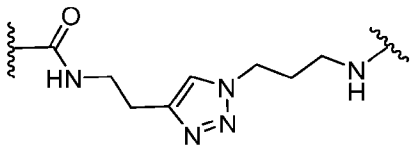
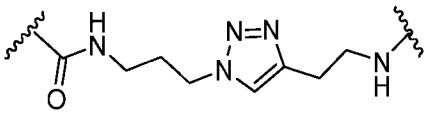
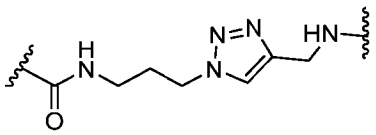
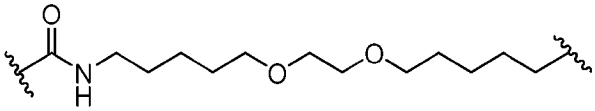
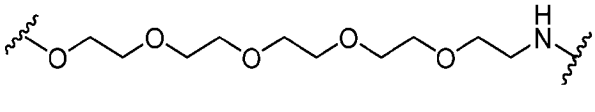
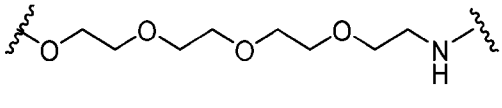
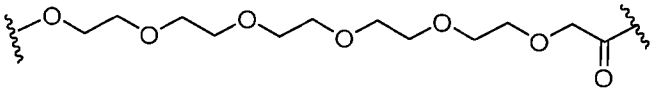
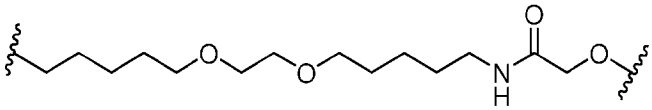
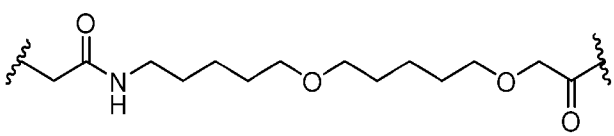
. In some embodiments, L is

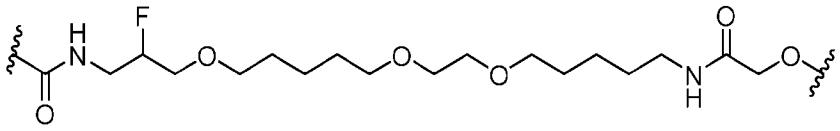


. In some embodiments, L is

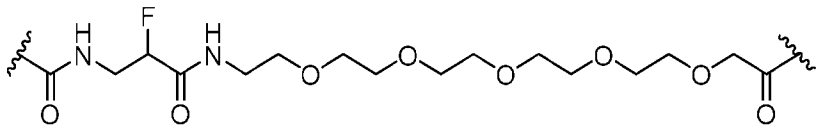


. In some embodiments, L is

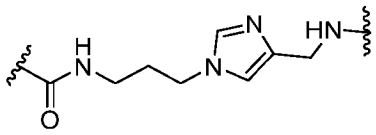
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is



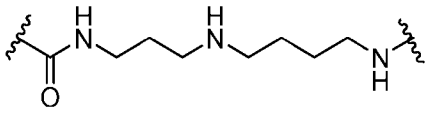
. In some embodiments, L is



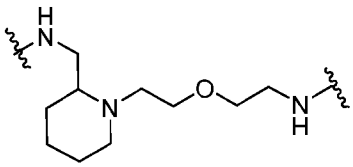
. In some embodiments, L is



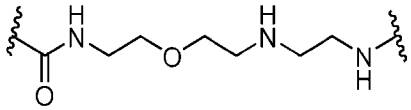
. In some embodiments, L is



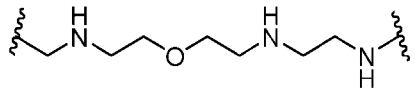
. In some embodiments, L is



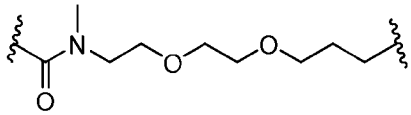
. In some embodiments, L is



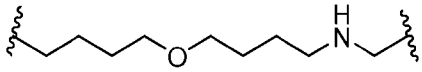
. In some embodiments, L is



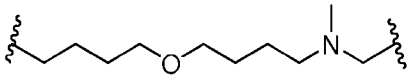
. In some embodiment, L is



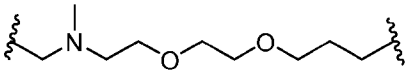
. In some embodiment, L is



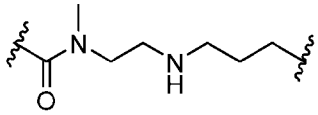
. In some embodiment, L is



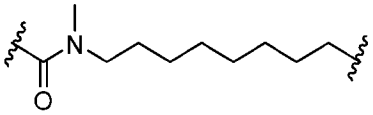
. In some embodiments, L is



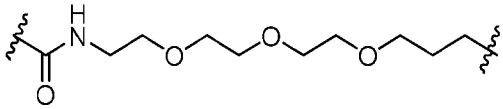
. In some embodiments, L is



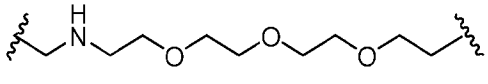
. In some embodiments, L is



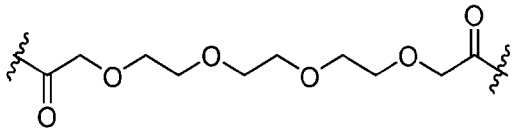
. In some embodiments, L is

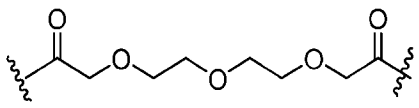
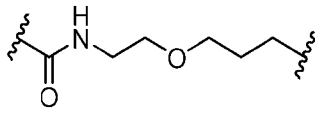
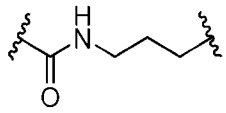
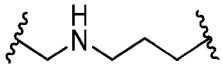
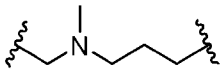
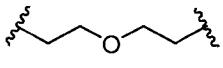
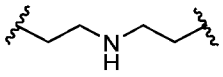
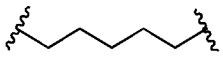
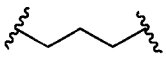
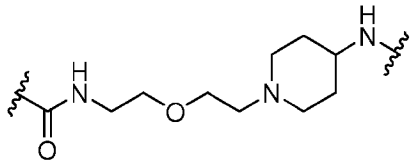
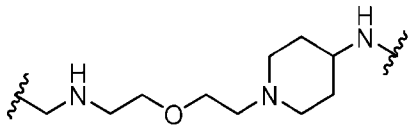
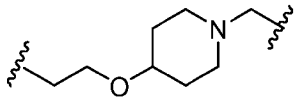
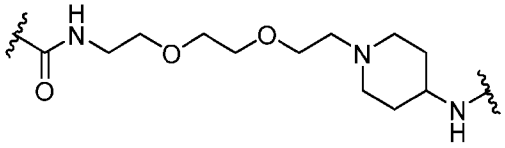
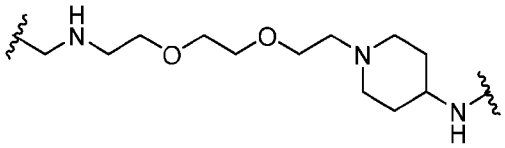
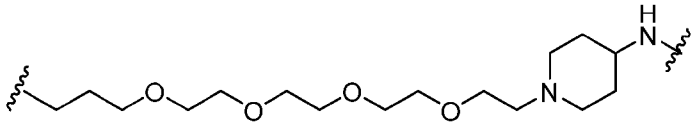
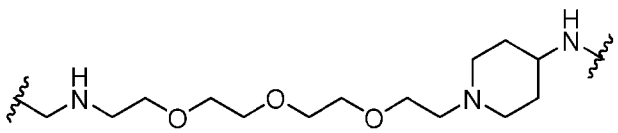


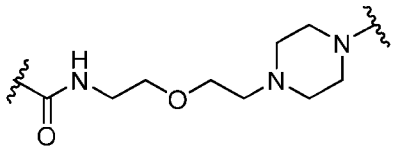
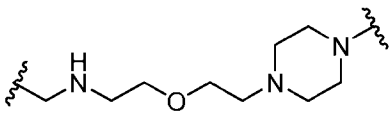
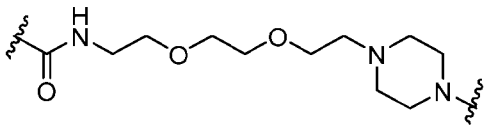
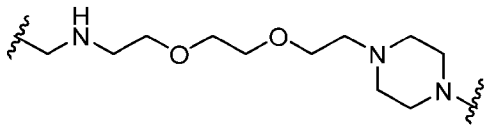
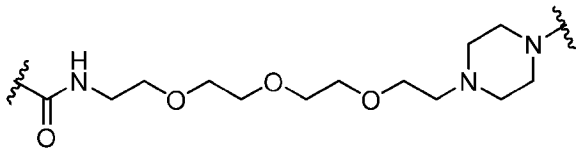
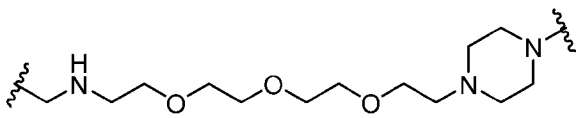
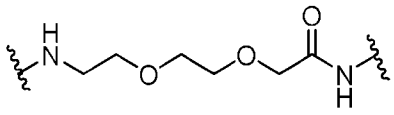
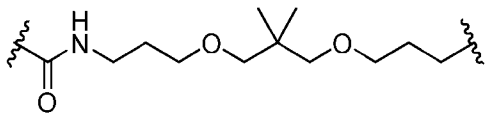
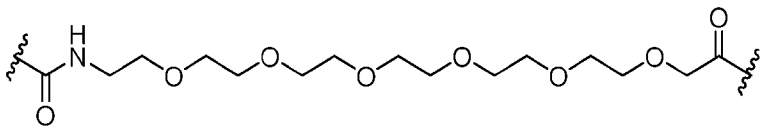
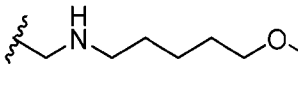
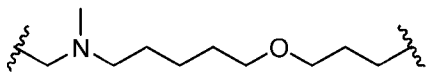
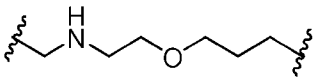
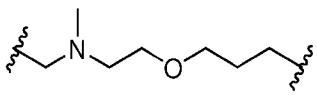
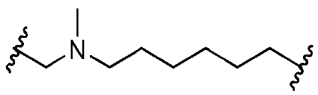
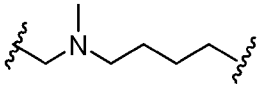
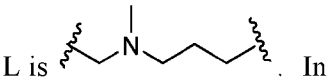
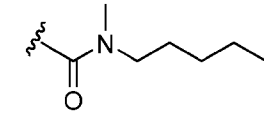
. In some embodiments, L is

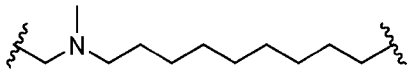
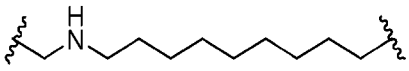
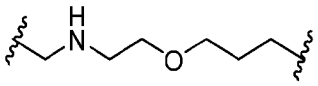
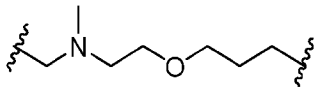
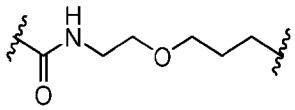
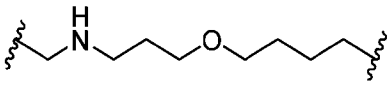
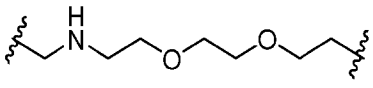
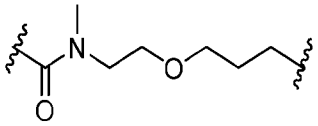
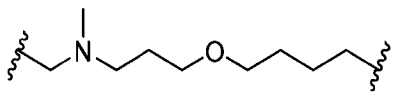
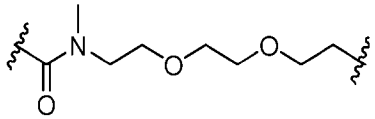
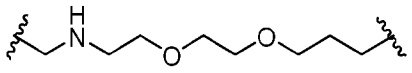
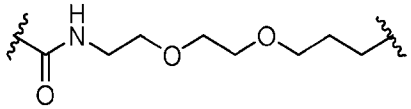
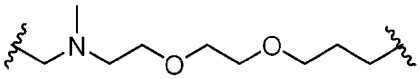
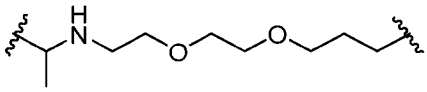
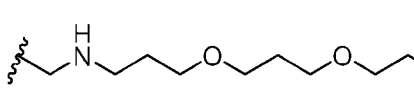
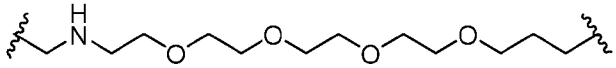
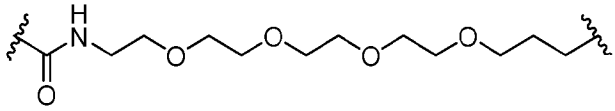
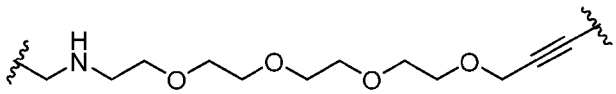
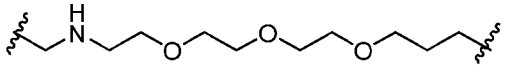


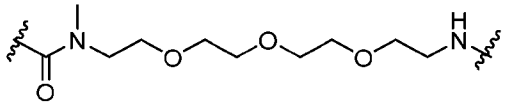
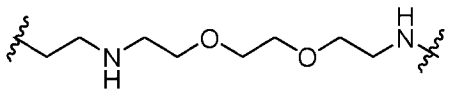
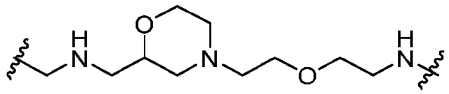
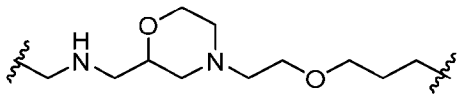
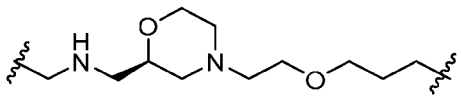
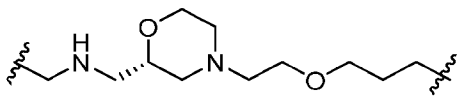
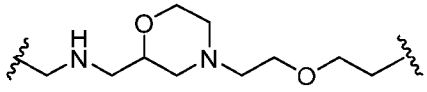
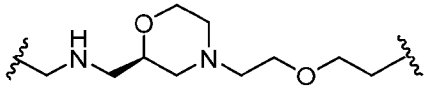
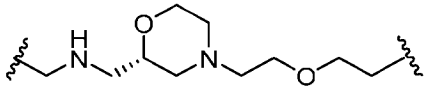
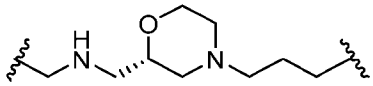
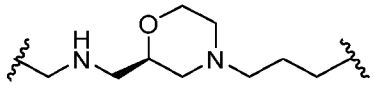
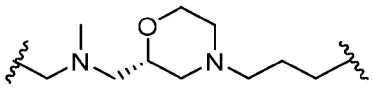
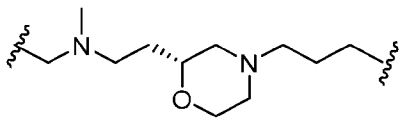
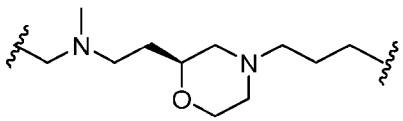
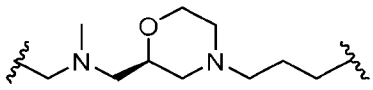
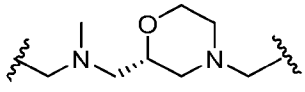
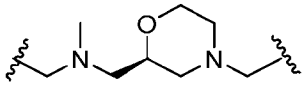
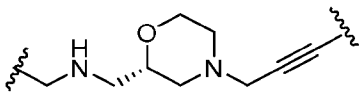
. In some embodiments, L is

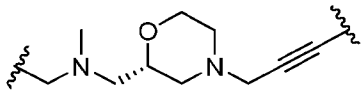
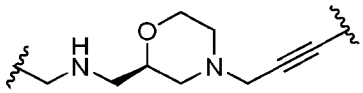
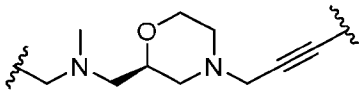
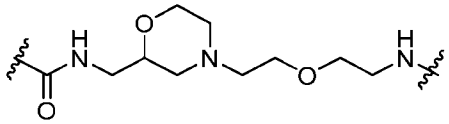
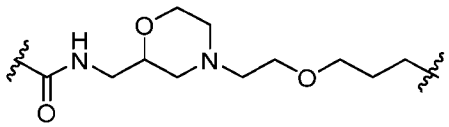
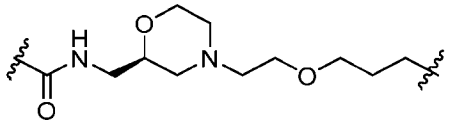
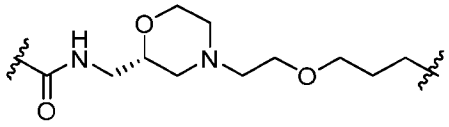
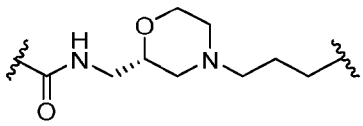
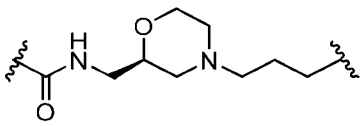
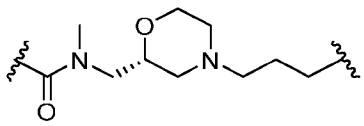
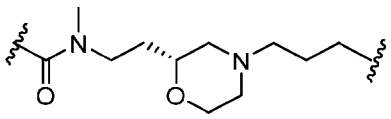
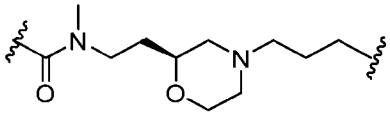
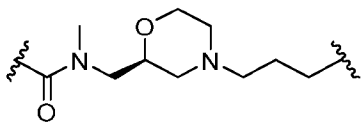
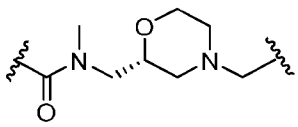
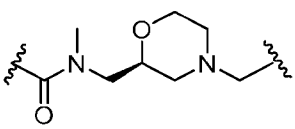
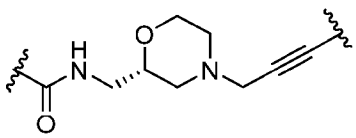


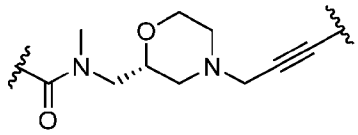
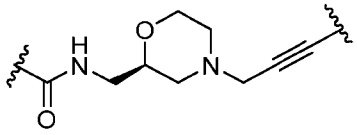
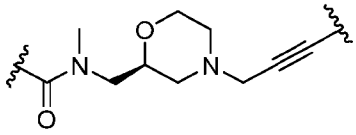
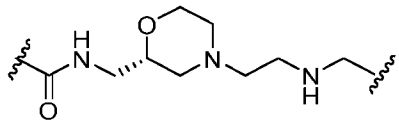
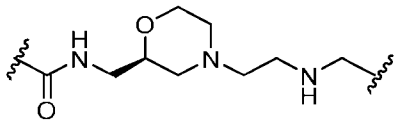
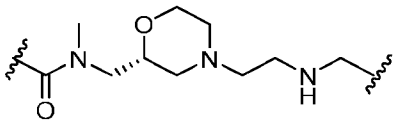
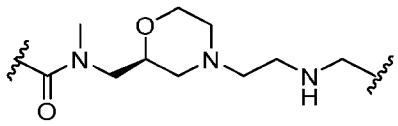
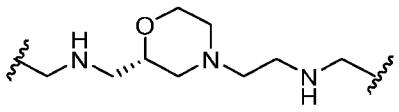
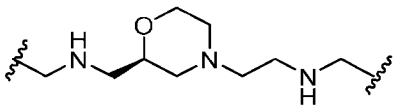
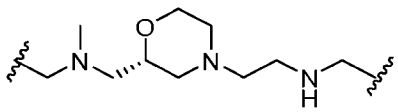
 . In In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

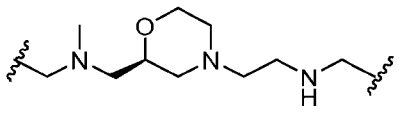
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is

 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is . In some embodiment, L is  . In some embodiment, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

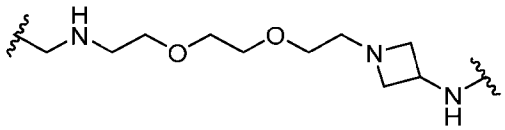
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

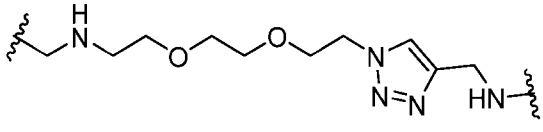
. In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is



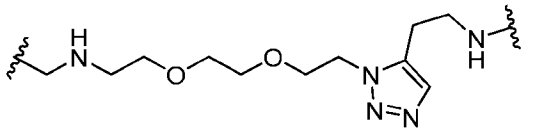
. In some embodiments, L is



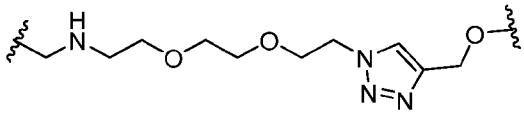
. In some embodiments, L is

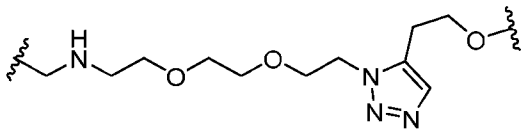


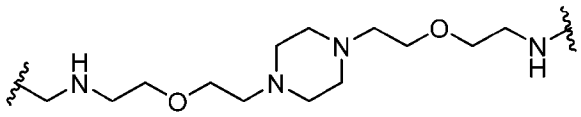
. In some embodiments, L is

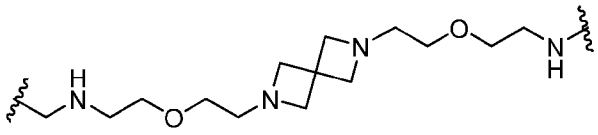


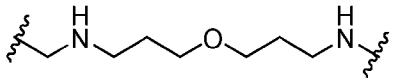
. In some embodiments, L is

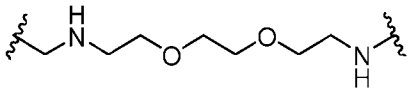

. In some embodiments, L is

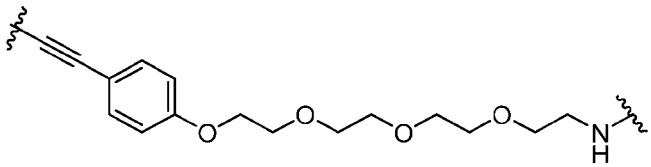

. In some embodiments, L is

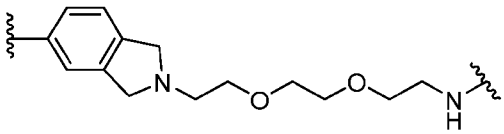

. In some embodiments, L is

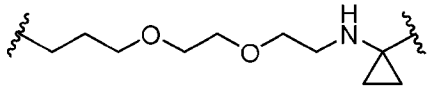

. In some embodiments, L is

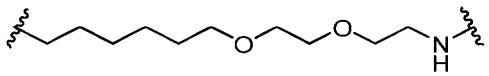

. In some embodiments, L is

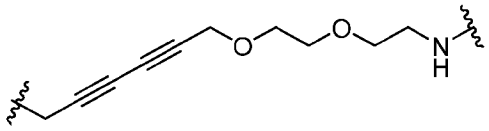

. In some embodiments, L is

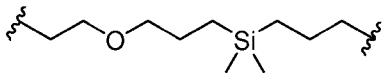

. In some embodiments, L is

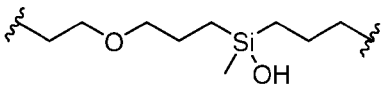

. In some embodiments, L is

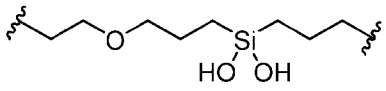

. In some embodiments, L is

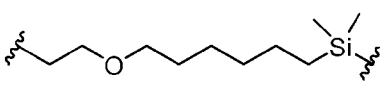

. In some embodiments, L is

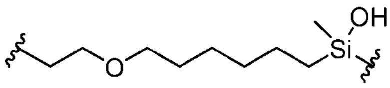
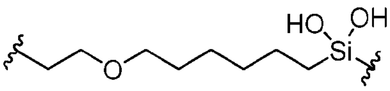
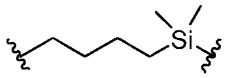
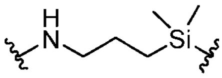
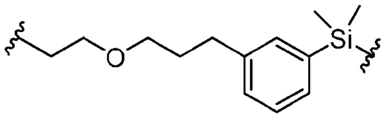
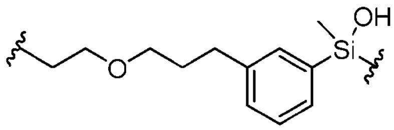
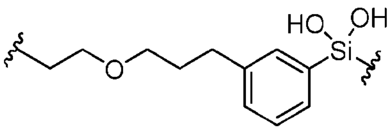
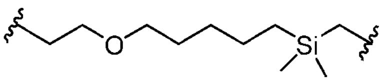
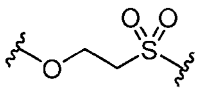
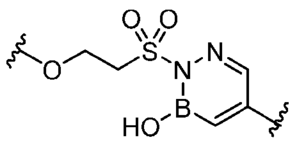
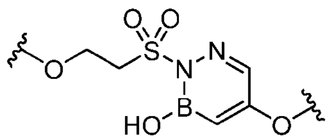
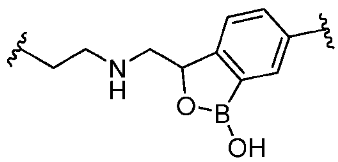
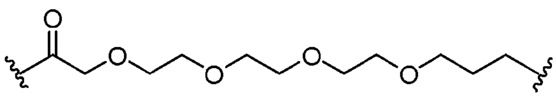
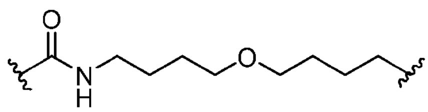
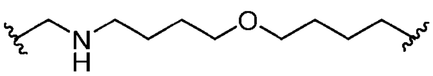
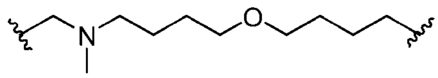
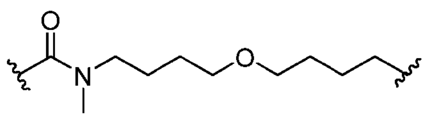
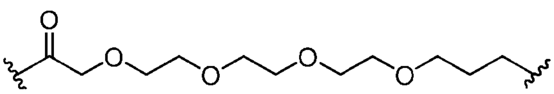
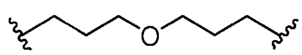

. In some embodiments, L is

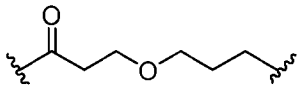
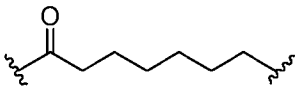
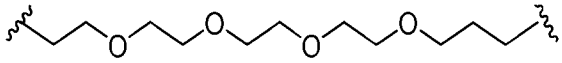
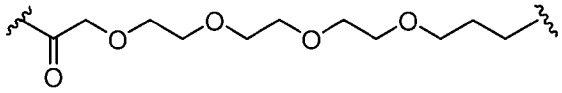
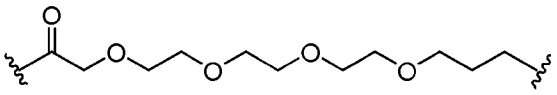
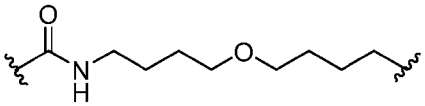
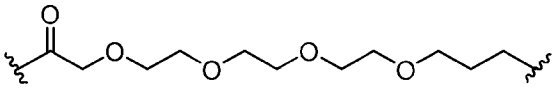
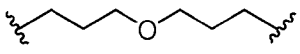
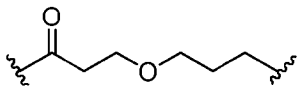
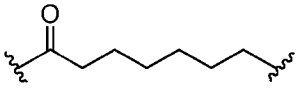
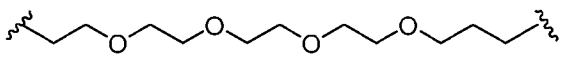
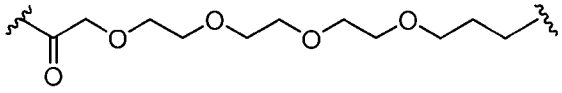
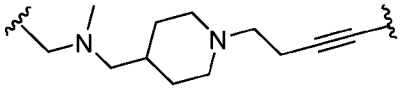
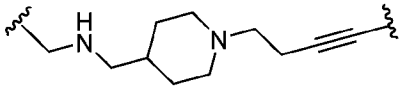
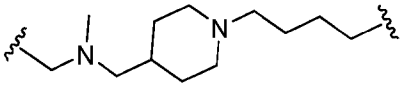
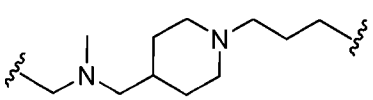
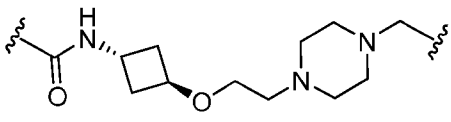
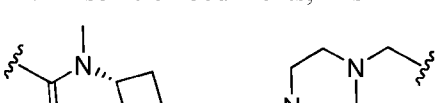

. In some embodiments, L is

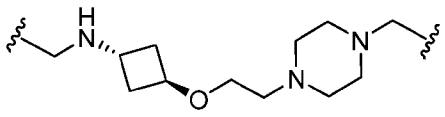
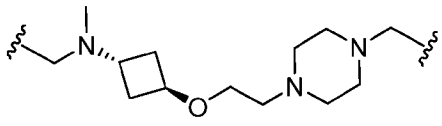
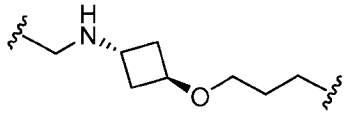
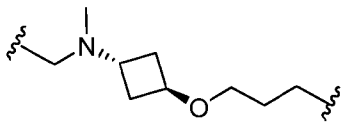
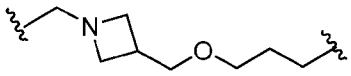
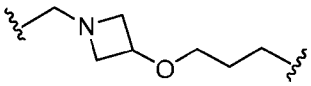
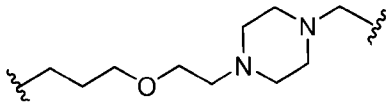
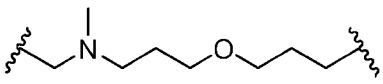
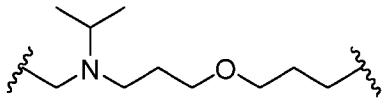
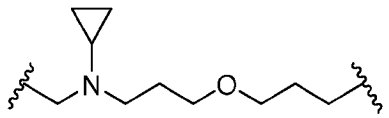
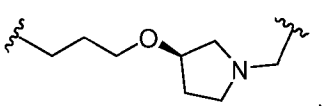
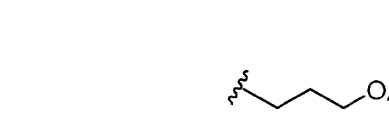

. In some embodiments, L is


. In some embodiments, L is


. In some

embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .


. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
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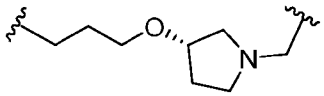
. In some embodiments, L is 
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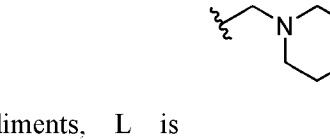
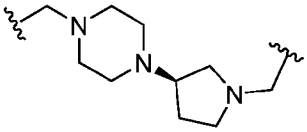
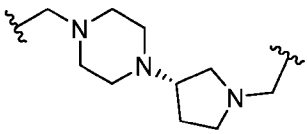
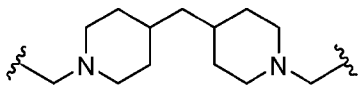
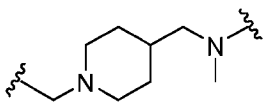
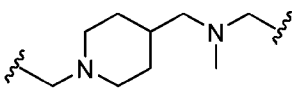
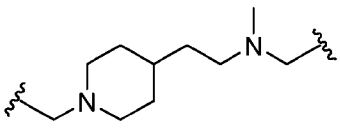
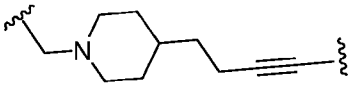
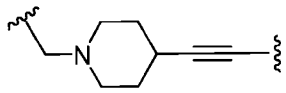
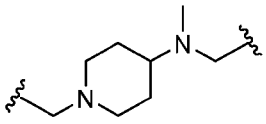
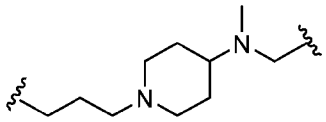
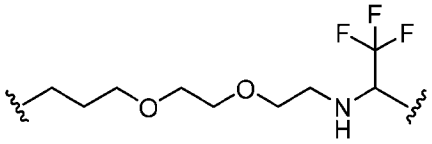
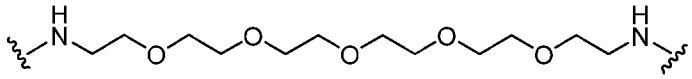
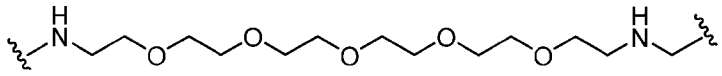
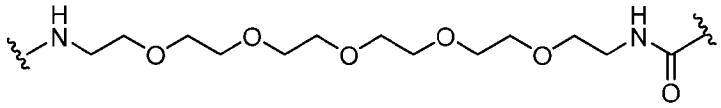
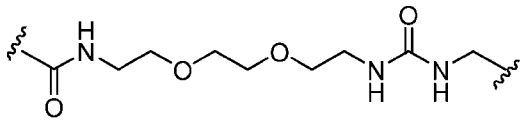
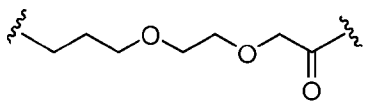
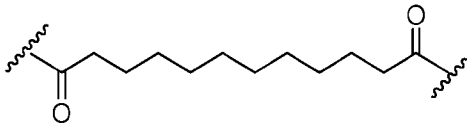
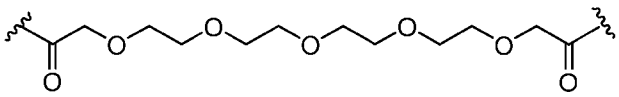
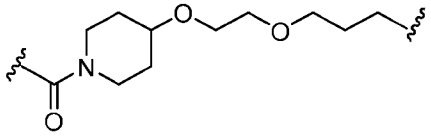
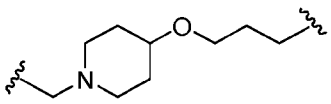
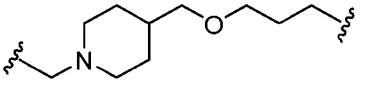
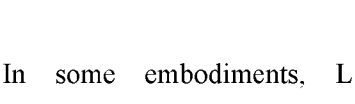
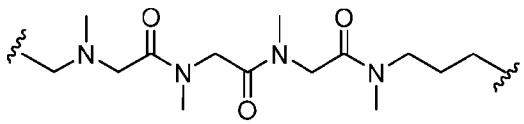
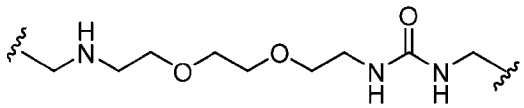
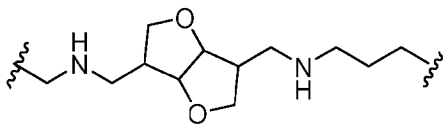
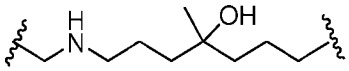
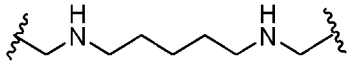
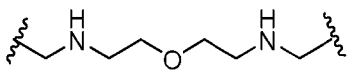
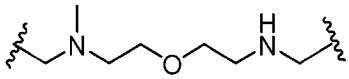
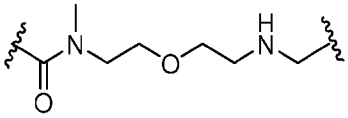
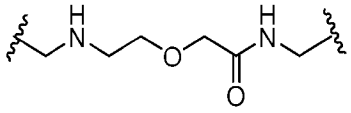
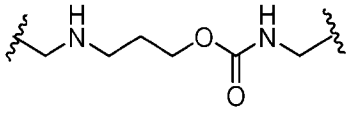
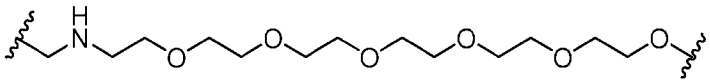
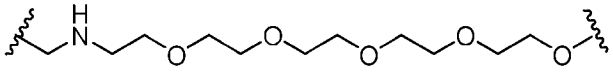
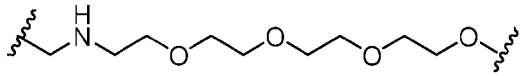
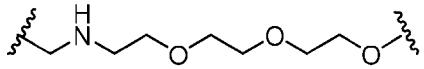
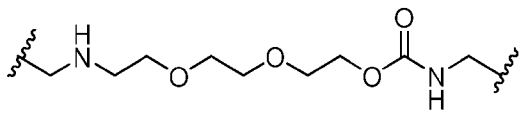
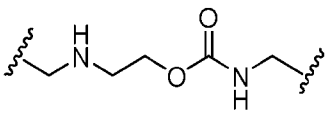
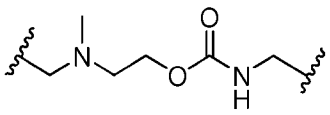
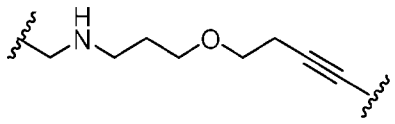
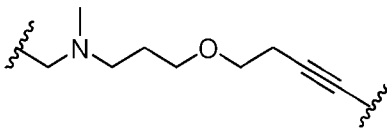
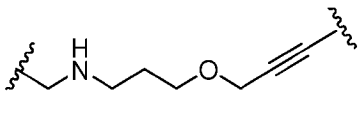
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is

 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiment, L is


. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is
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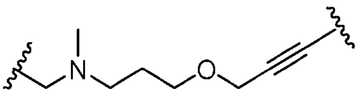
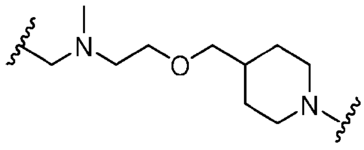
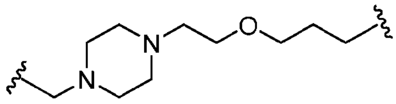
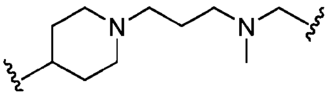
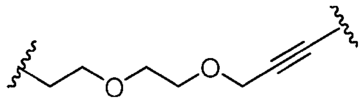
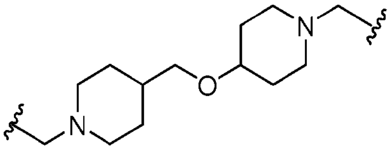
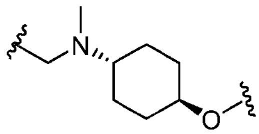
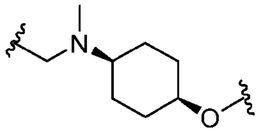
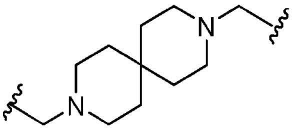
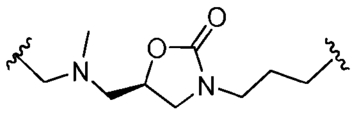
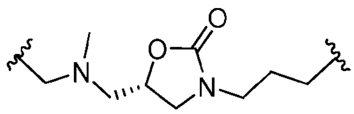
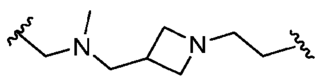
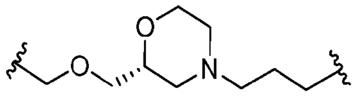
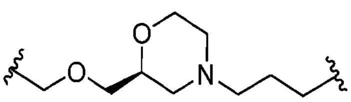
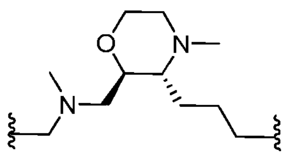
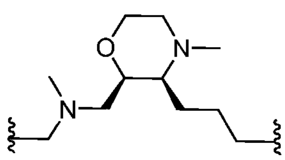
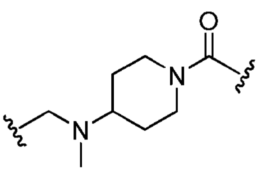
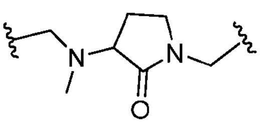
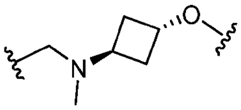
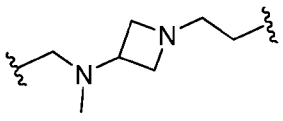
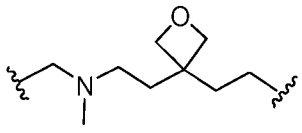
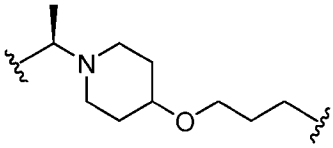
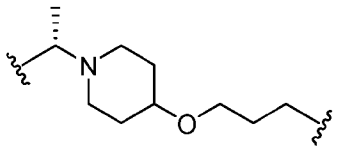
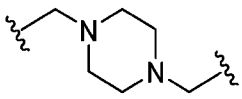
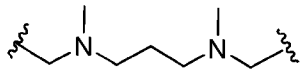
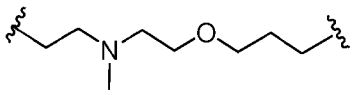
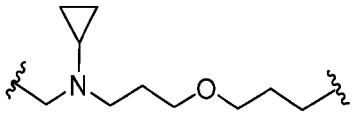
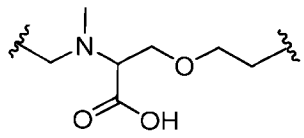
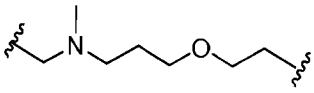
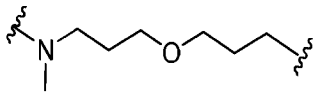
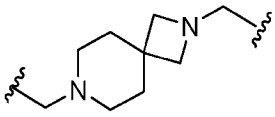
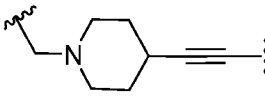
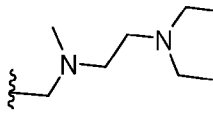
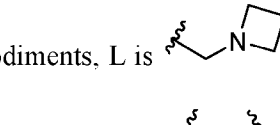
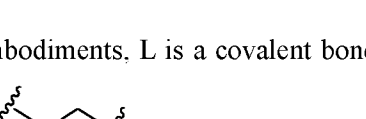
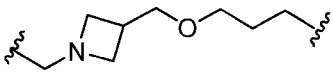
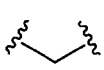
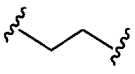
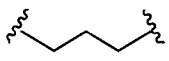
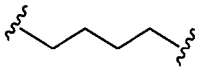
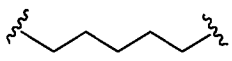
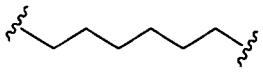
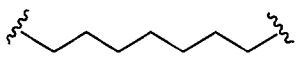
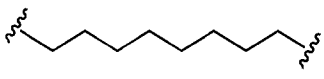
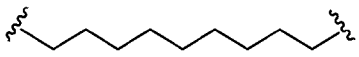
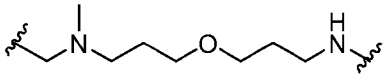
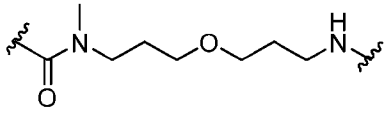
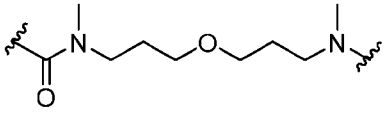
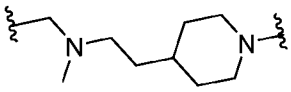
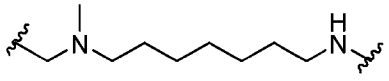
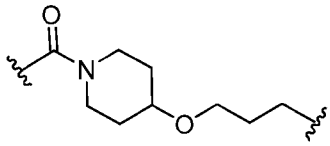
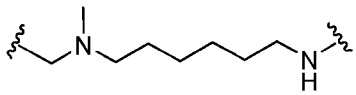
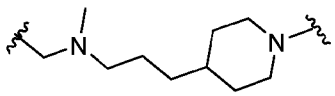
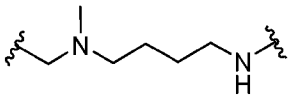
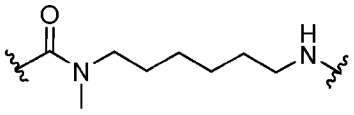
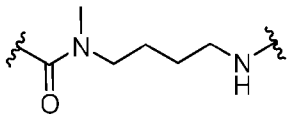
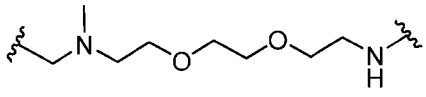
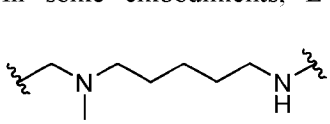
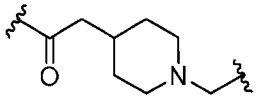
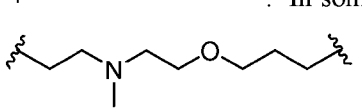
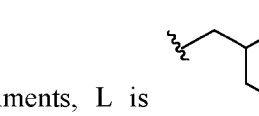
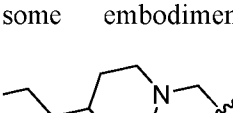
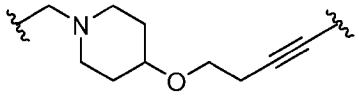
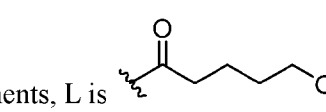
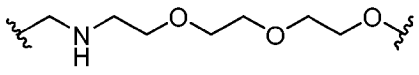
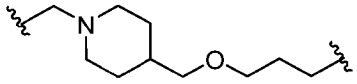
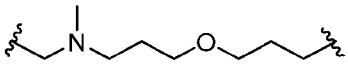
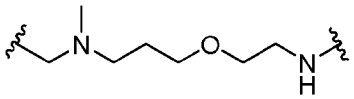
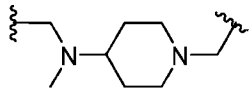
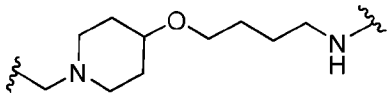
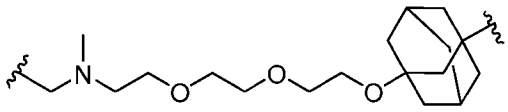
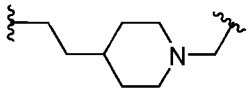
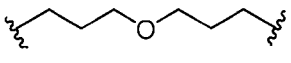
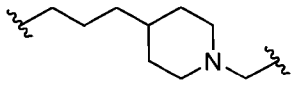
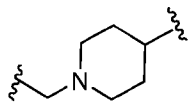
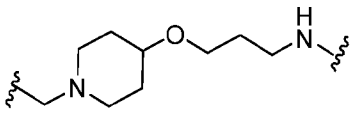
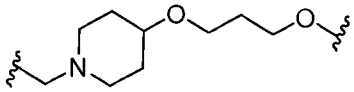
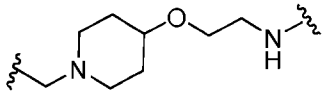
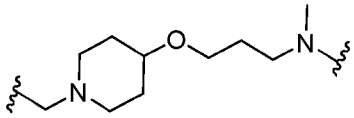
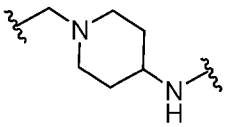
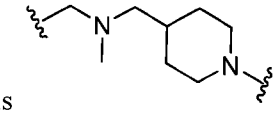
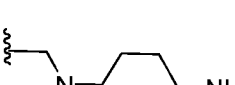
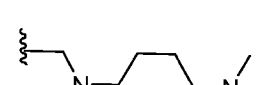
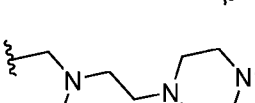
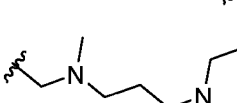
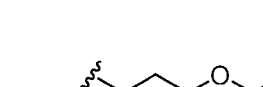
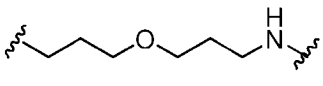
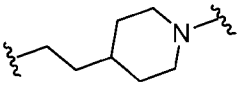
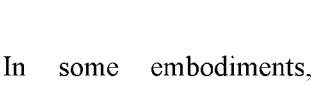
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some

embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is a covalent bond. In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some

embodiments, L is  . In some embodiments, L is a covalent bond. In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is .

In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  .

In some embodiments, L is



. In some embodiments, L is

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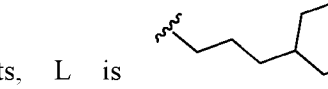
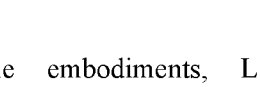


. In some embodiments, L is



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In some embodiments, L is

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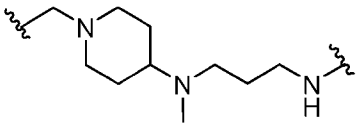
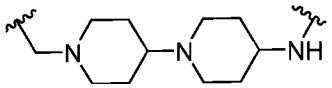
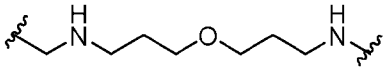
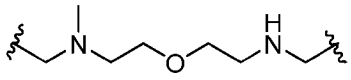
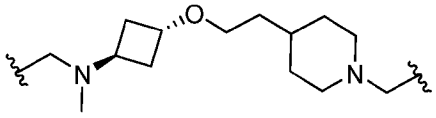
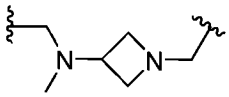
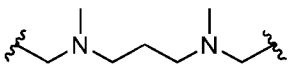
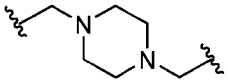
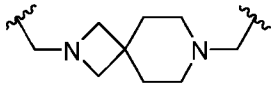
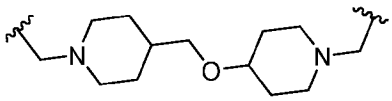
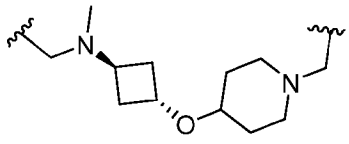
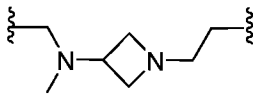
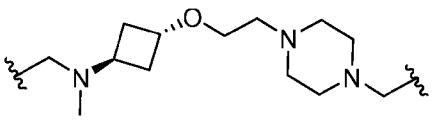
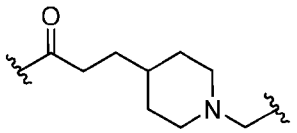
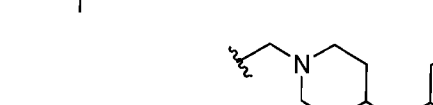
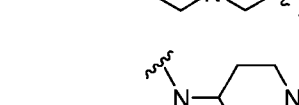
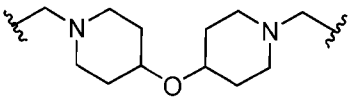
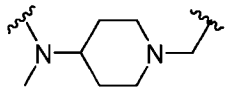
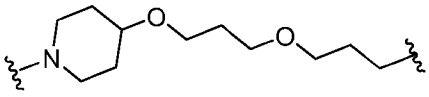
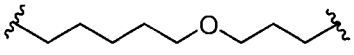
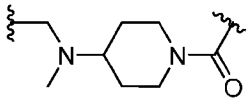
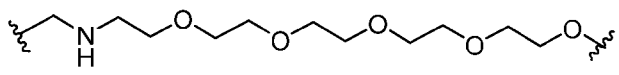
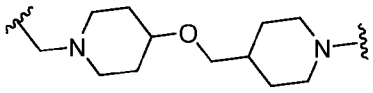
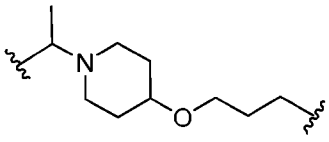
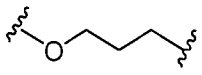
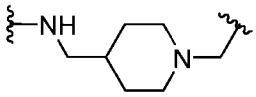
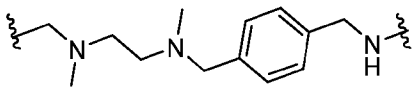
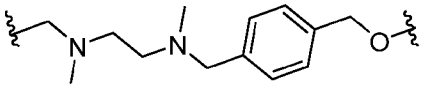
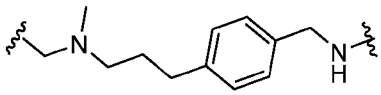
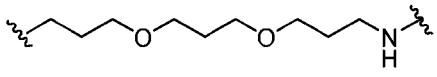
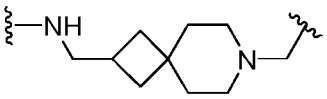
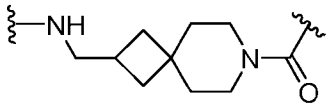
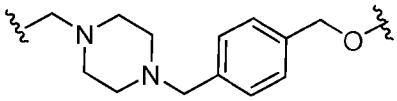
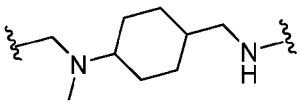
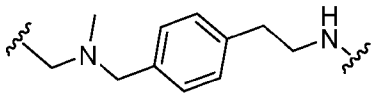
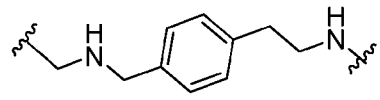
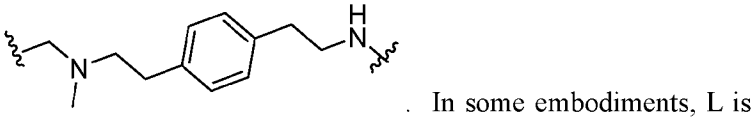
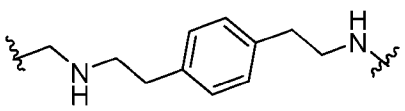
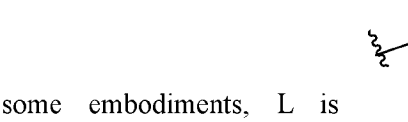
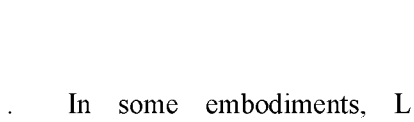
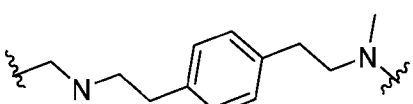
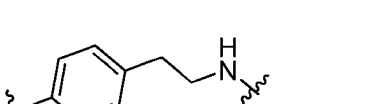
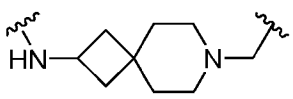
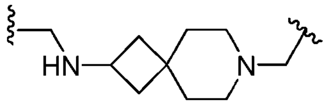
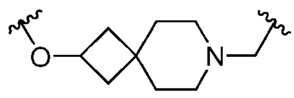
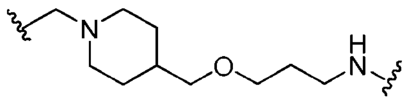
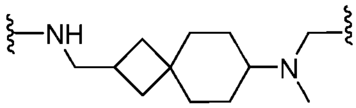
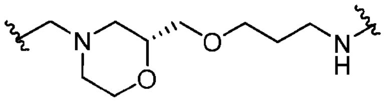
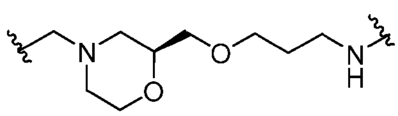
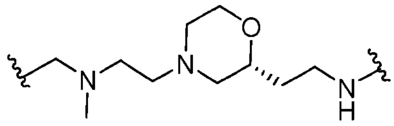
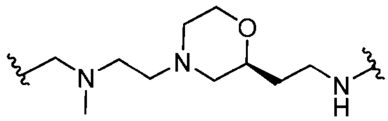
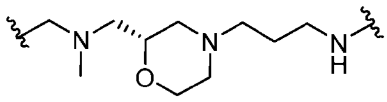
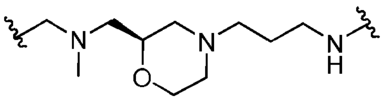
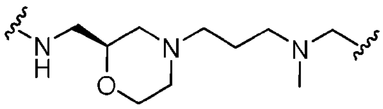
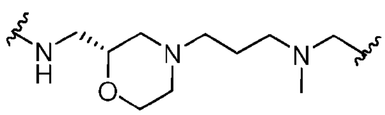
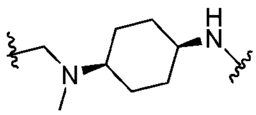
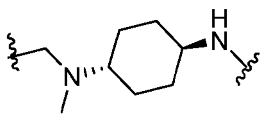
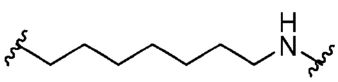
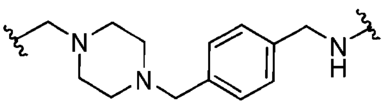
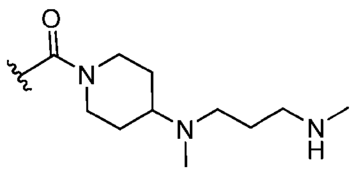
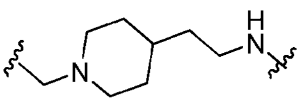
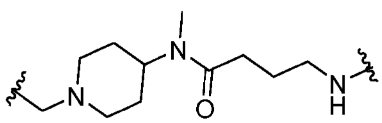
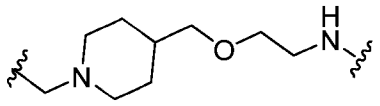
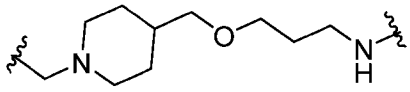
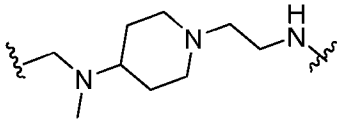
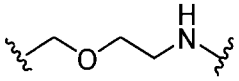
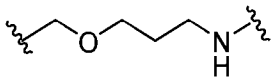
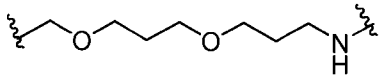
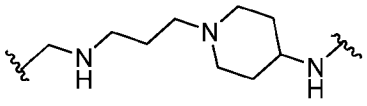
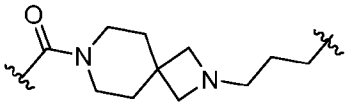
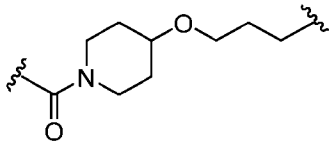
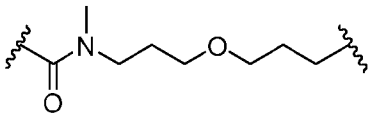
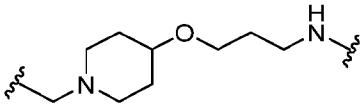
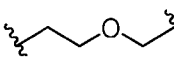
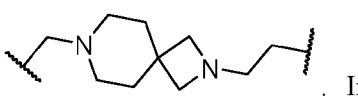
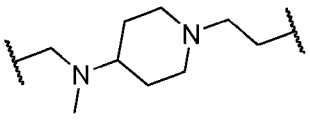
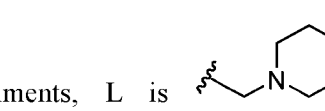
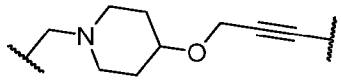
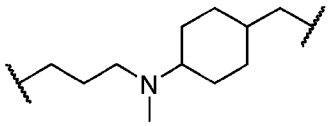
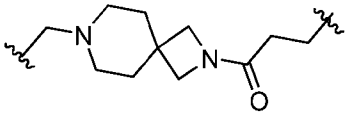
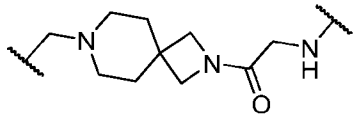
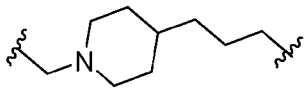
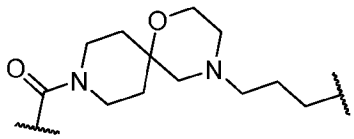
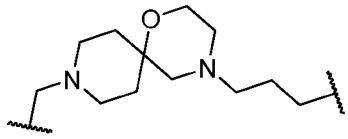
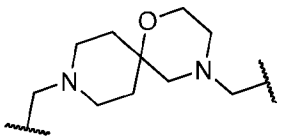
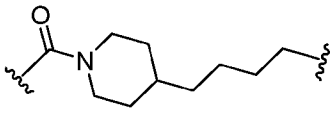
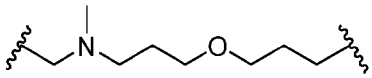
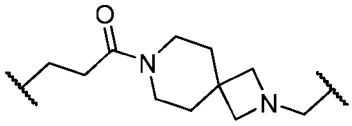
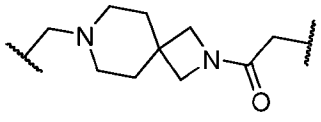
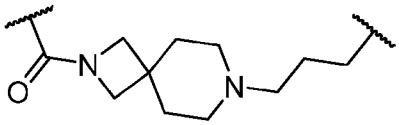
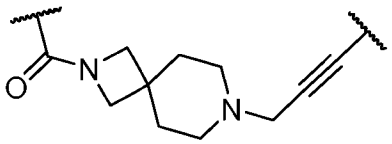
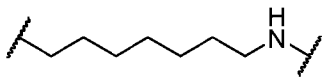
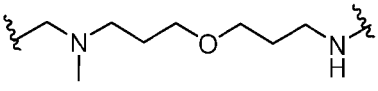
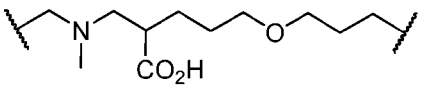
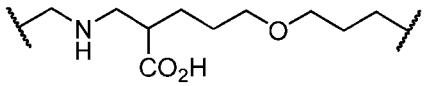
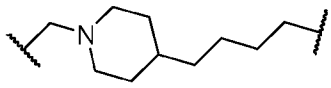
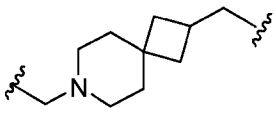
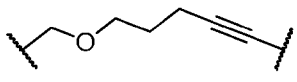
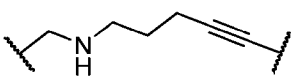
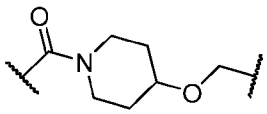
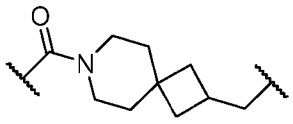
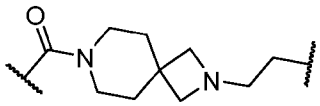
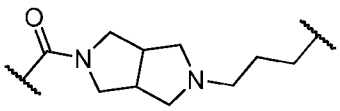
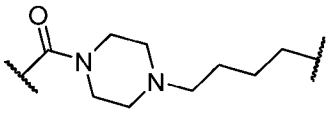
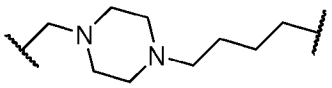
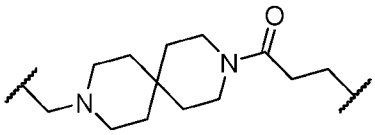
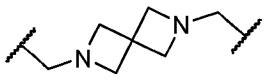
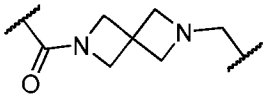
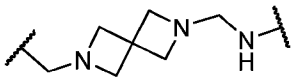
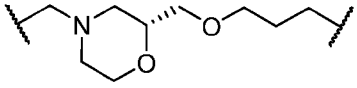
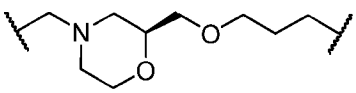
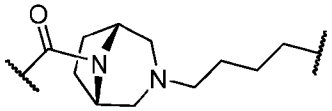
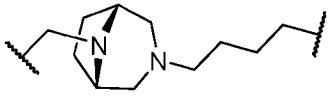
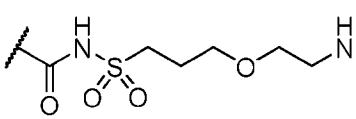
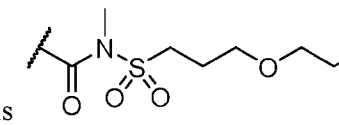
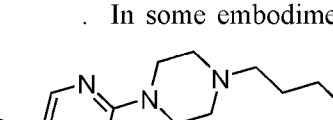
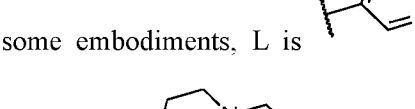
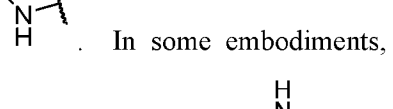
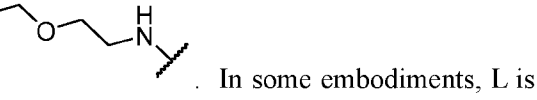
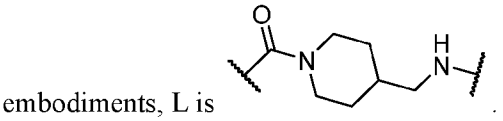
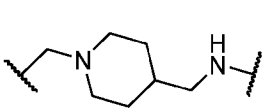
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is .

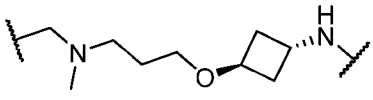
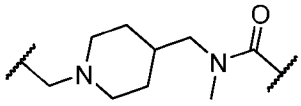
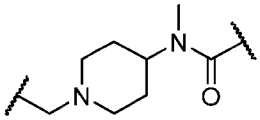
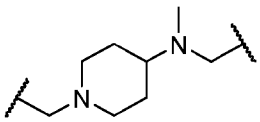
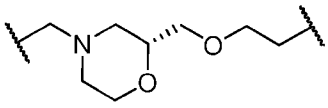
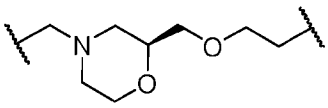
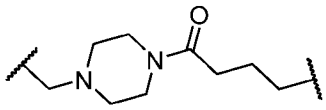
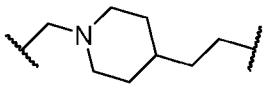
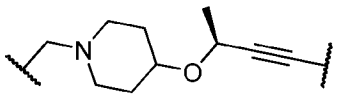
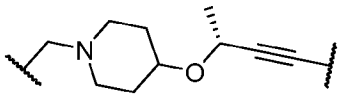
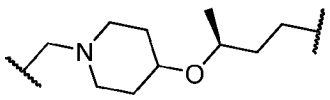
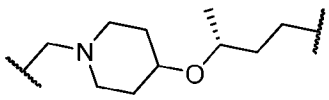
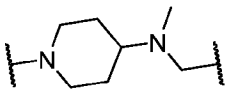
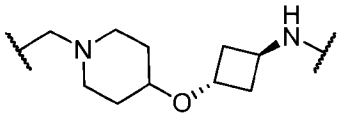
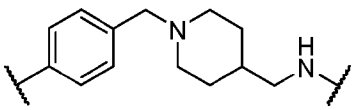
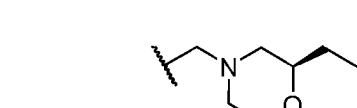
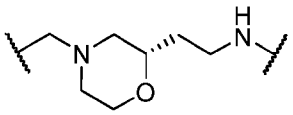
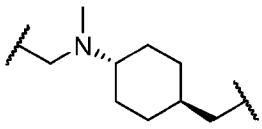
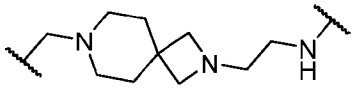
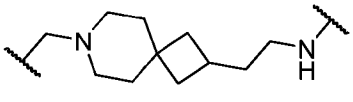
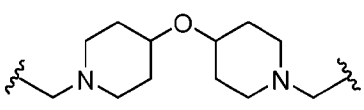
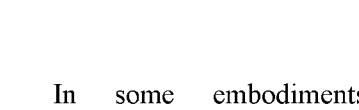

. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is
. In some embodiments, L is
. In In some embodiments, L is 
. In some In In some embodiments, L is

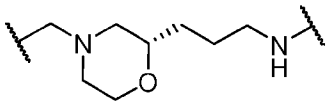
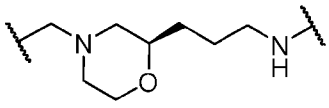
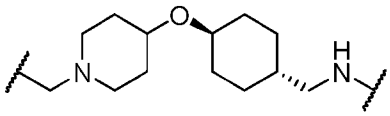
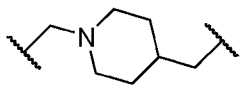
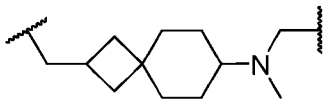
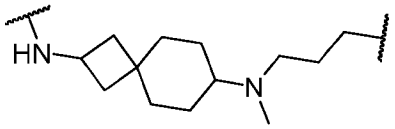
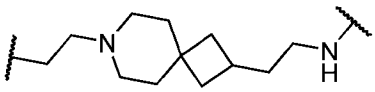
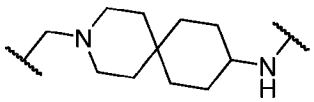
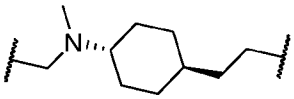
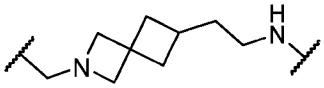
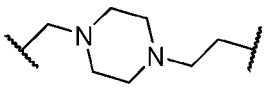
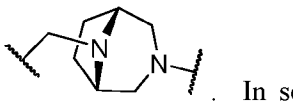
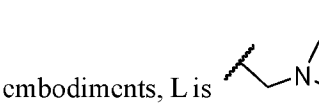
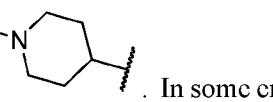
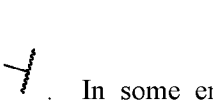
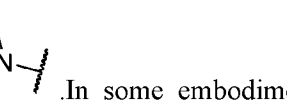
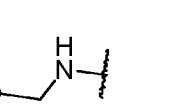
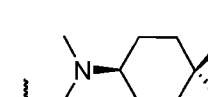
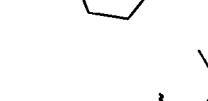
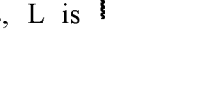
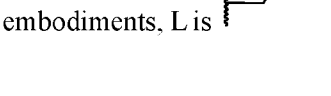
 . embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments,

L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some

embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .


. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is 
.In some embodiments, L is 
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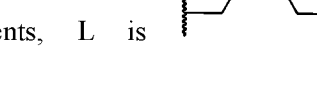
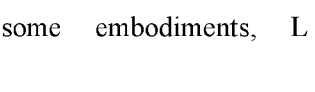
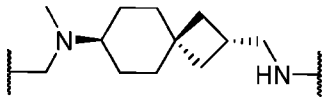
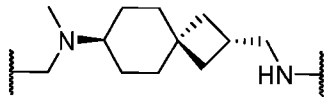
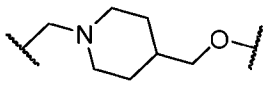
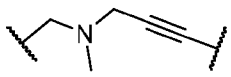
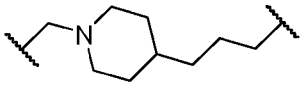
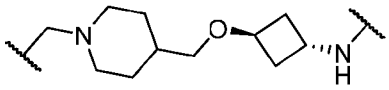
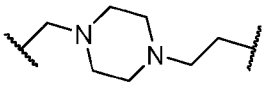
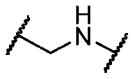
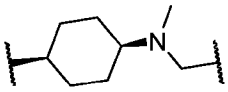
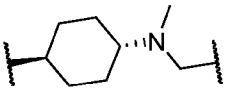
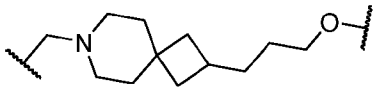
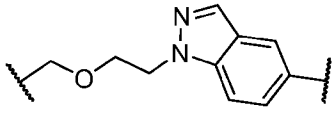
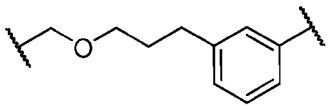
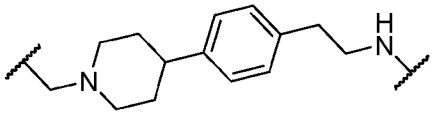
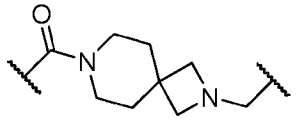
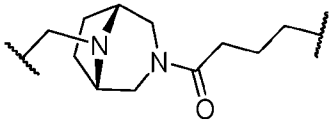
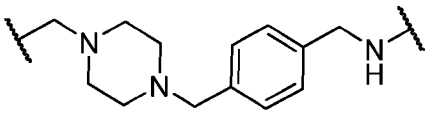
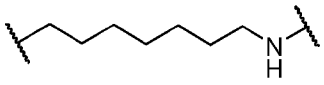
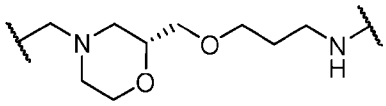
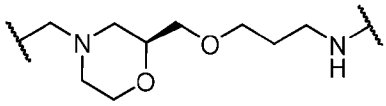
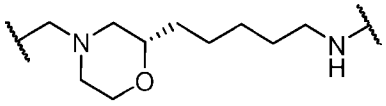
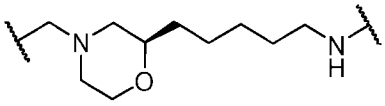
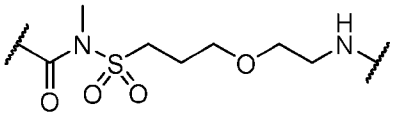
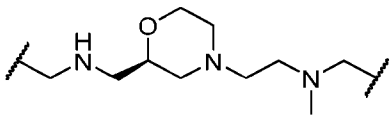
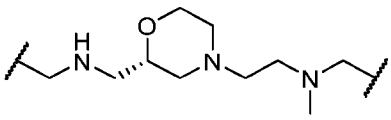
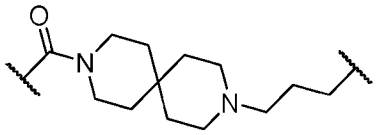
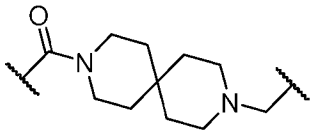
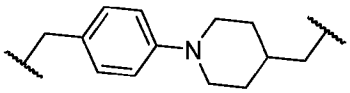
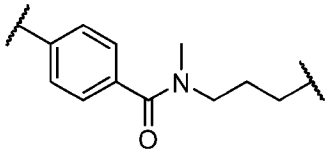
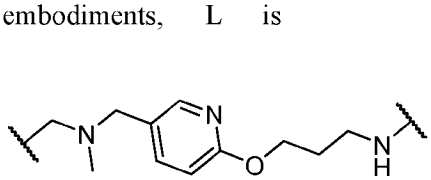
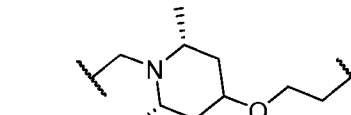
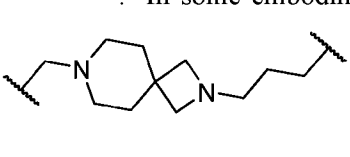
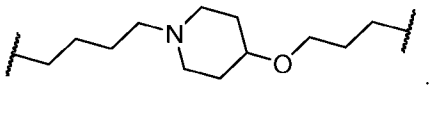
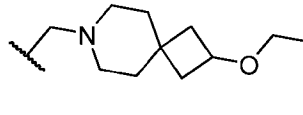
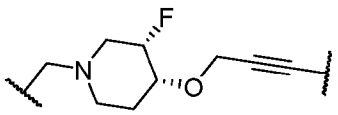
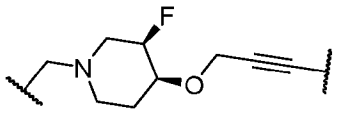
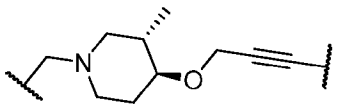
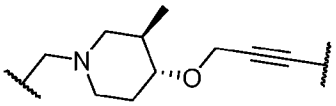
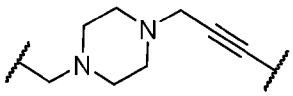
. In some embodiments, L is 
. In some embodiments, L is 
. In some embodiments, L is
. In some embodiments, L is

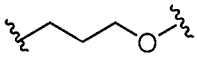
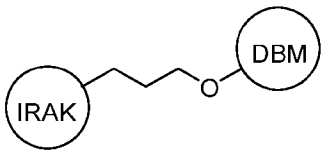
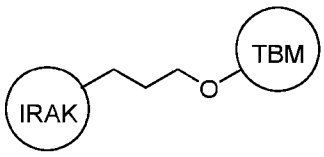
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is

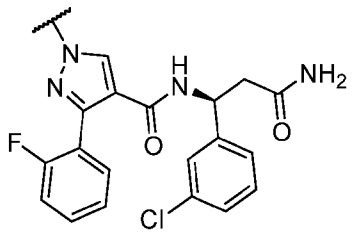
embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is . In some embodiments, L is . In

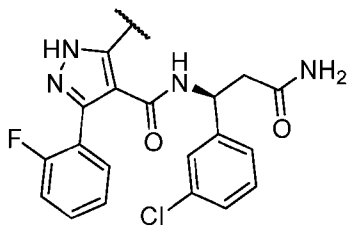
some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

[00515] In some embodiments, L is selected from those depicted in **Table B**, below.

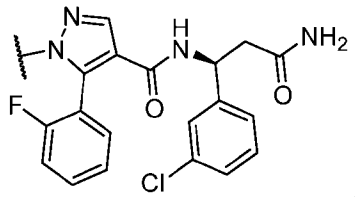
[00516] In some embodiments, L is selected from those depicted in **Table 1**, below.

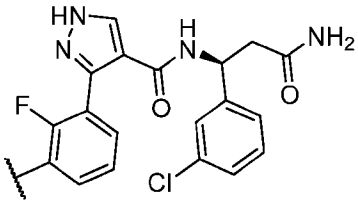
[00517] Without limitation, the point of attachment of L to IRAK and DBM can be, for example when L is  , either  or  .

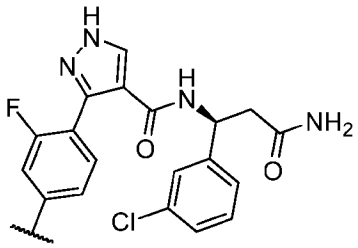
[00518] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

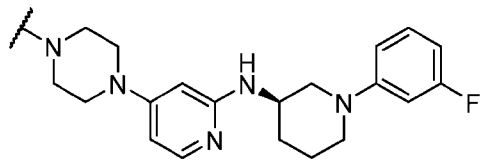
[00519] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

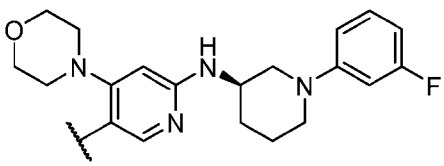
[00520] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is

selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

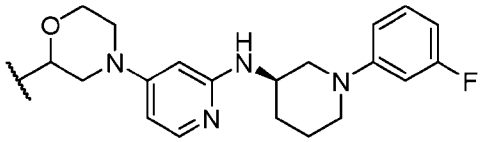
[00521] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00522] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00523] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00524] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00525] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is

selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

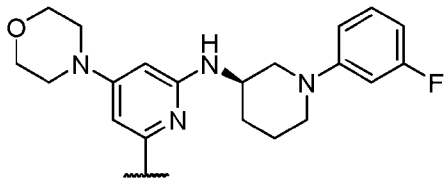
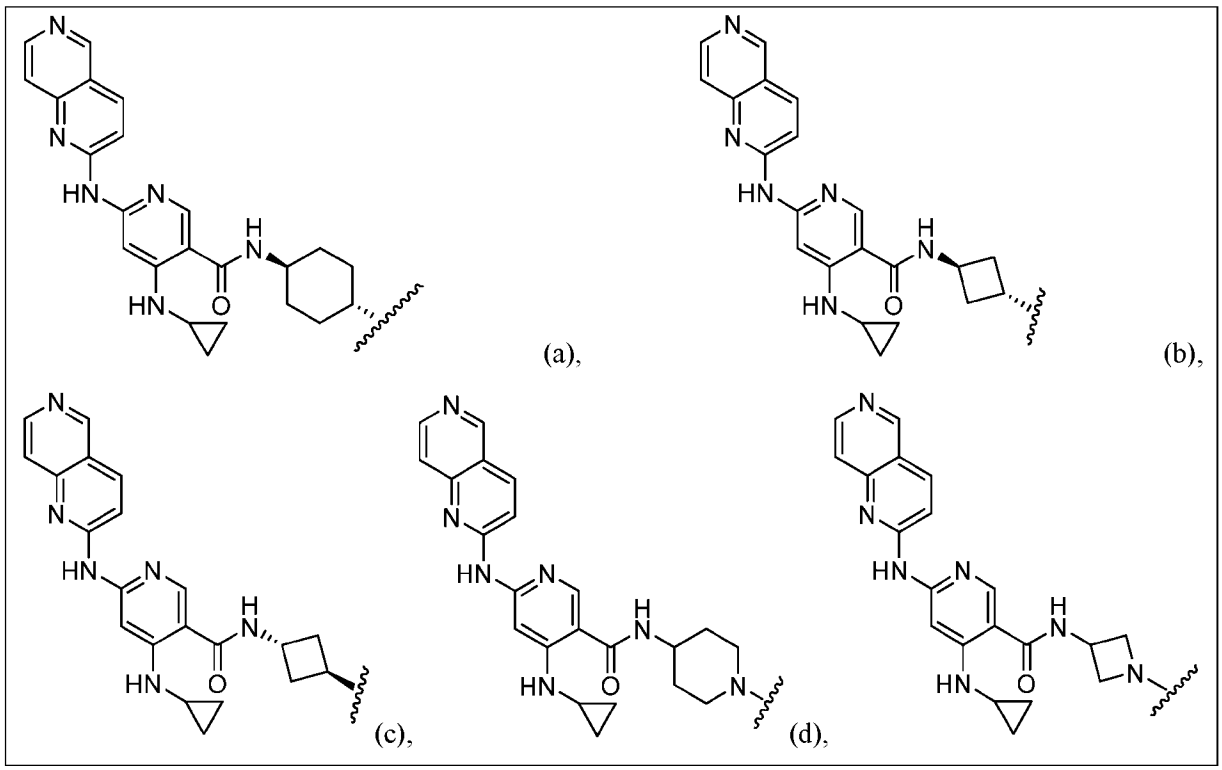
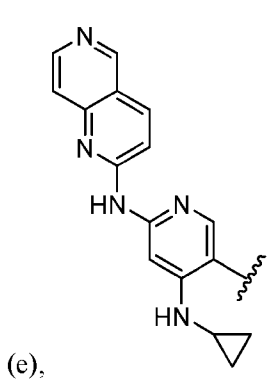
[00526] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein DBM is  , TBM is selected from but not limited to any of those in **Table A** below, and L is selected from any of those in **Table B** below.

Table A. Exemplified IRAK binders (IRAK)

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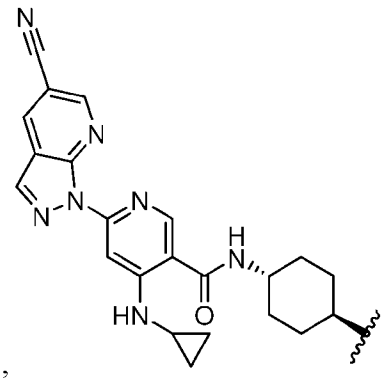
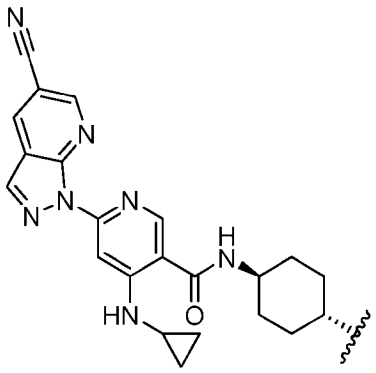
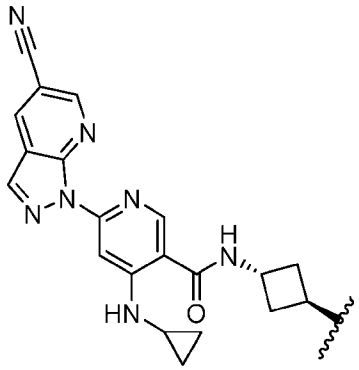

(f),


(g),

(h),(i),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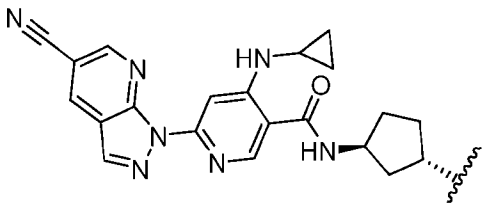
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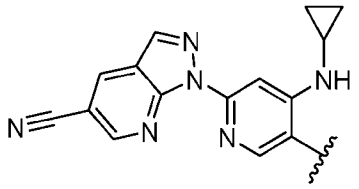
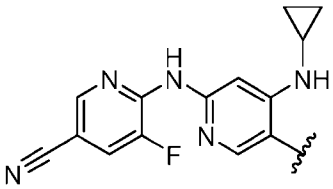

(l),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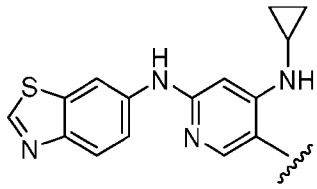
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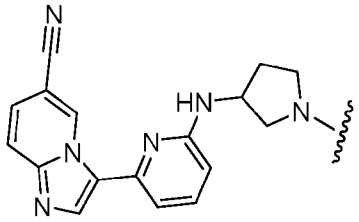
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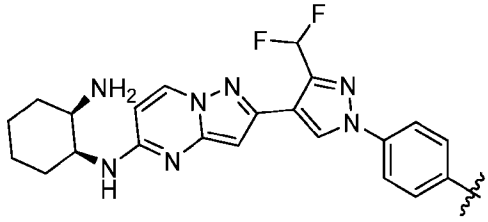
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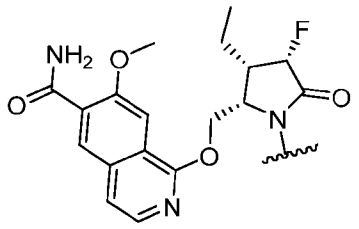
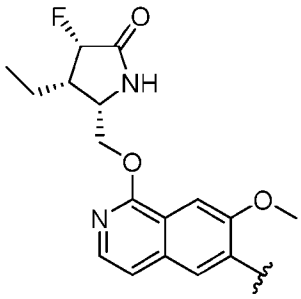
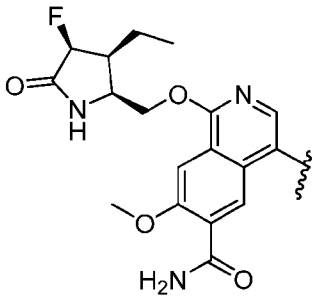
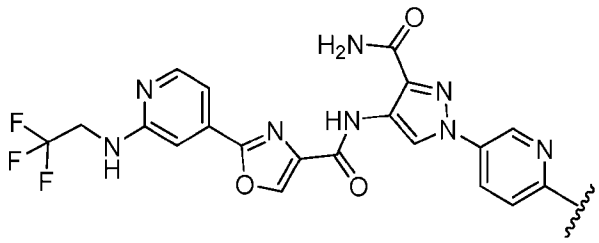
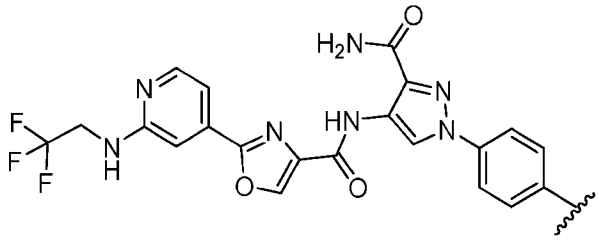

(q),


(r),

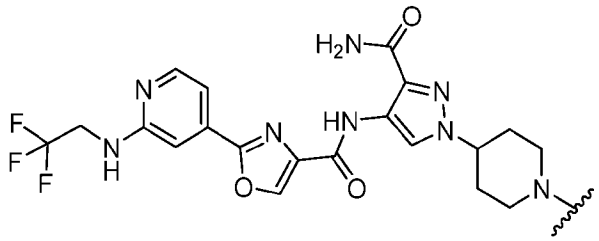

(s),



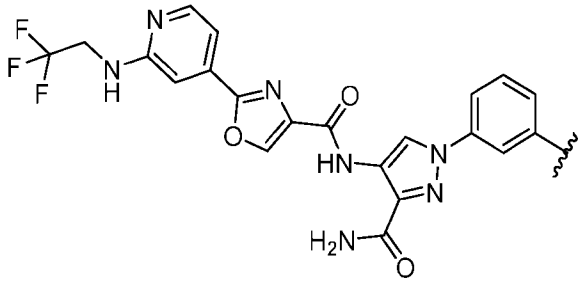
(t),



(u),



(v),



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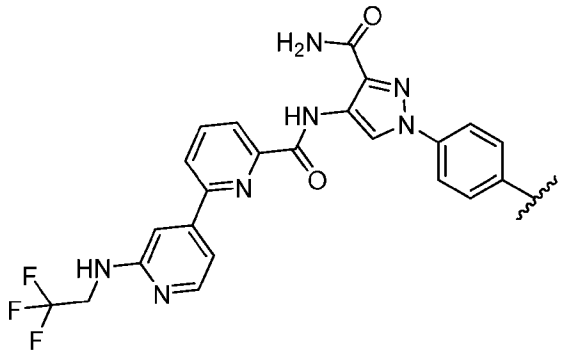

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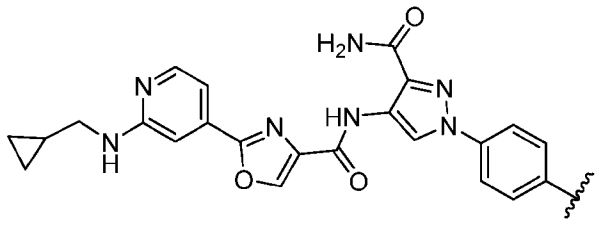
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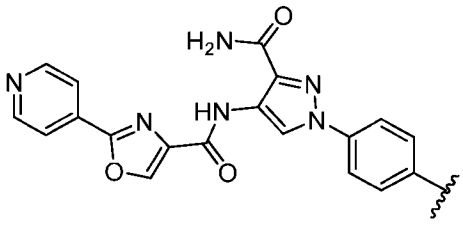
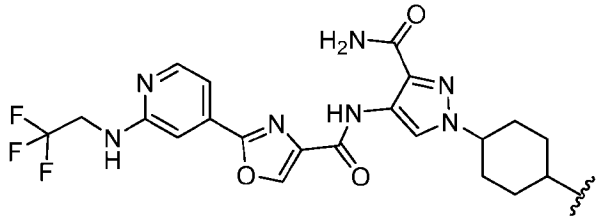

(z),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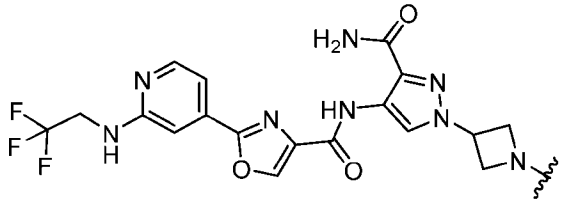
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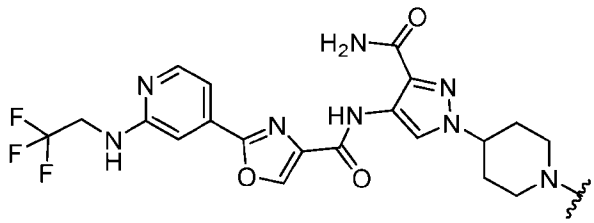
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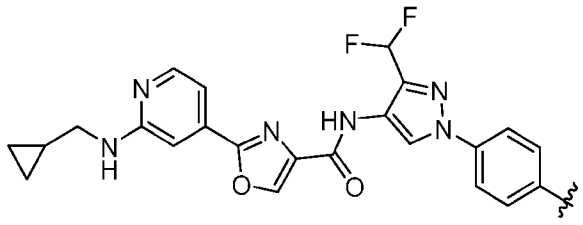
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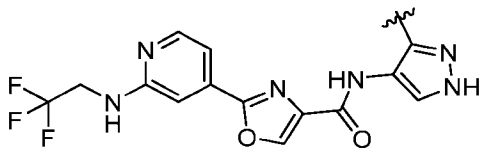
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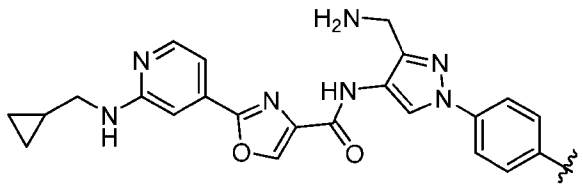
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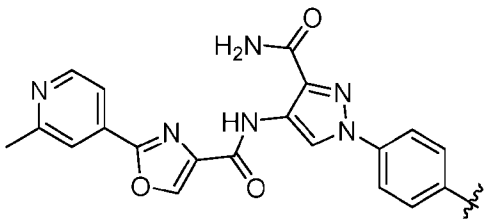
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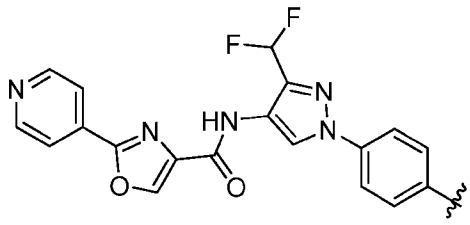
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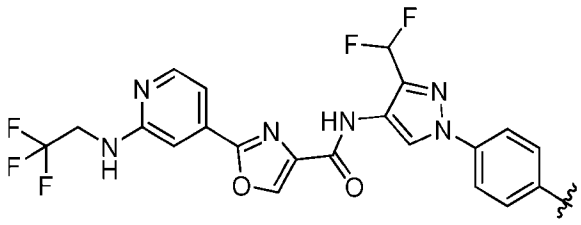
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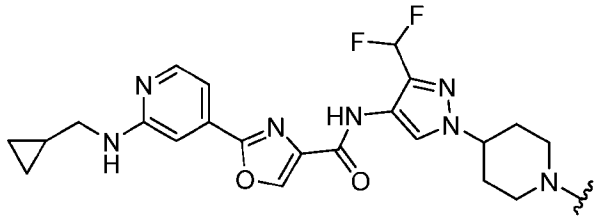
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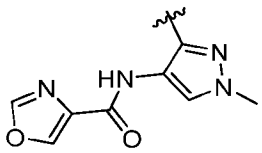
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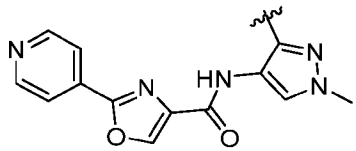
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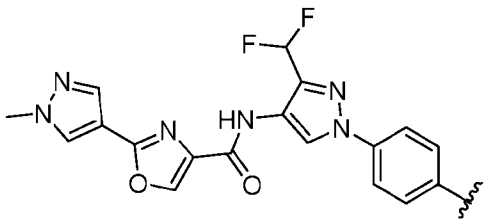
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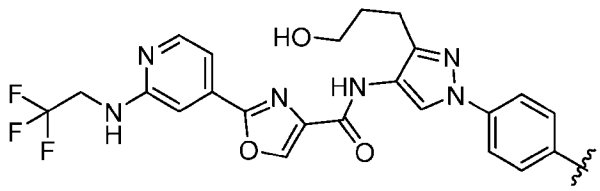
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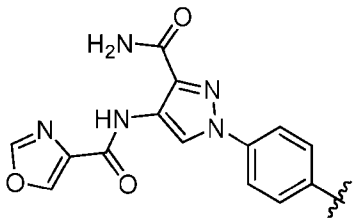
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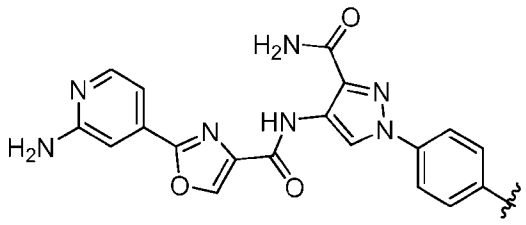
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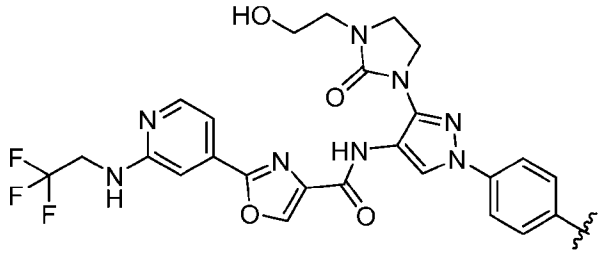
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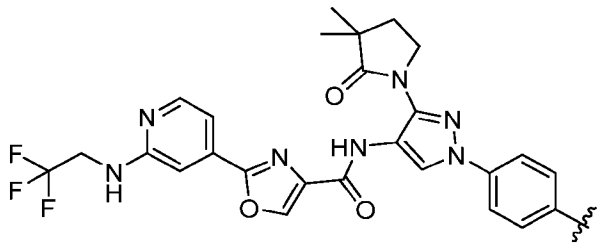
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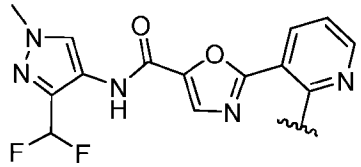
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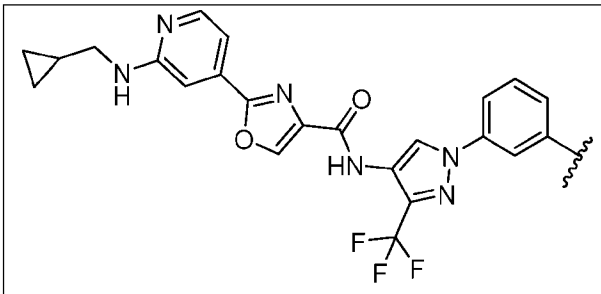

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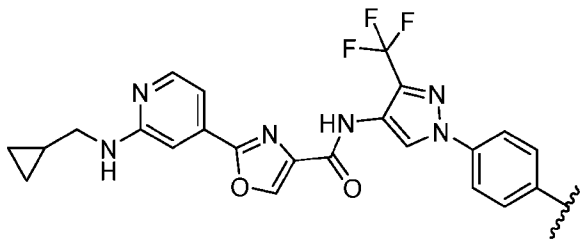

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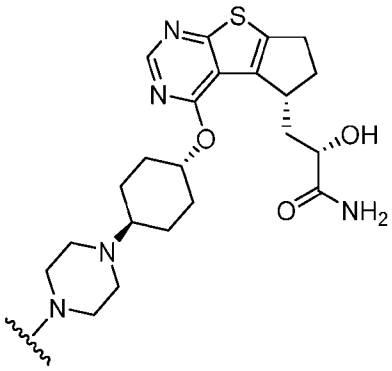

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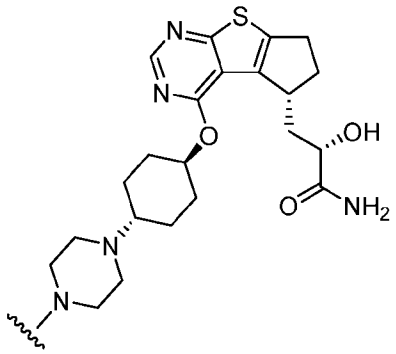

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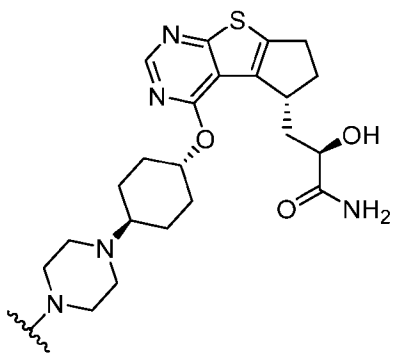

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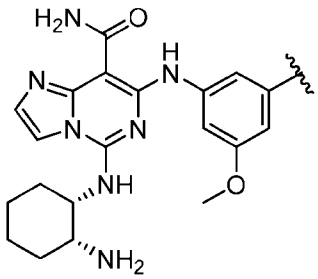

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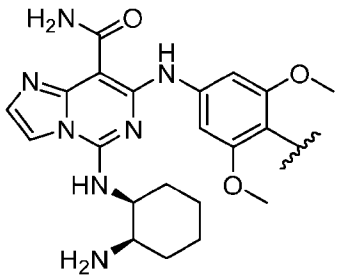

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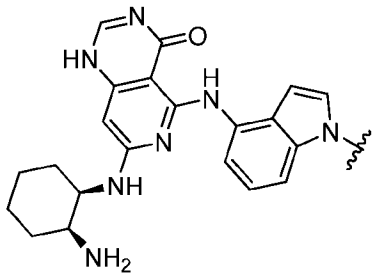

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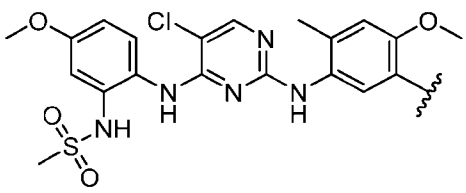

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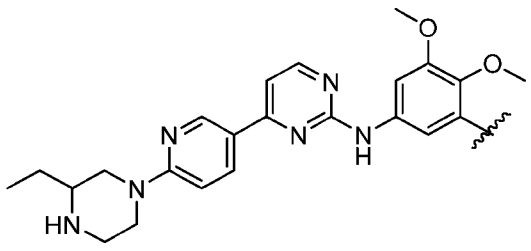
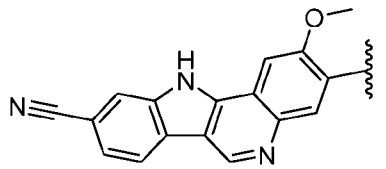
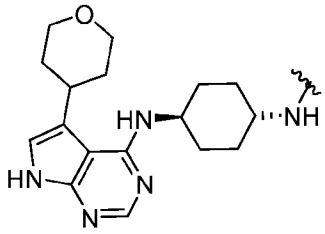


(ccc), 

(ddd), 

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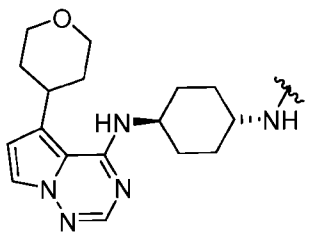
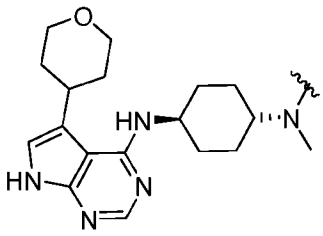
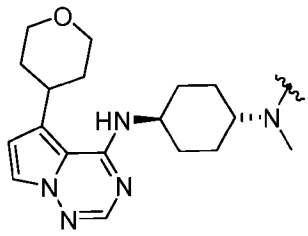


(fff), 

(ggg), 

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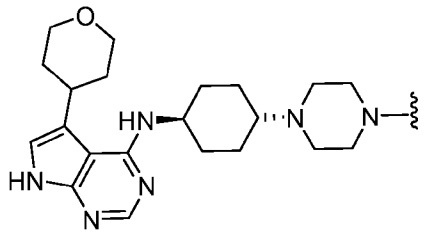
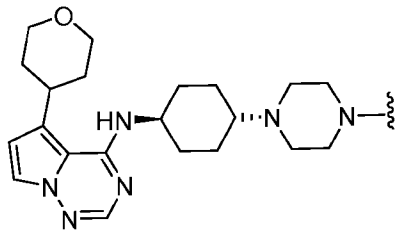


(iii), 

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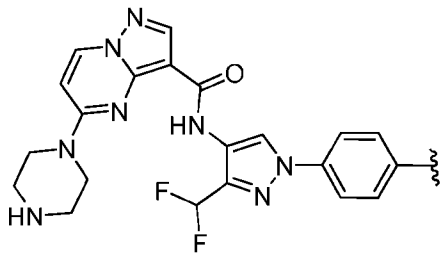
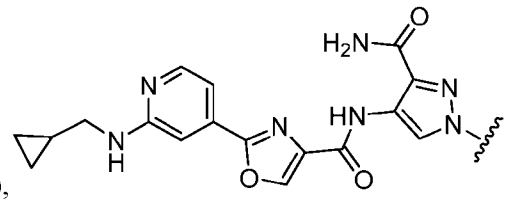
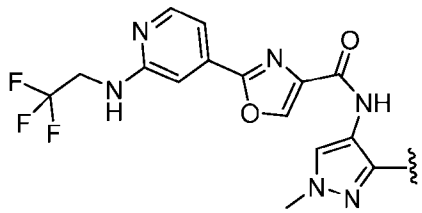
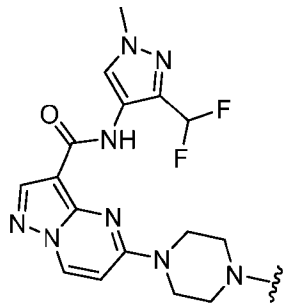


(kkk), 



(lll), 

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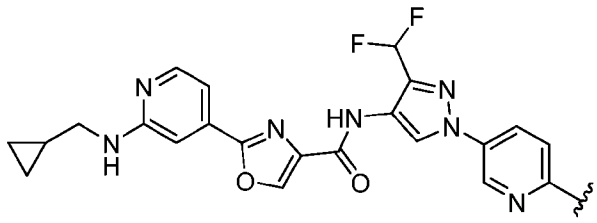

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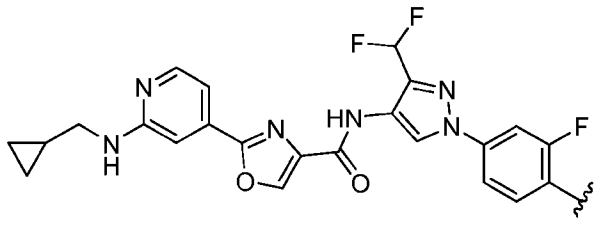

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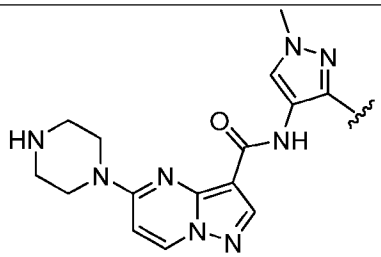

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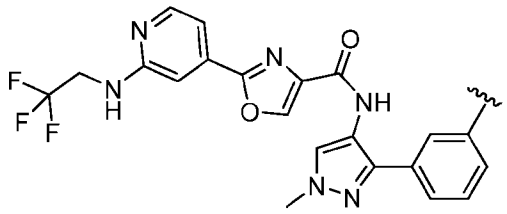

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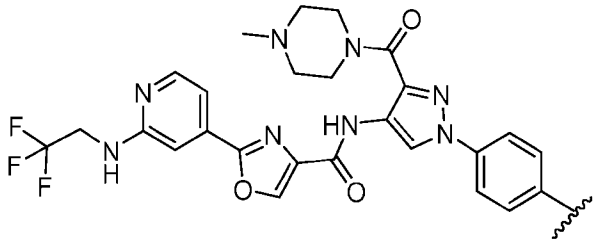

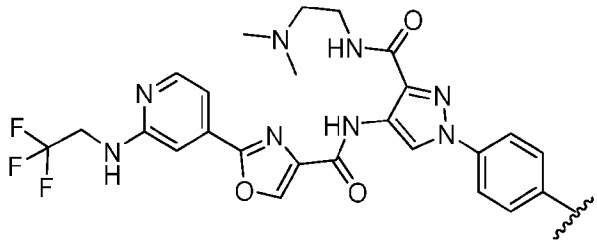

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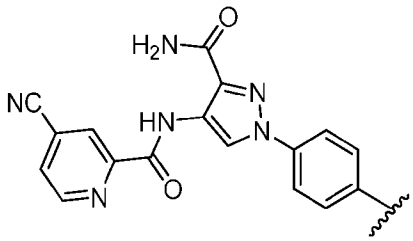

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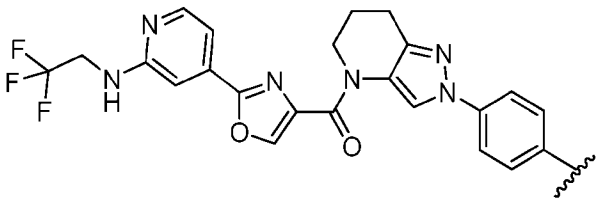

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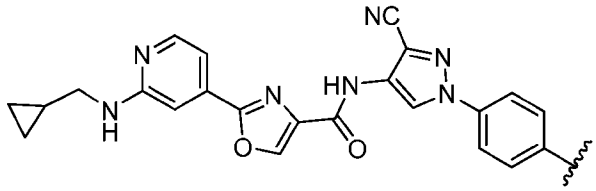

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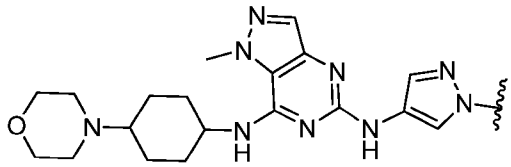

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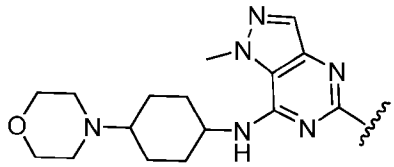

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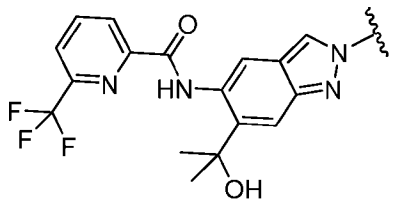

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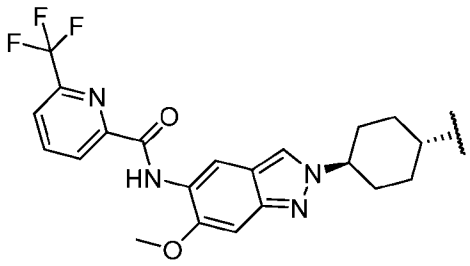

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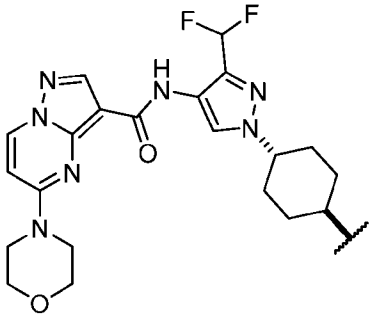

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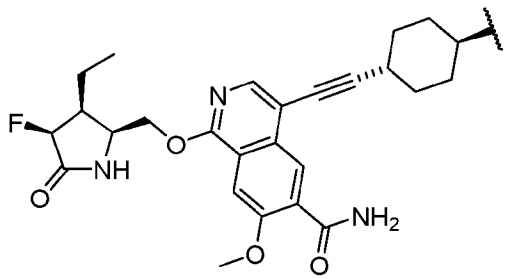

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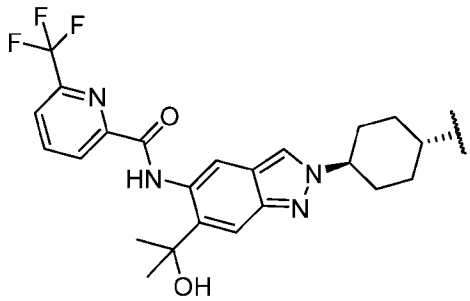

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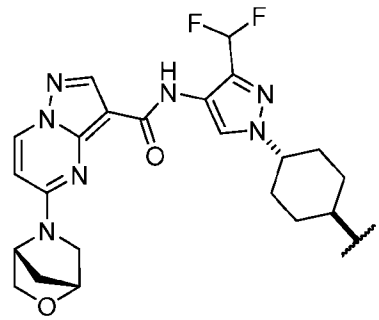

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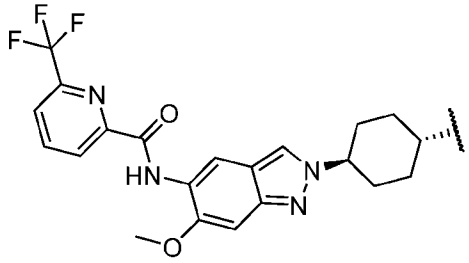

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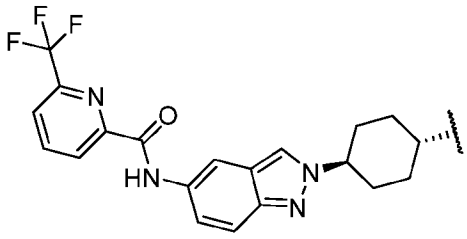

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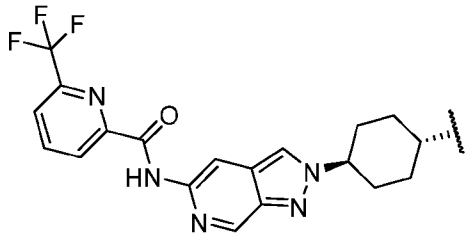

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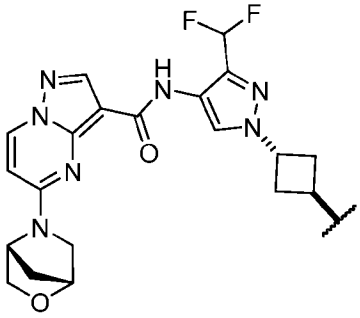

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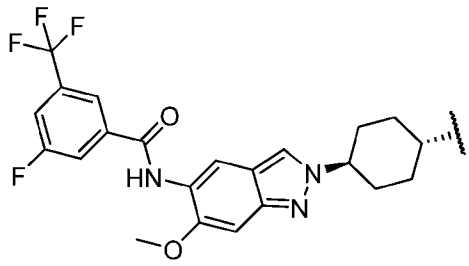

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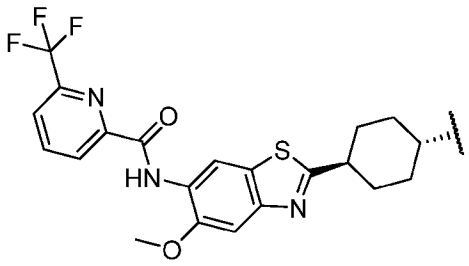

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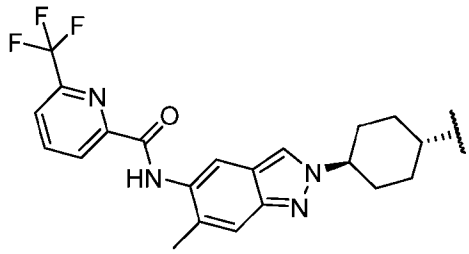

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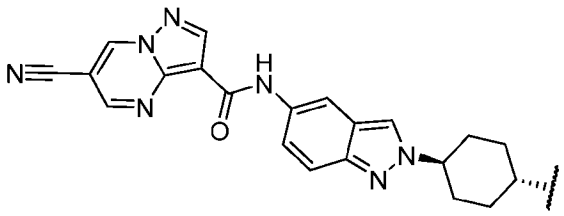

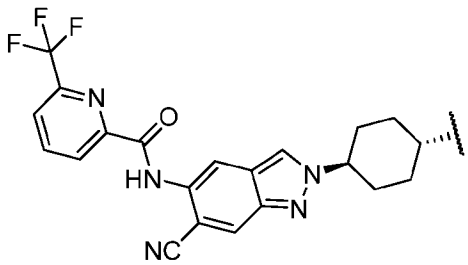

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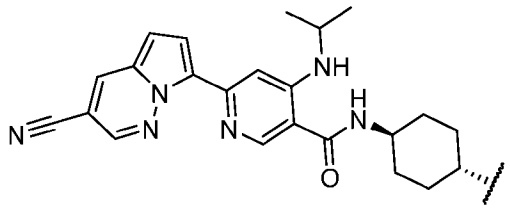

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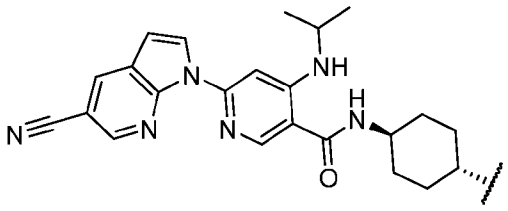

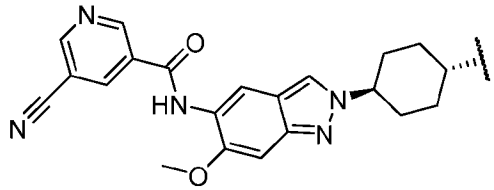

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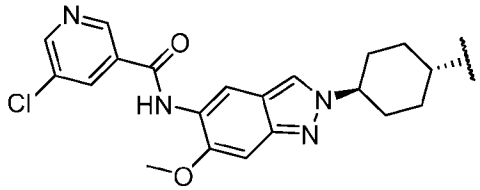

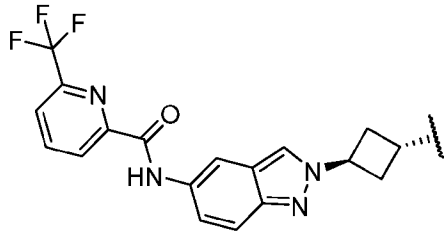

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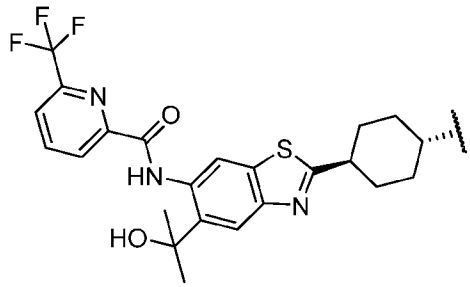

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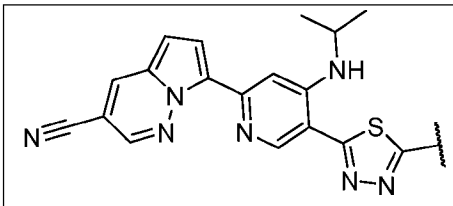
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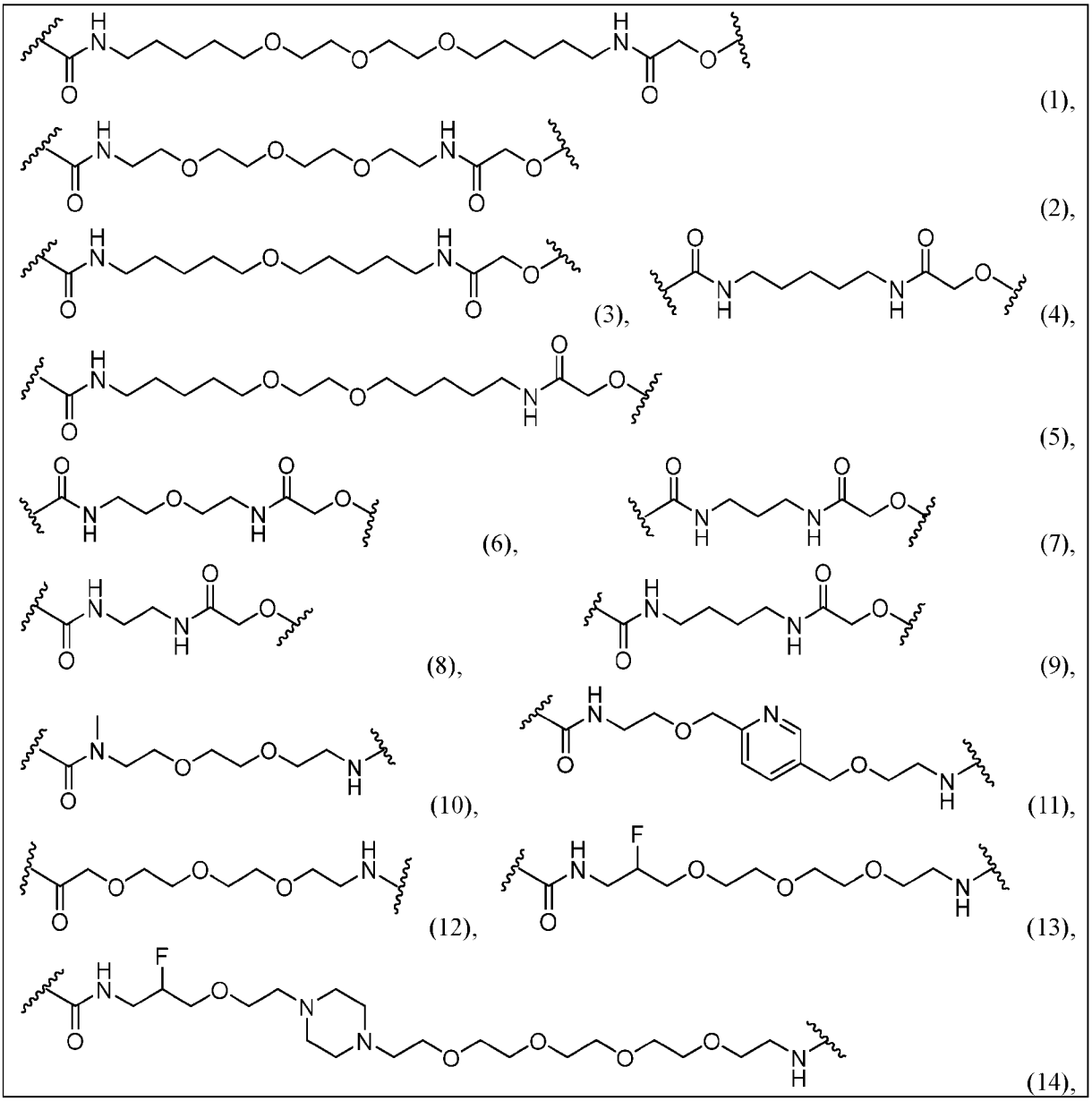
Table B. Exemplified Linkers (L)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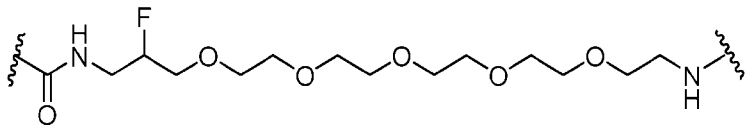
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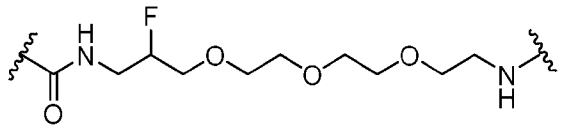
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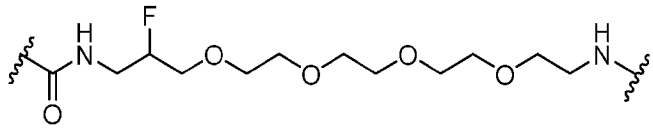
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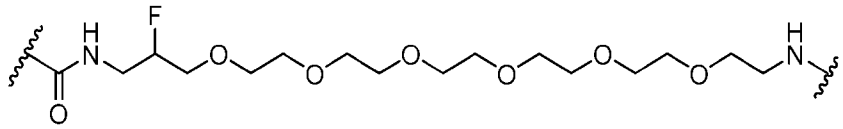
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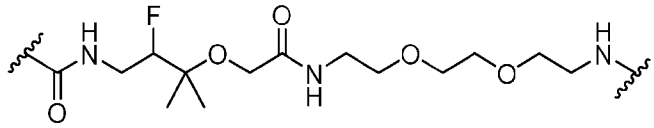
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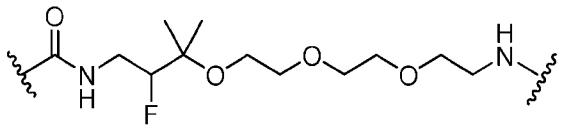
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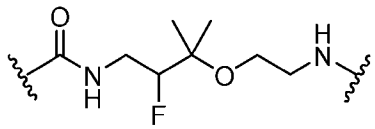
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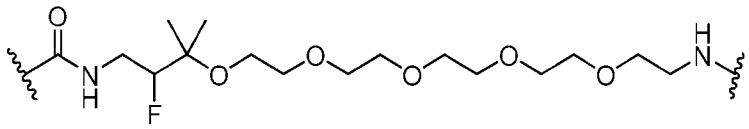
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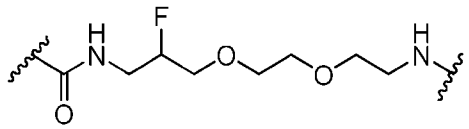
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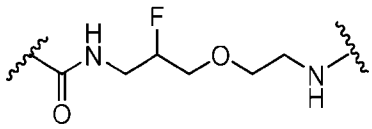
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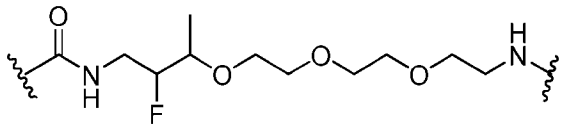
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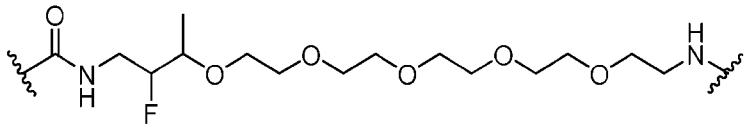
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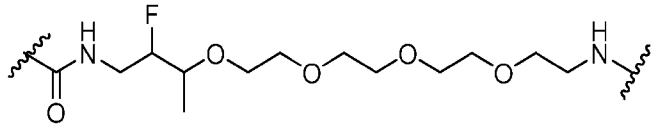
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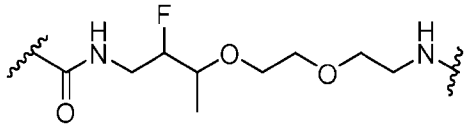
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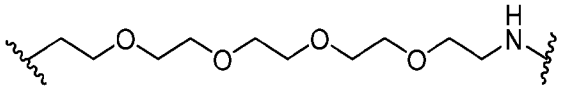
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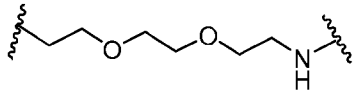
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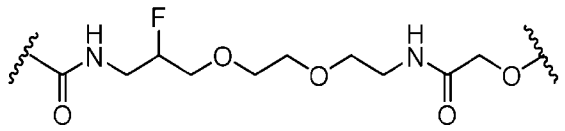

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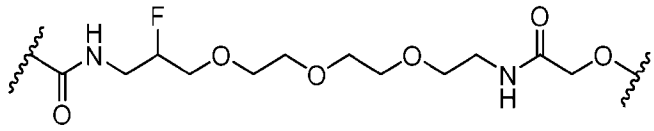

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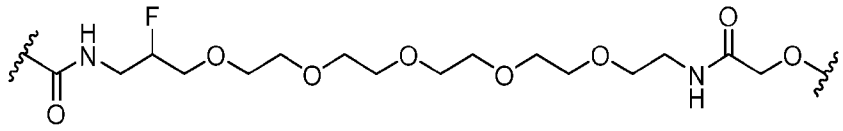

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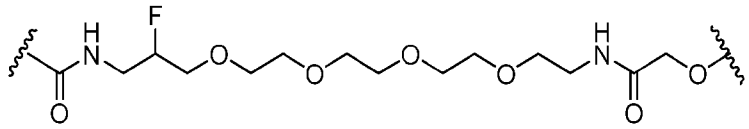

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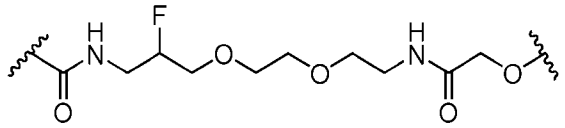

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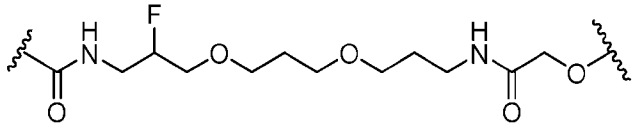

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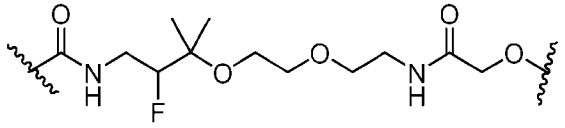

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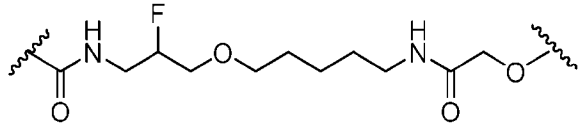

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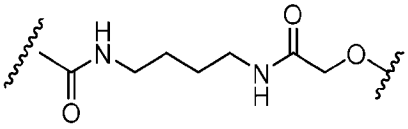

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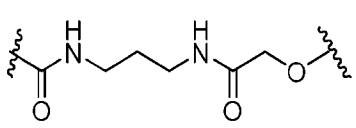

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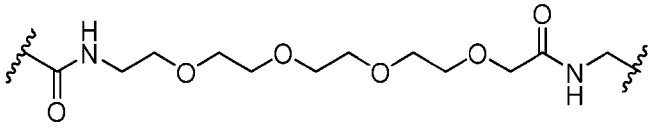

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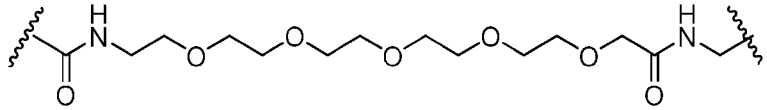

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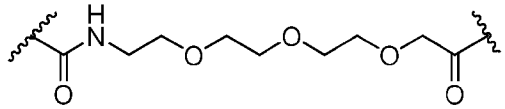

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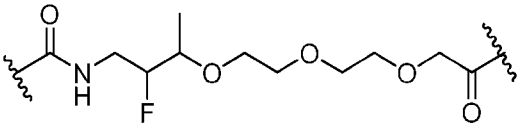

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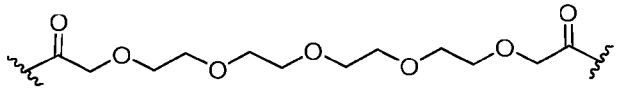

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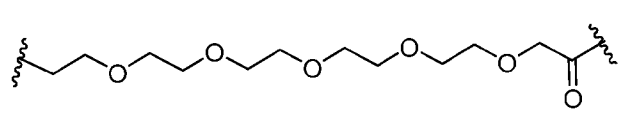

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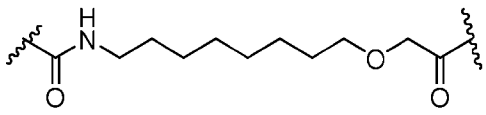

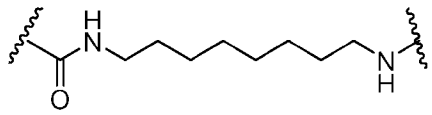

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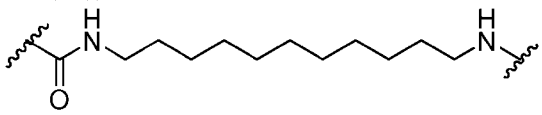

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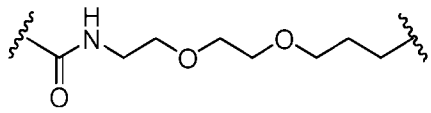

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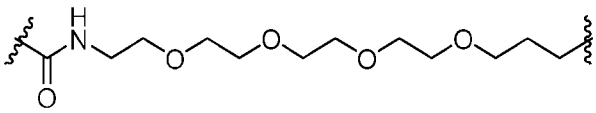

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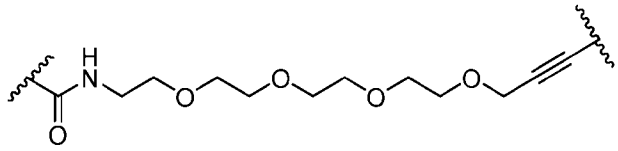

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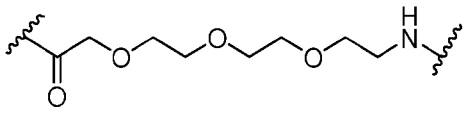

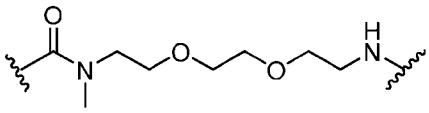

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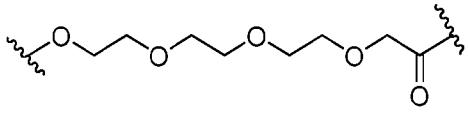

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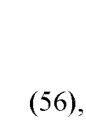

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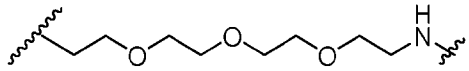

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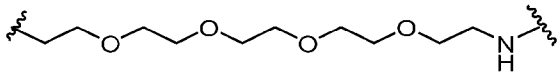

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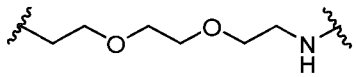

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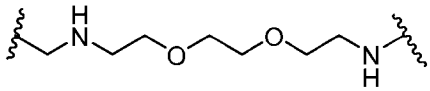

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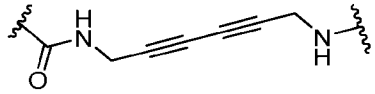

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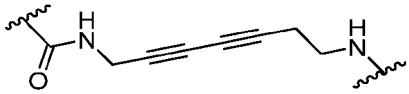

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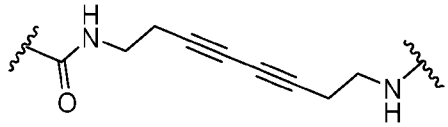

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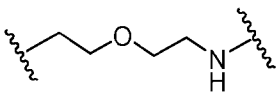

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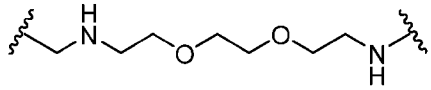

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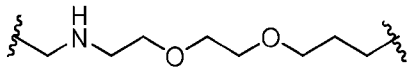

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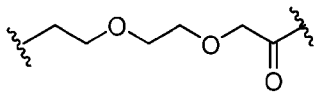

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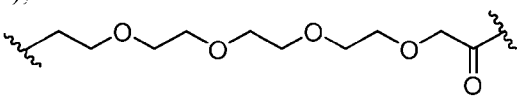

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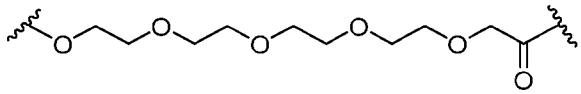

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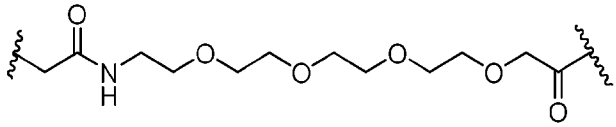

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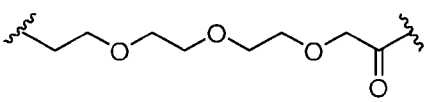

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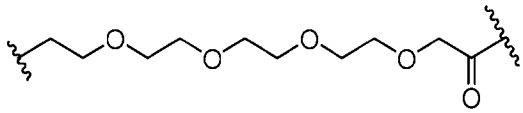

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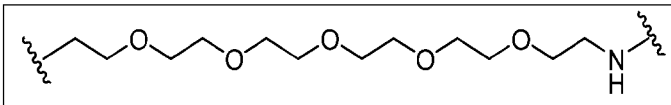
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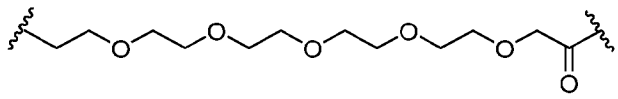
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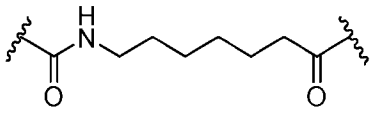
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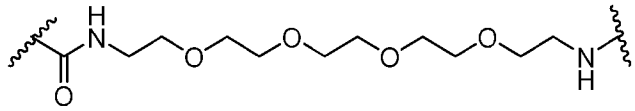
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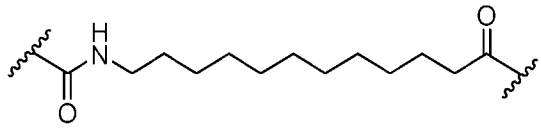
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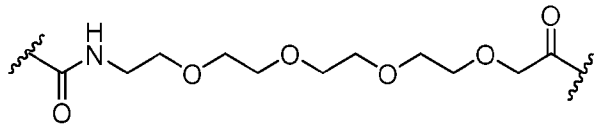
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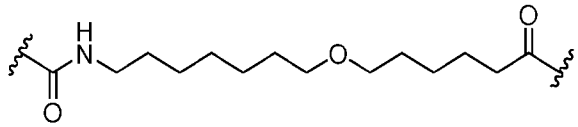
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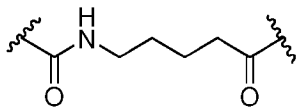
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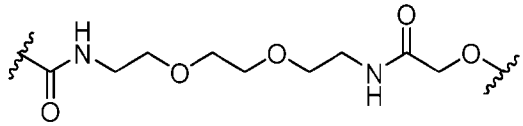
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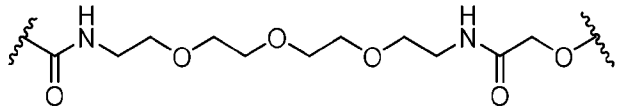
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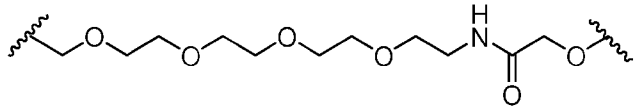
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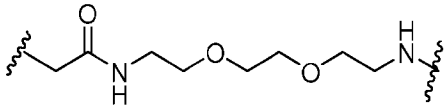
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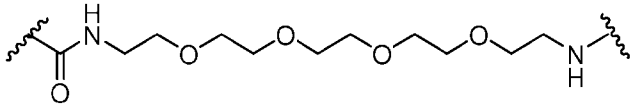
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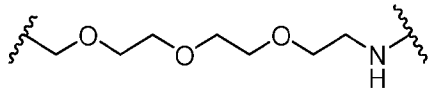
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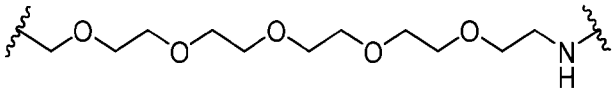
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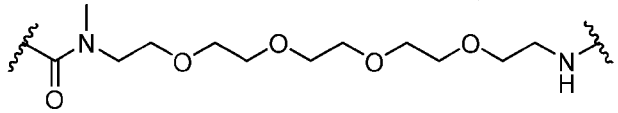
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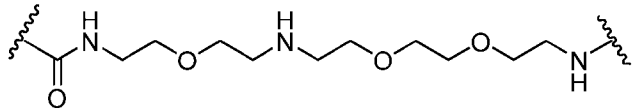
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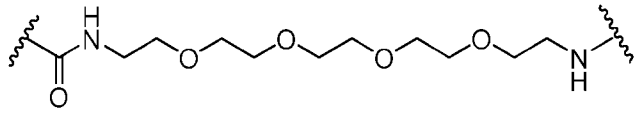
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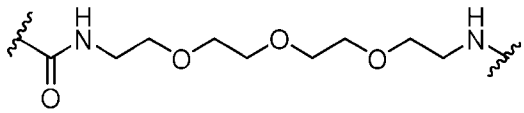
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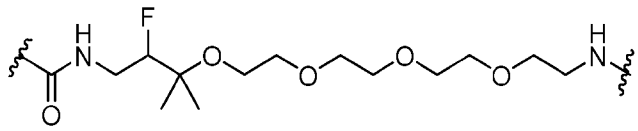
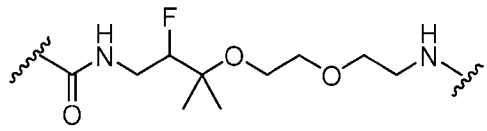
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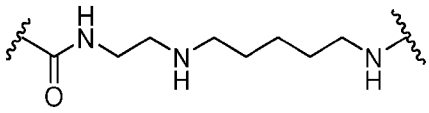
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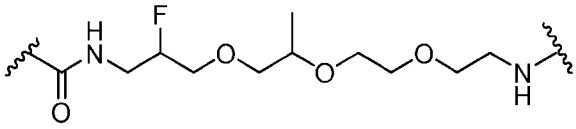
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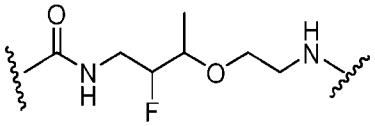
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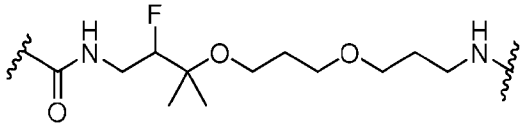
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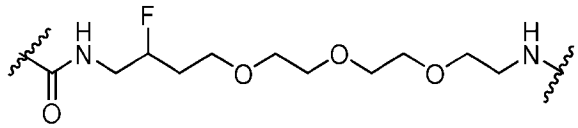
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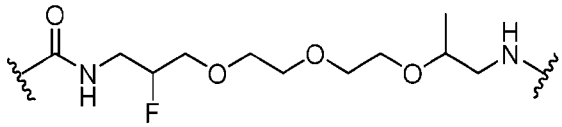
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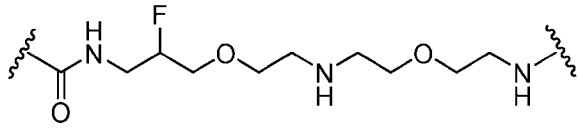
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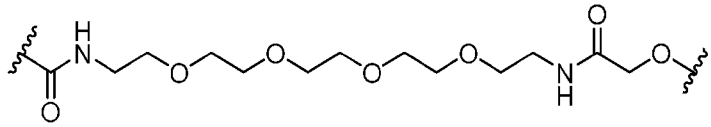
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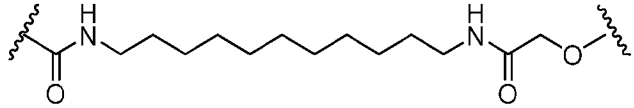
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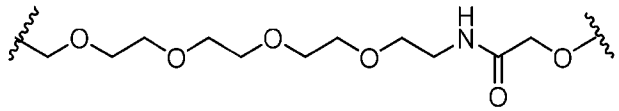
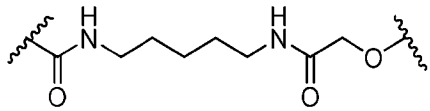
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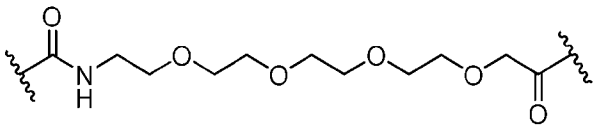
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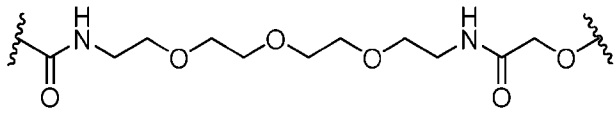
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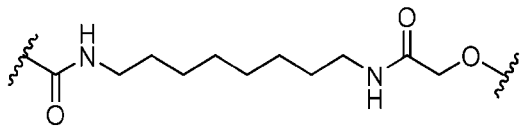
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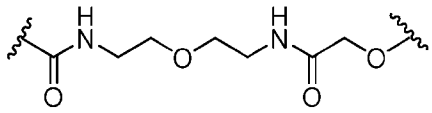
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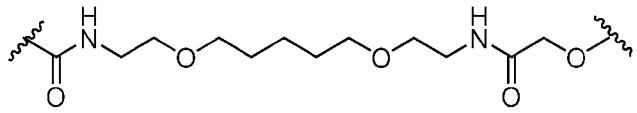
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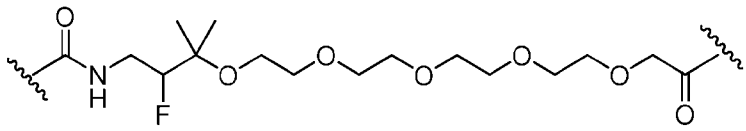
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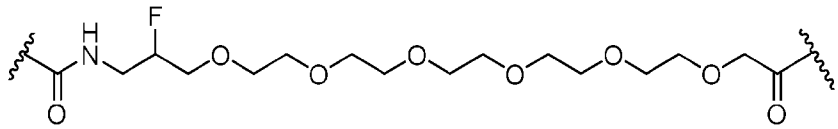
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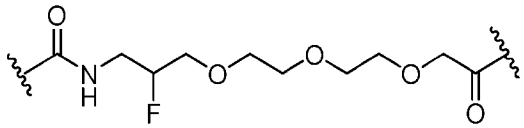
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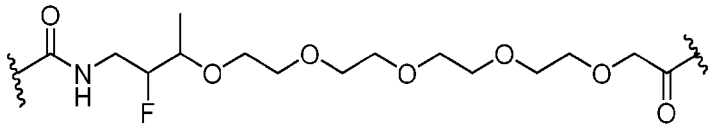
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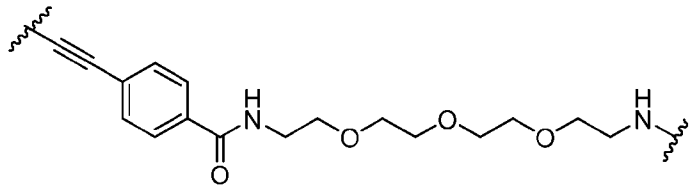
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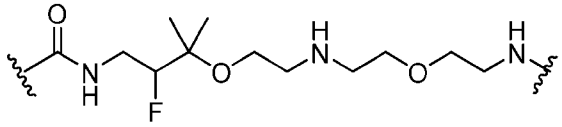
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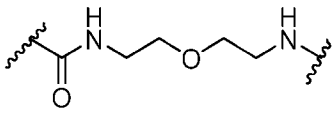
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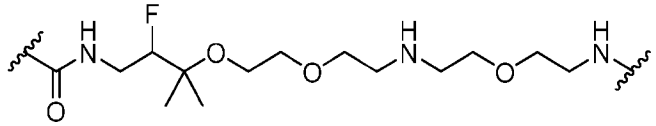
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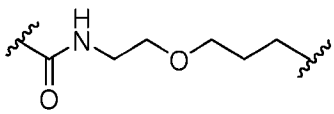
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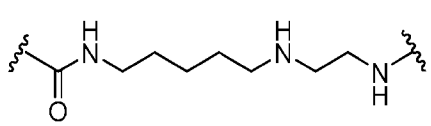
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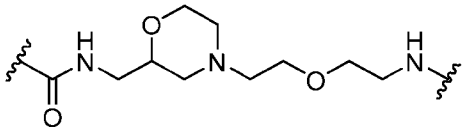
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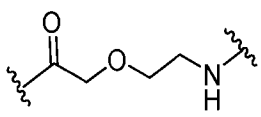
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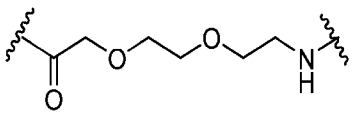
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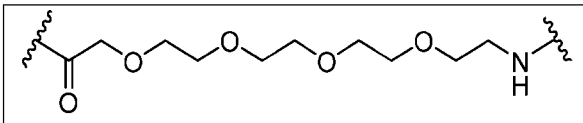

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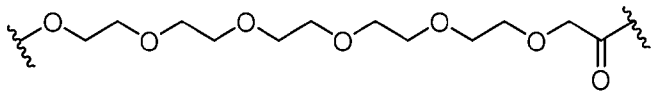

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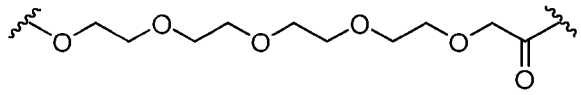

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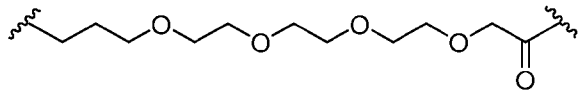

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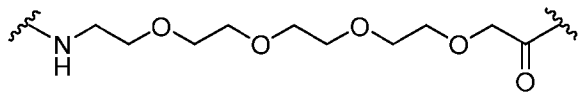

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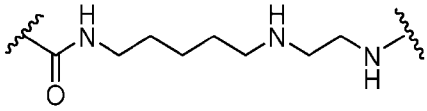

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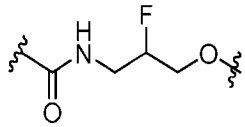

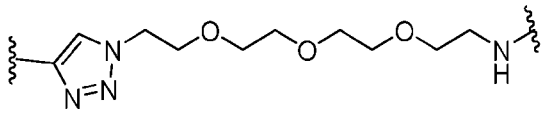

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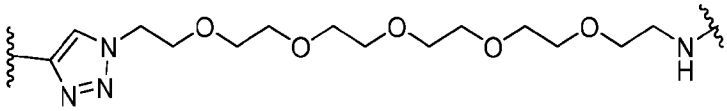

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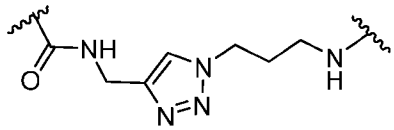

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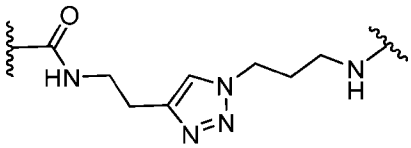

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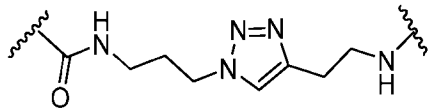

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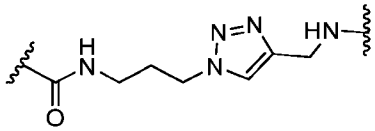

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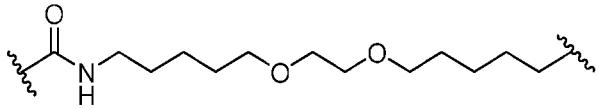

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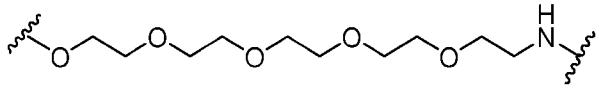

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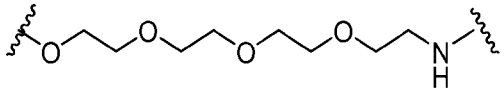

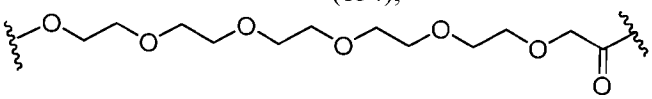

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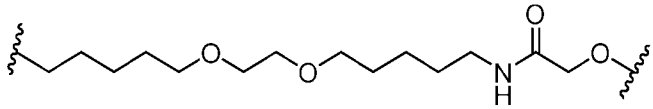

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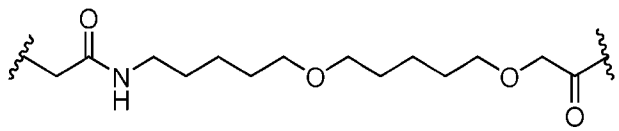

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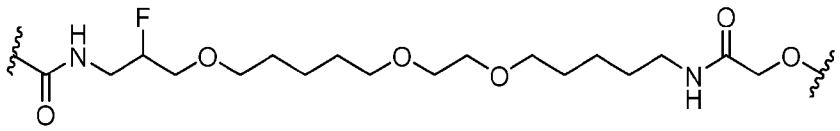
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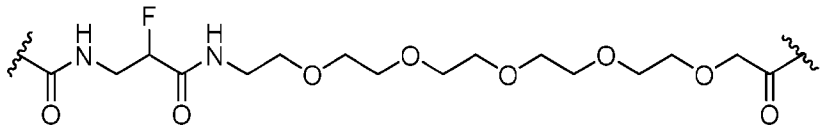
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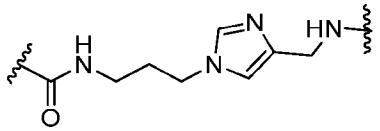
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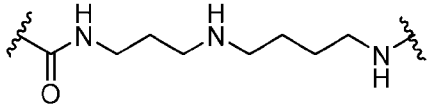
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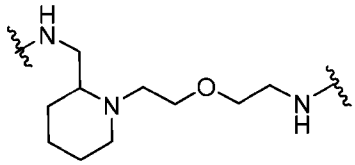
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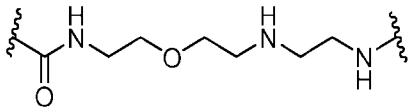
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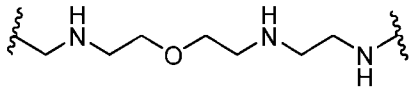
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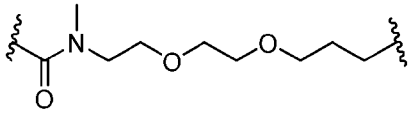
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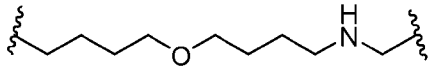
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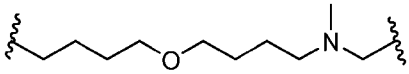
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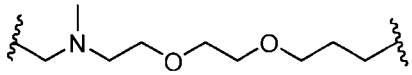
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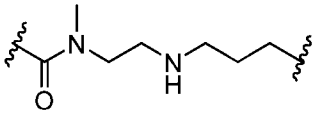
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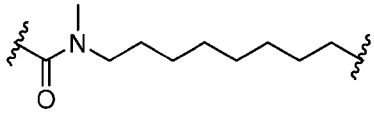
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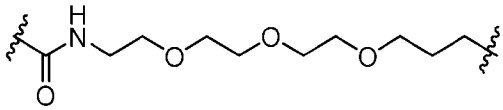
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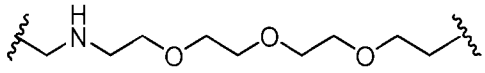
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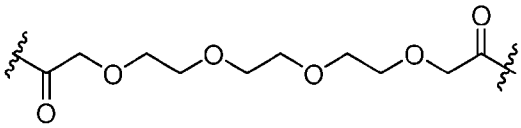
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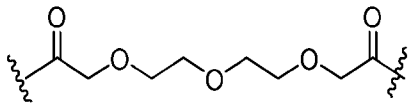
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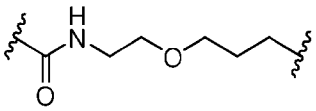
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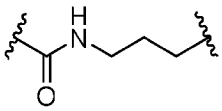
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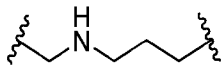
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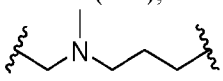
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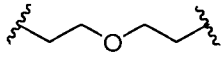
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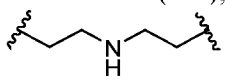

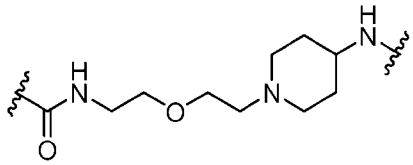
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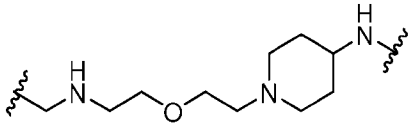
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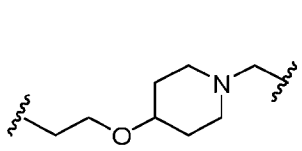
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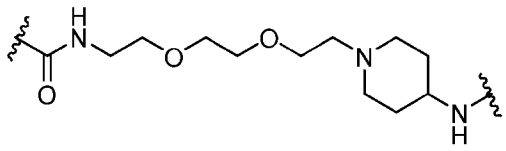
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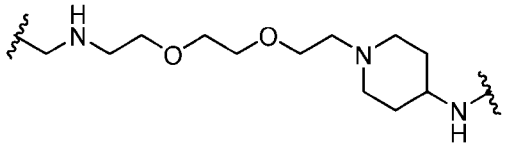
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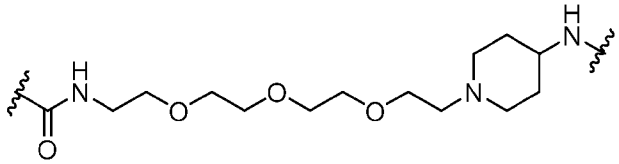
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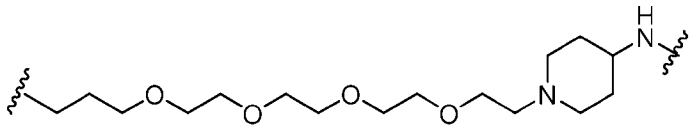
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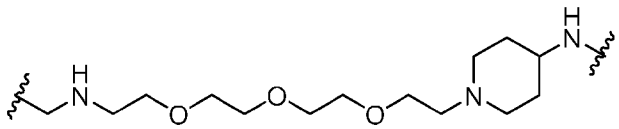
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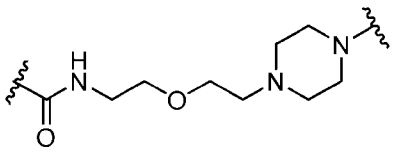
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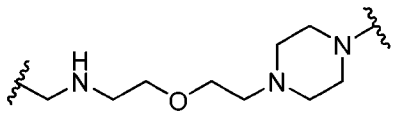
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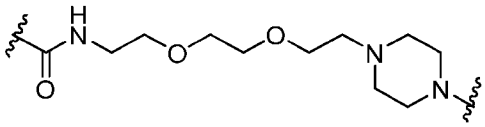
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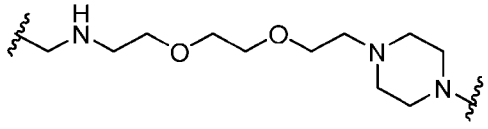
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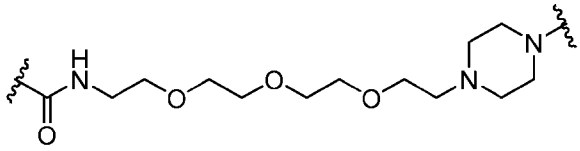
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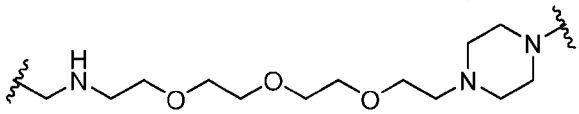
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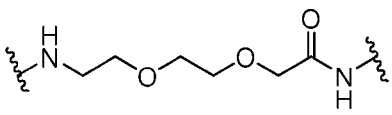
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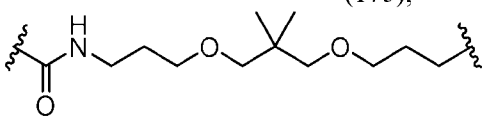
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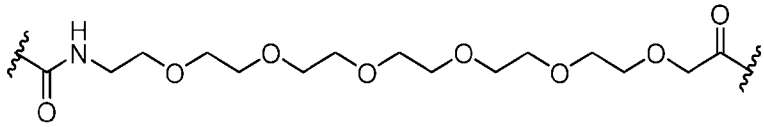
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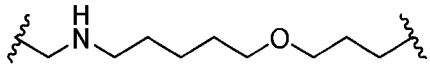
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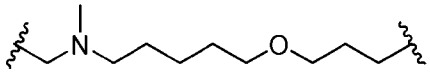
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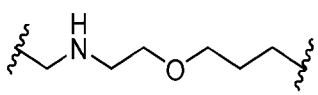
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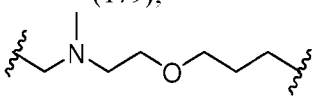
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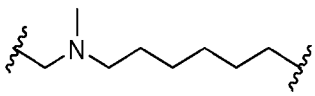
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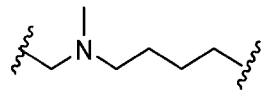
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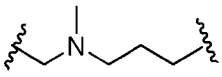
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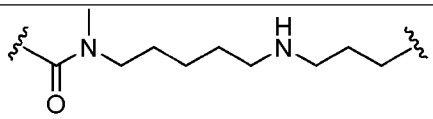
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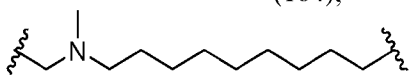
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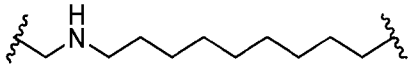
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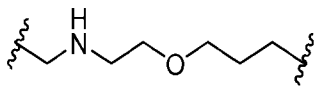
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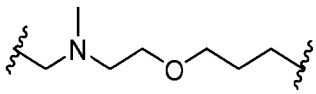
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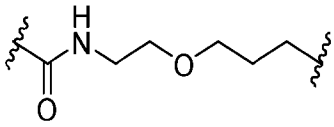
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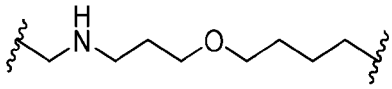
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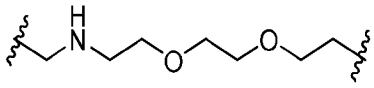
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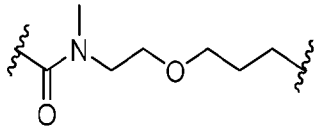
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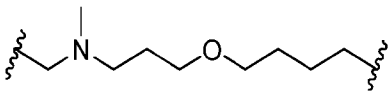
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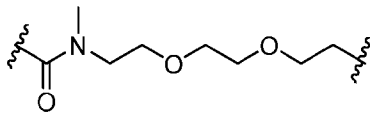
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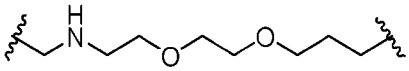
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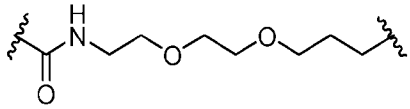
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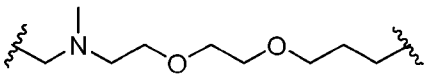
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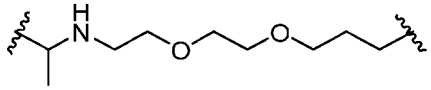
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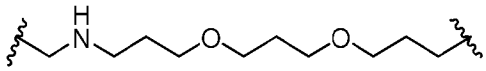
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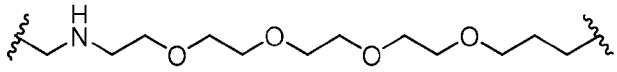
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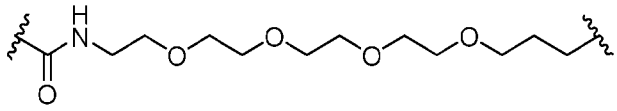
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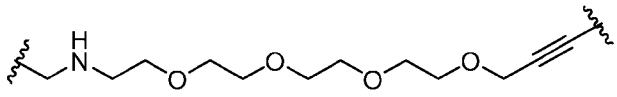
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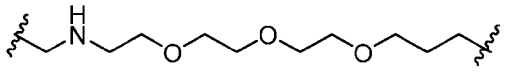
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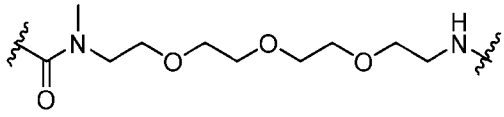
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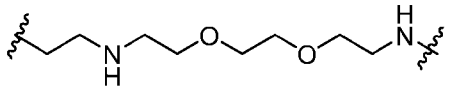
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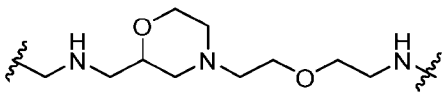
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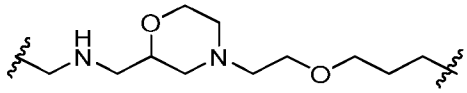
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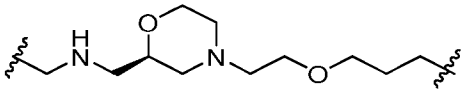
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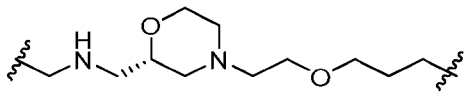
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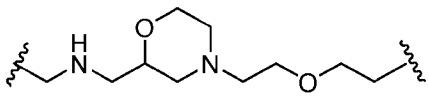
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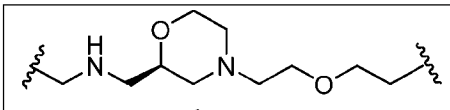
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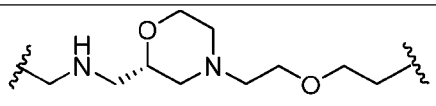
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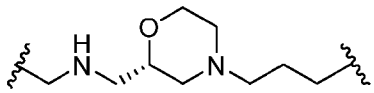
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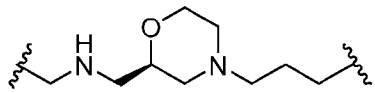
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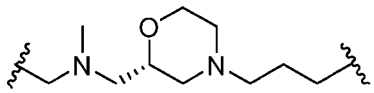
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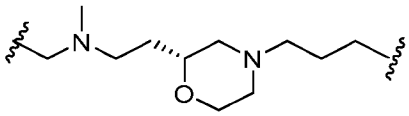
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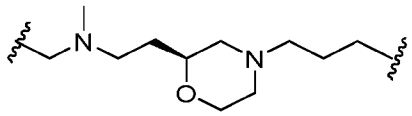
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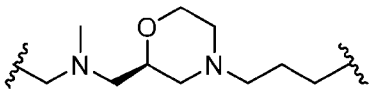
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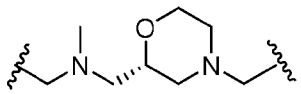
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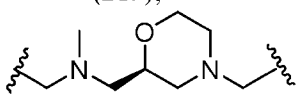
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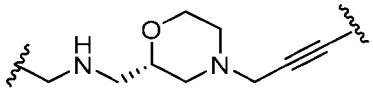
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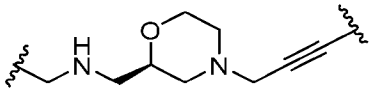
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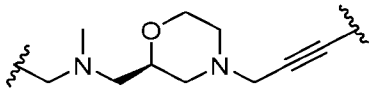
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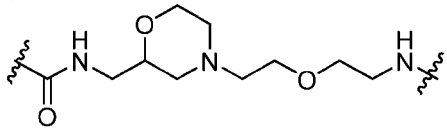
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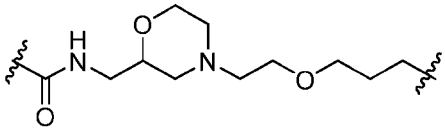
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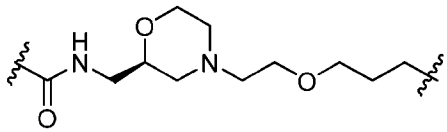
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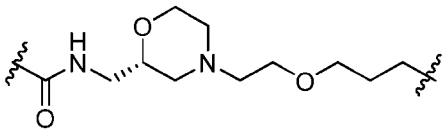
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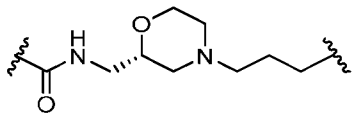
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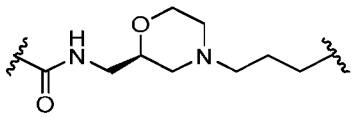
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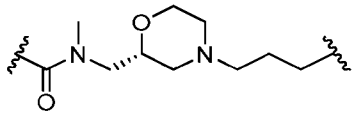
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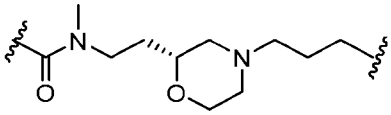
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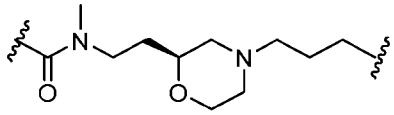
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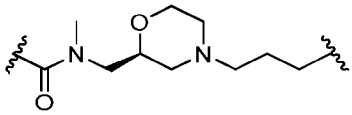
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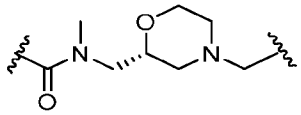
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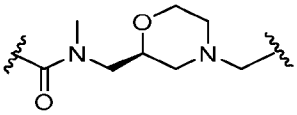
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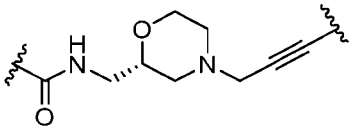
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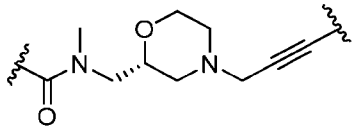
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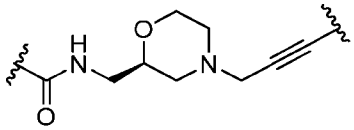
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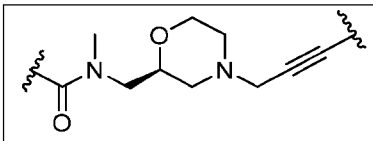

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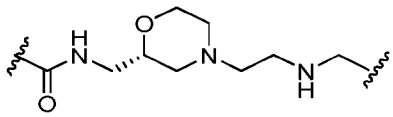

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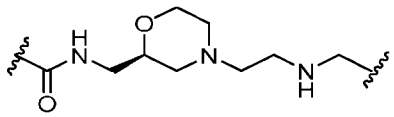

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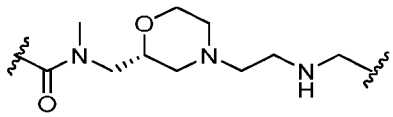

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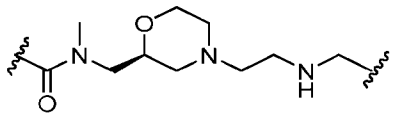

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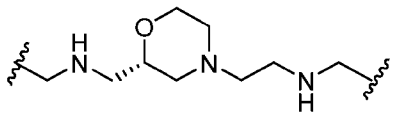

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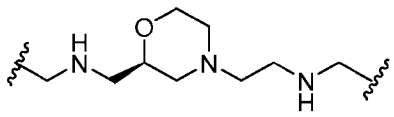

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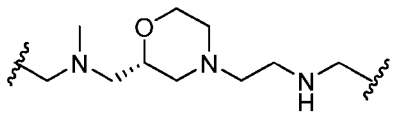

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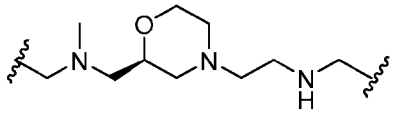

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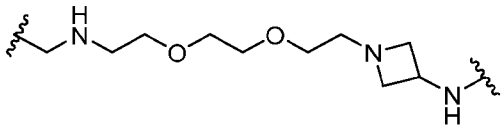

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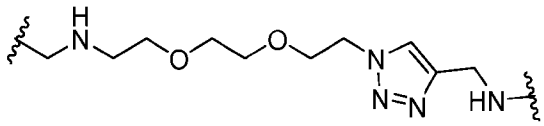

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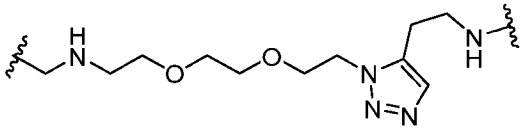

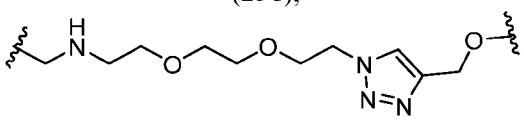

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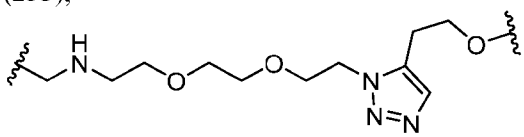

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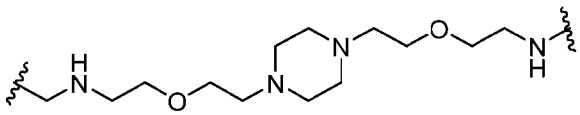

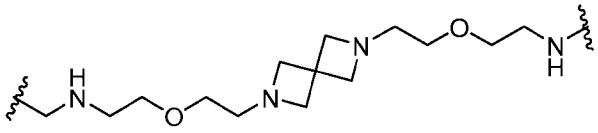

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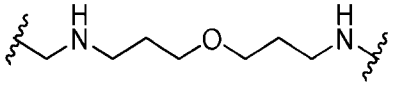

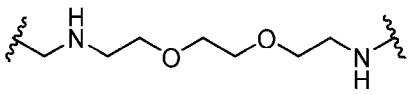

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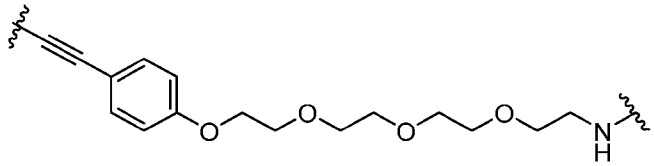

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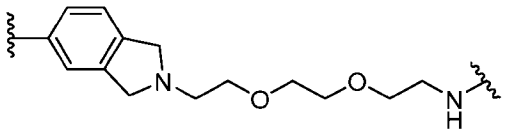

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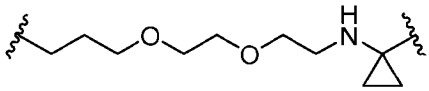

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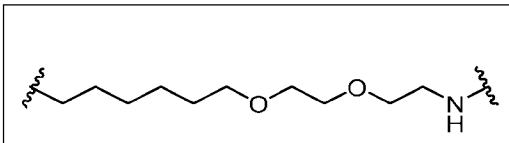
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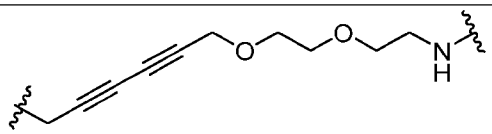
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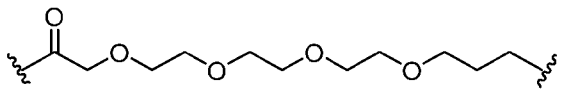
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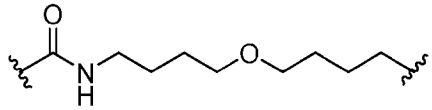
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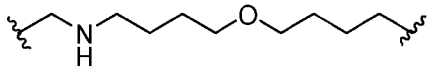
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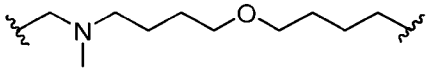
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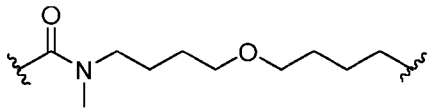
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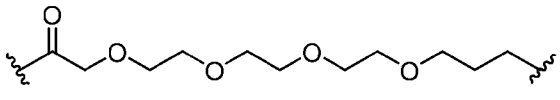
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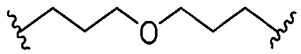
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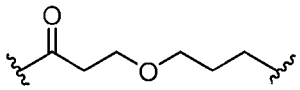
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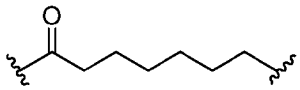
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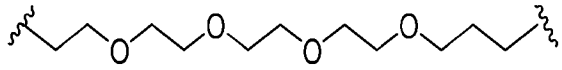
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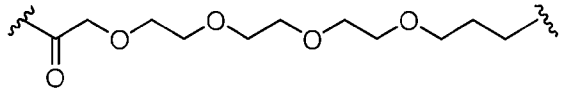
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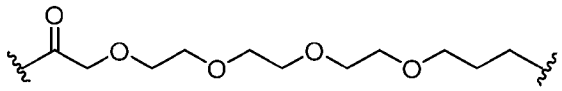
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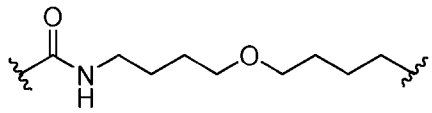
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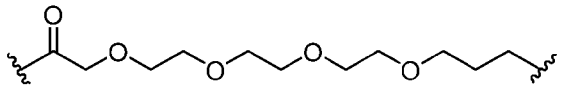
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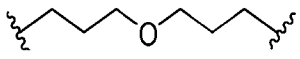
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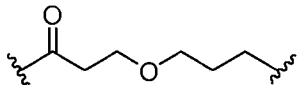
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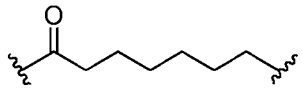
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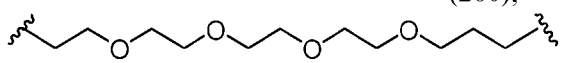
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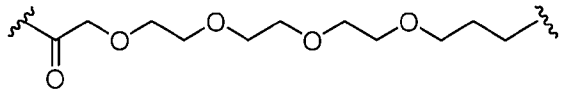
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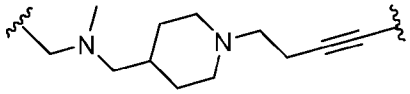
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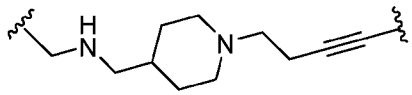
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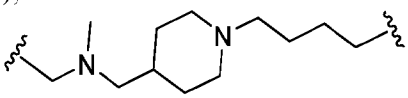
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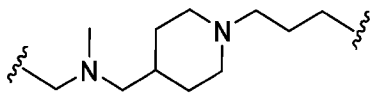
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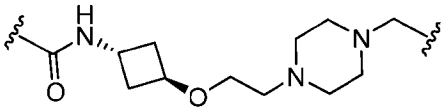
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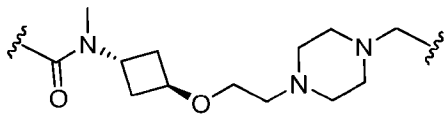
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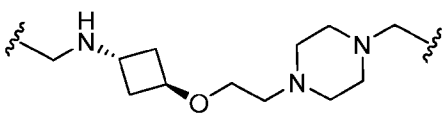
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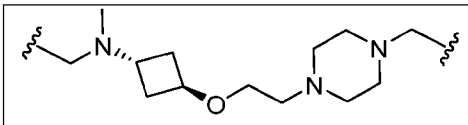
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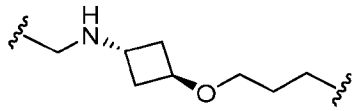
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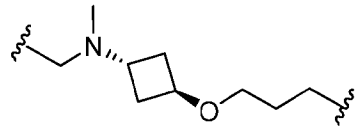
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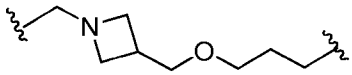
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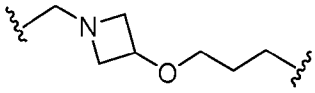
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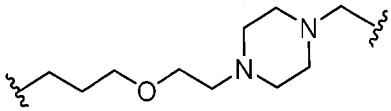
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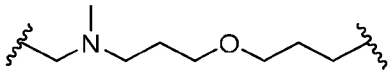
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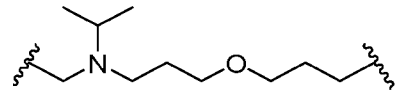
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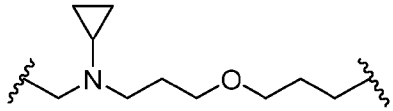
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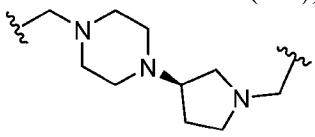
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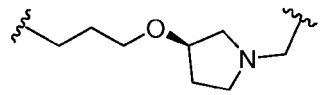
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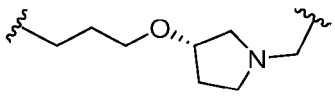
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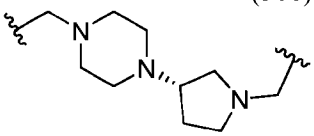
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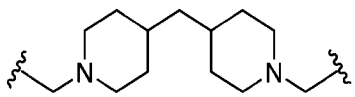
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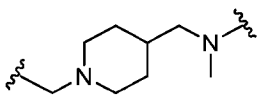
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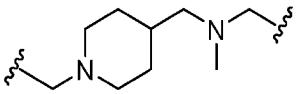
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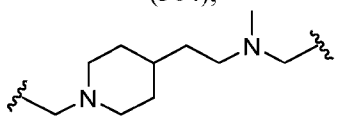
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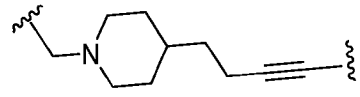
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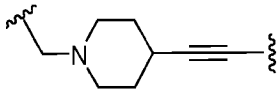
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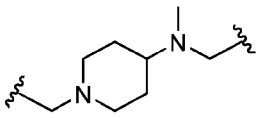
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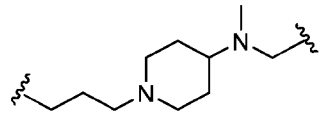
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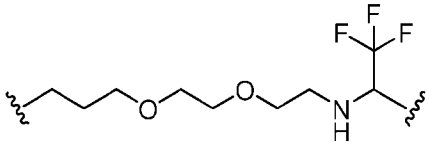
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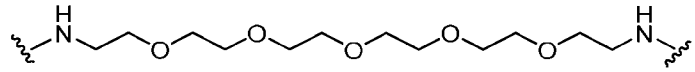
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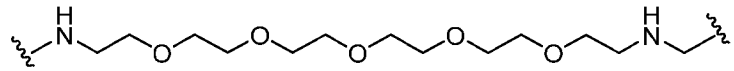
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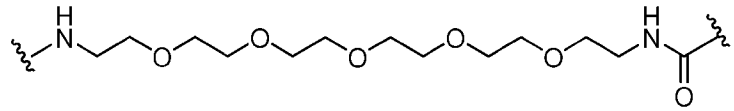
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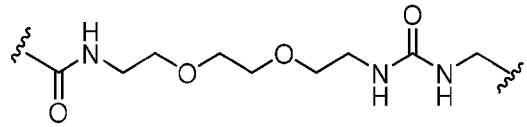
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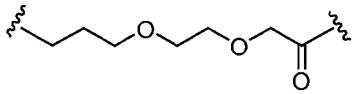
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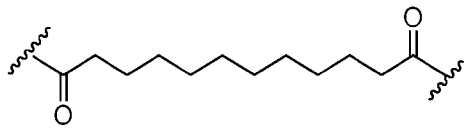
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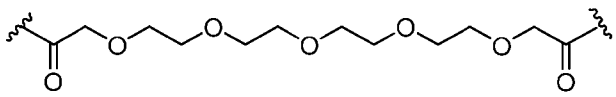

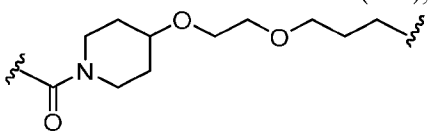
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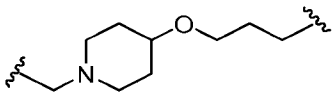
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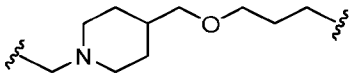
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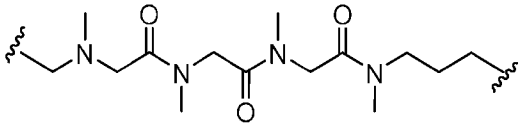
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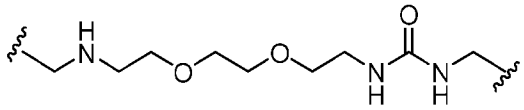
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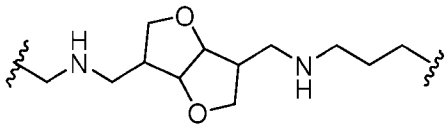
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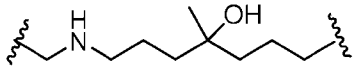
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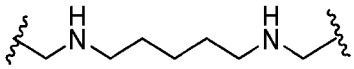
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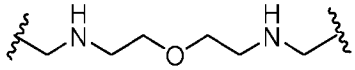
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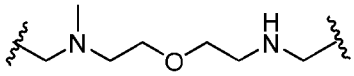
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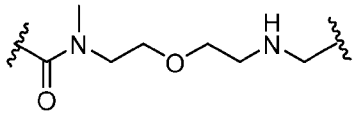
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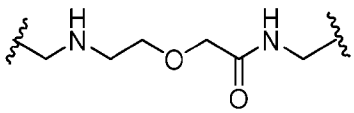
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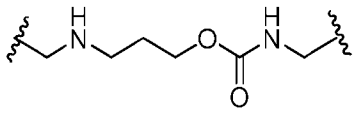
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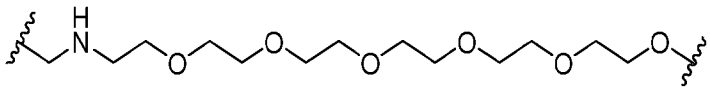

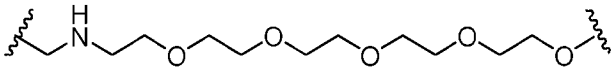
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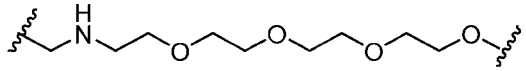
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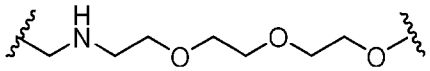
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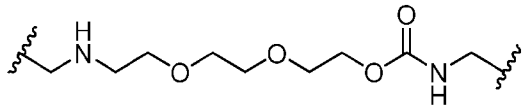
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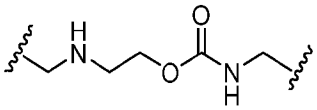
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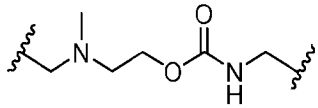
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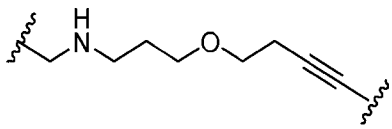
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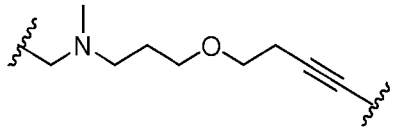
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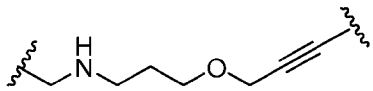
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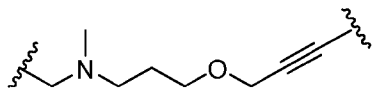
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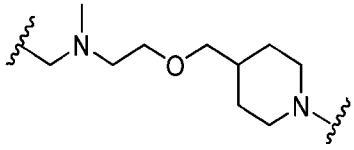
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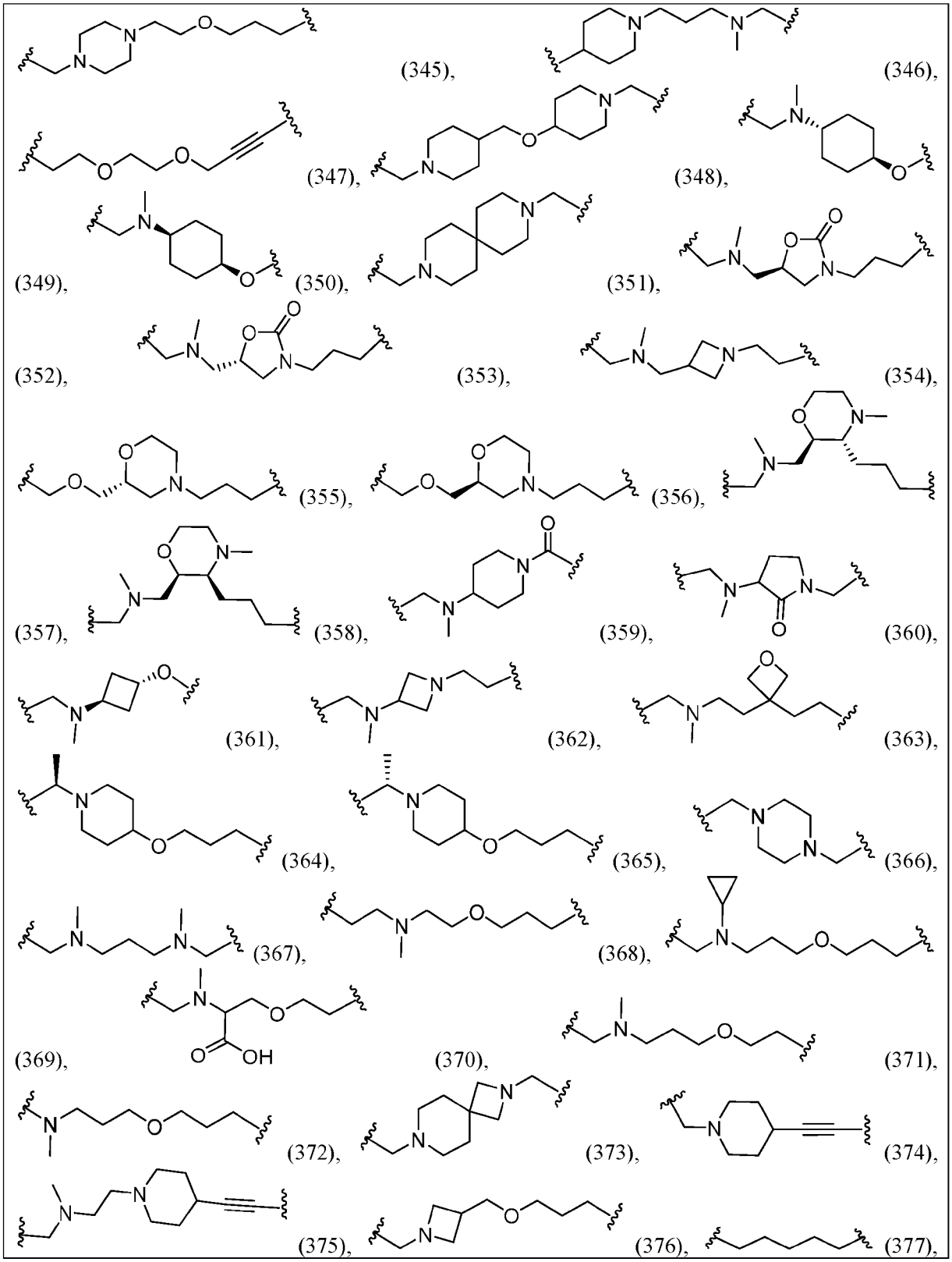
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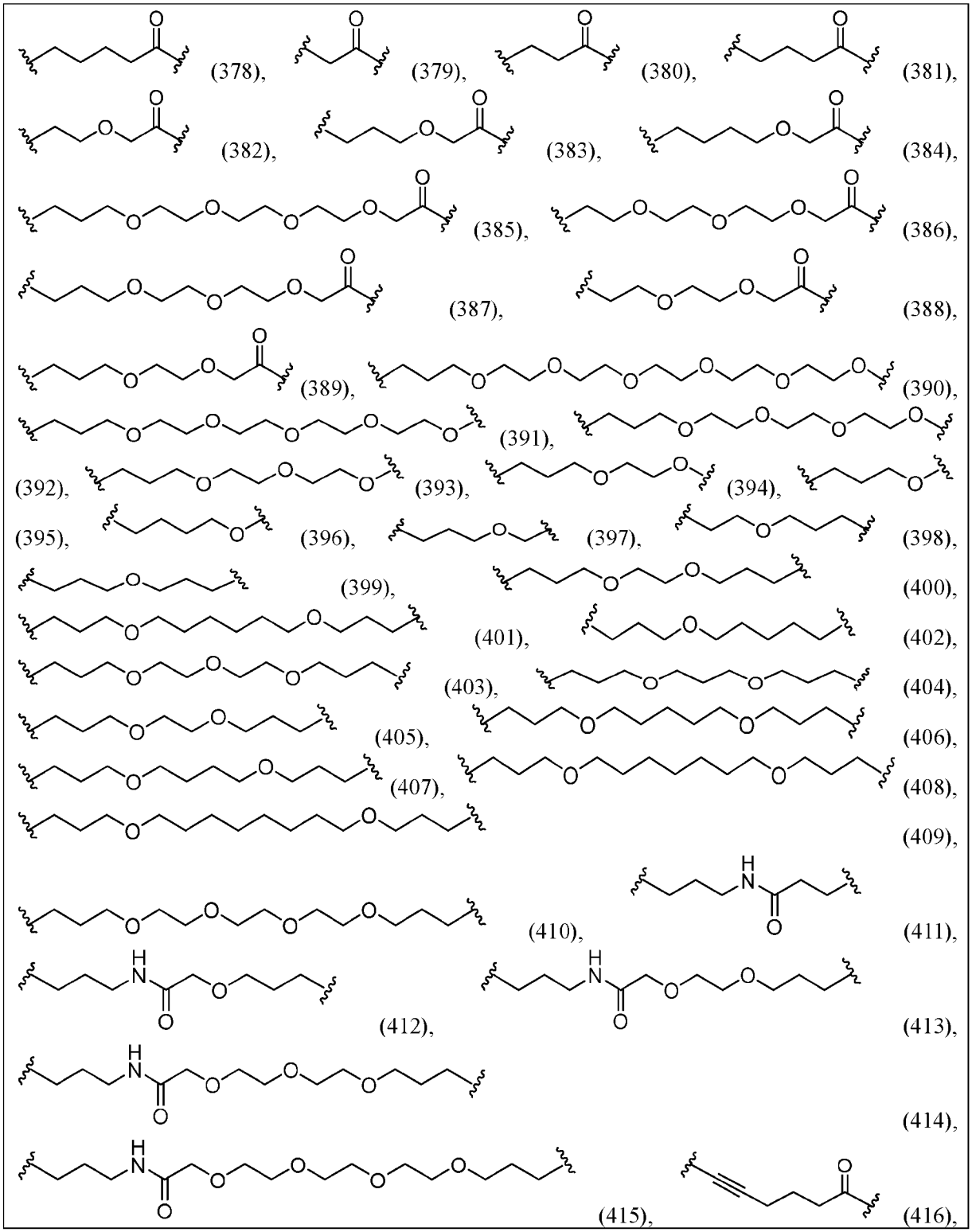
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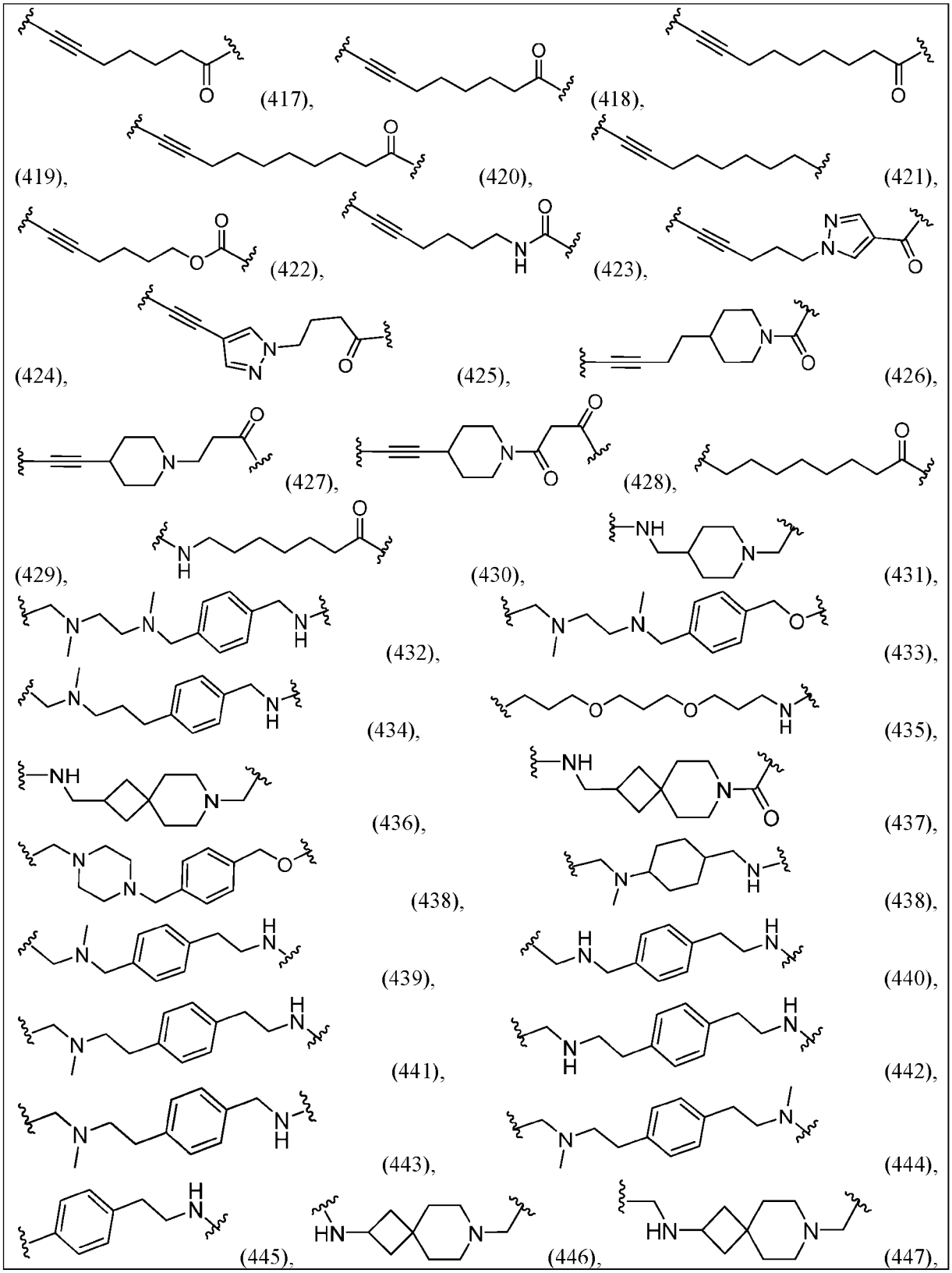
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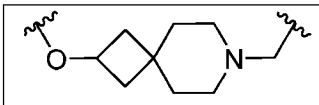
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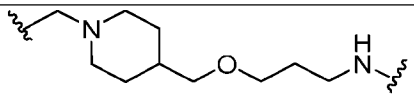
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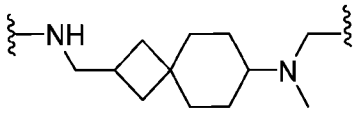
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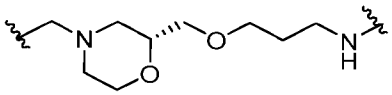
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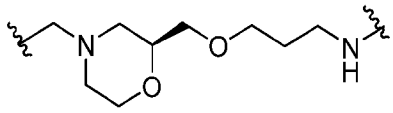
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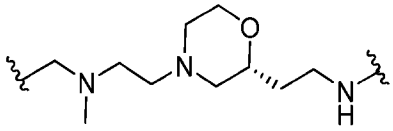
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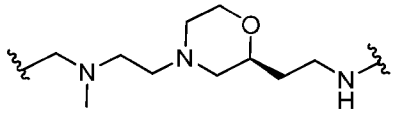
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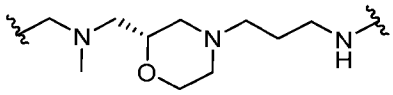
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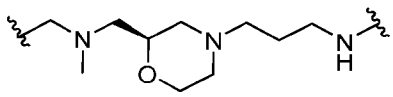
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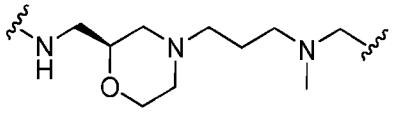
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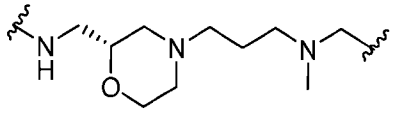
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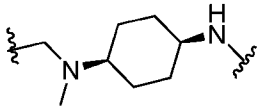
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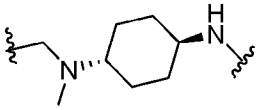
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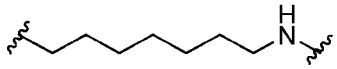
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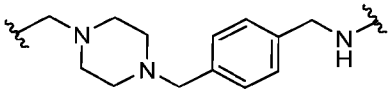
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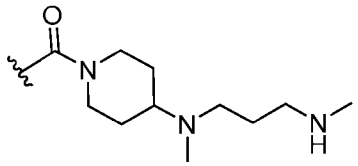
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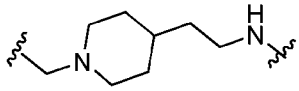
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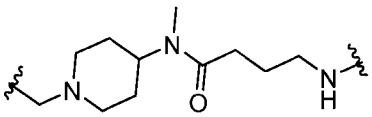
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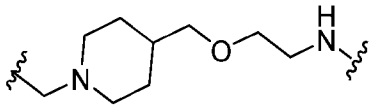
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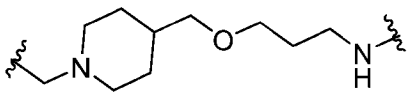
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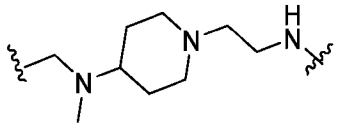
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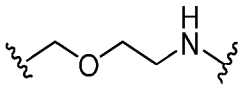
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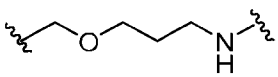
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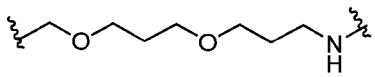
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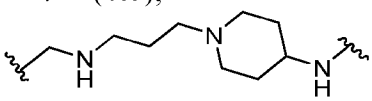
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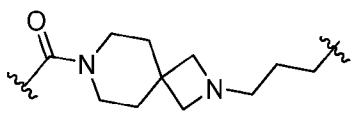
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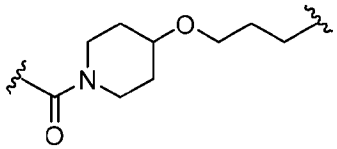
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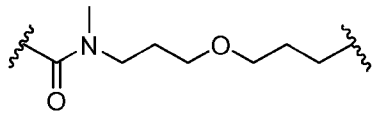
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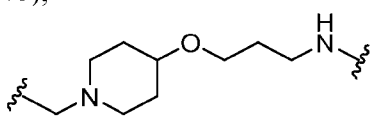
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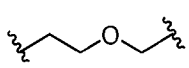
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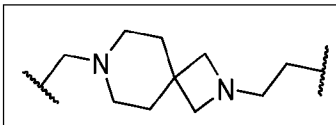
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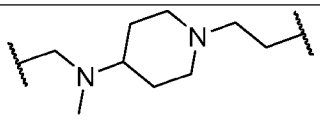
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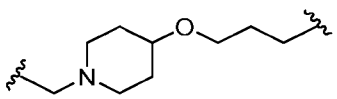
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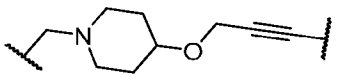
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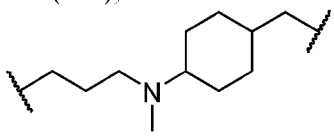
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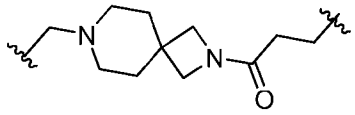
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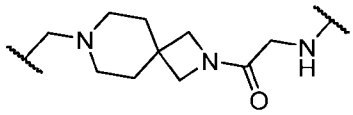
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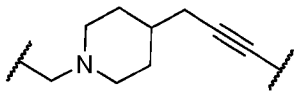
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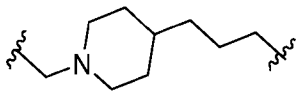
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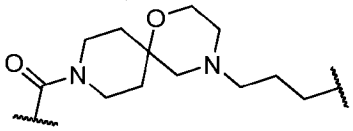
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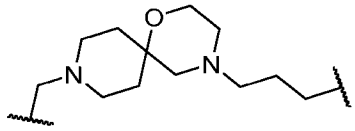
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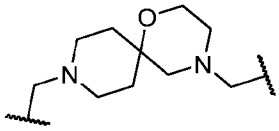
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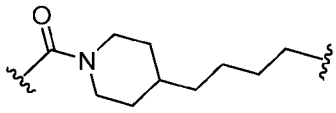
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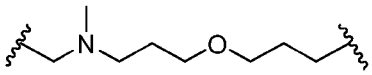
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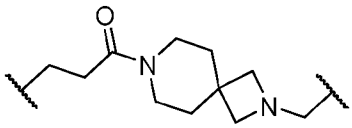
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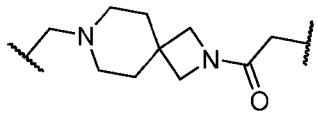
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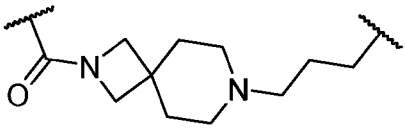
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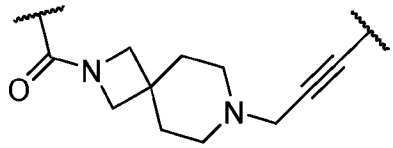
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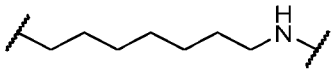
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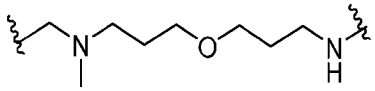
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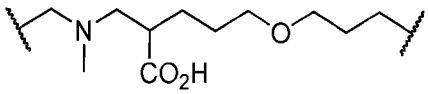
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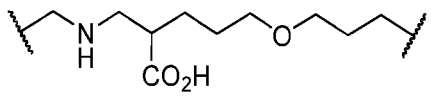
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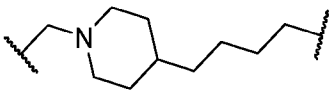
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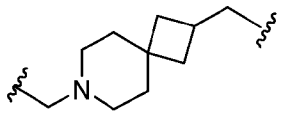
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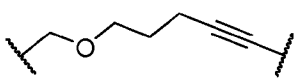
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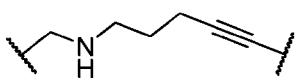
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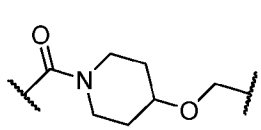
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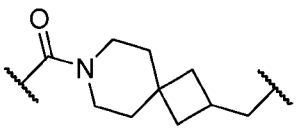
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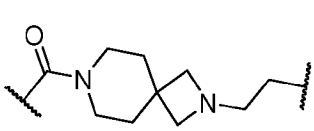
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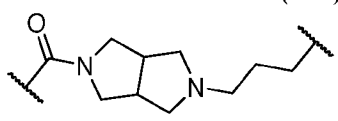
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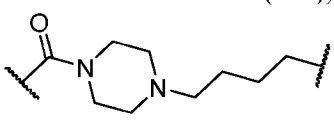
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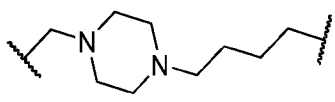
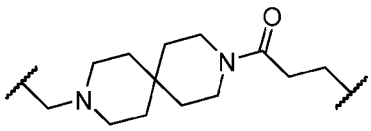
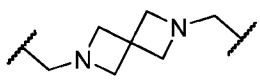
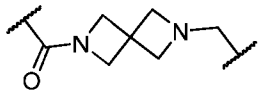
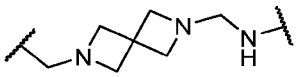
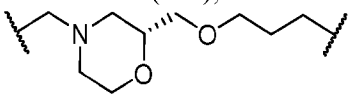


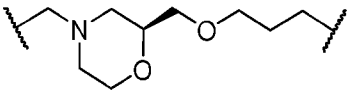
(508), 

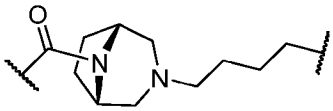
(509), 

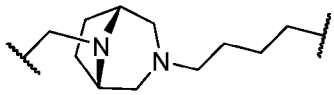
(510), 

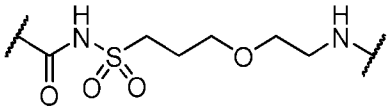
(511), 

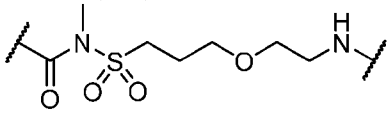
(512), 

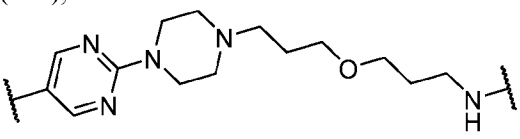
(513), 

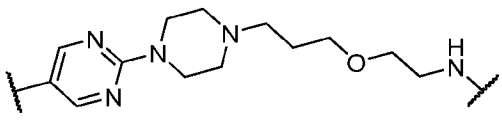
(514), 

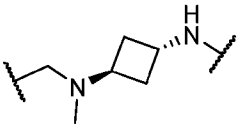
(515), 

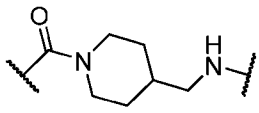
(516), 

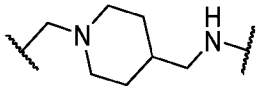
(517), 

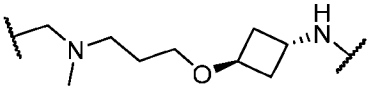
(518), 

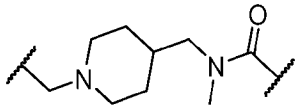
(519), 

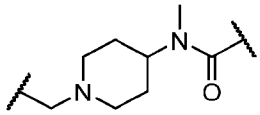
(520), 

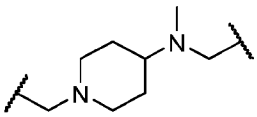
(521), 

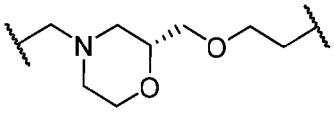
(522), 

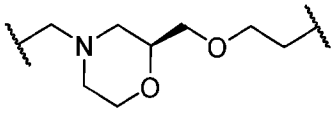
(523), 

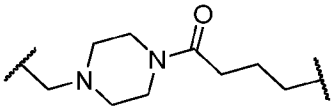
(524), 

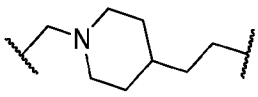
(525), 

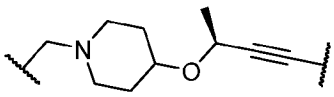
(526), 

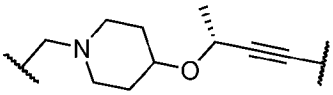
(527), 

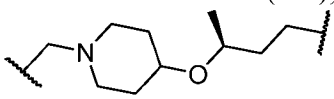
(528), 

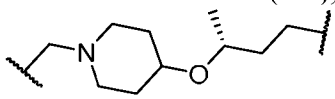
(529), 

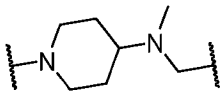
(530), 

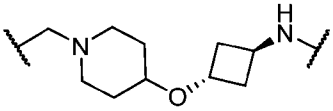
(531), 

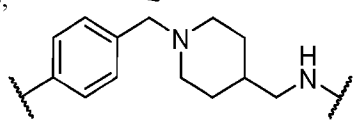
(532), 

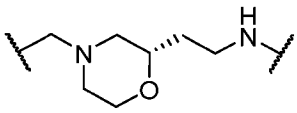
(533), 

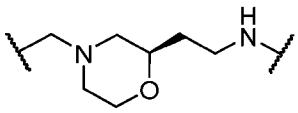
(534), 

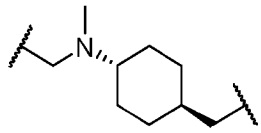
(535), 

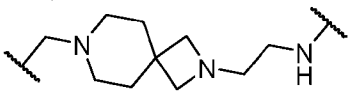
(536), 

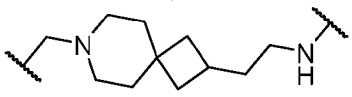
(537), 

(538), 

(539), 

(540), 

(541), 

(542), 

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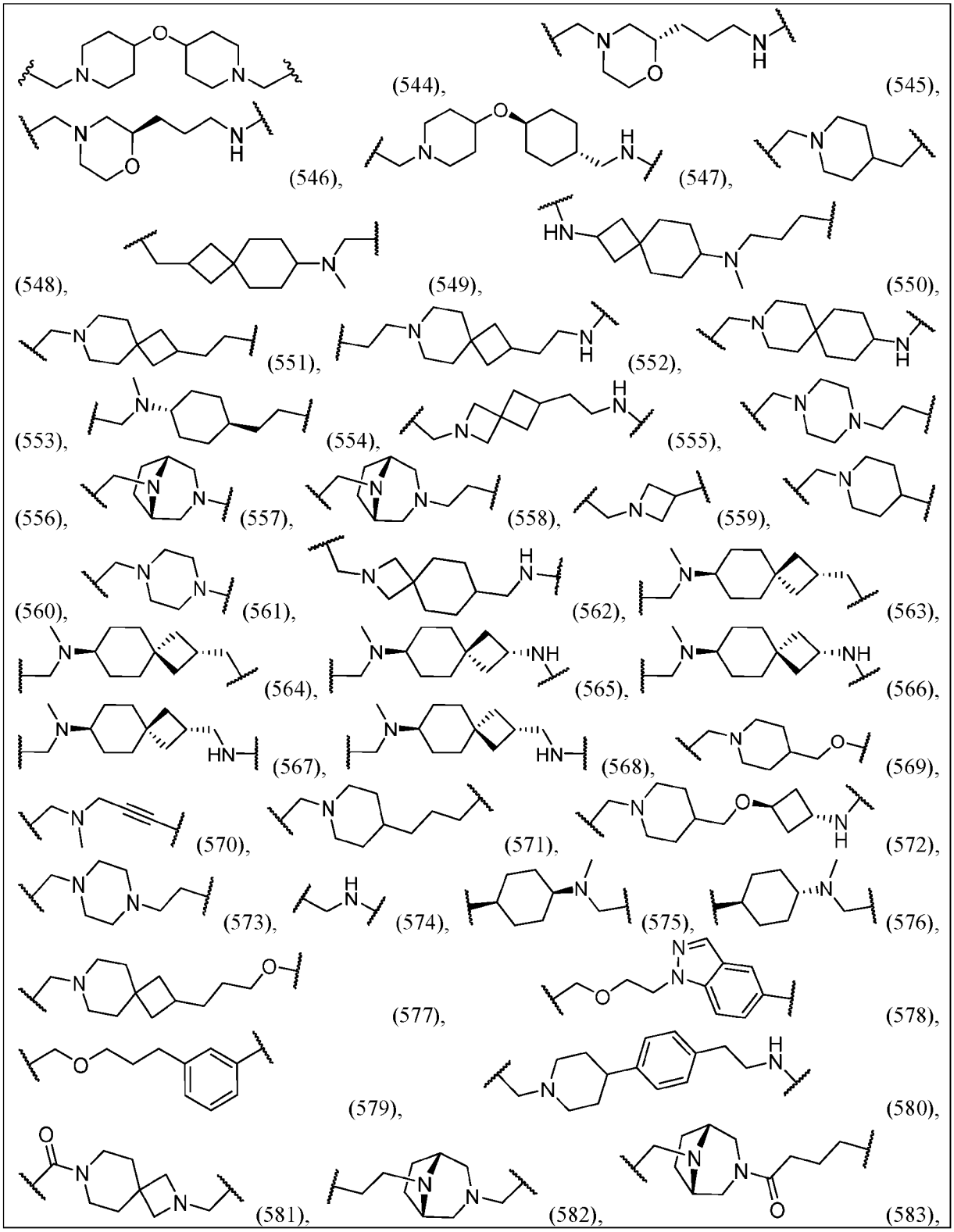
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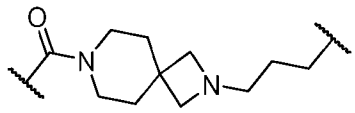
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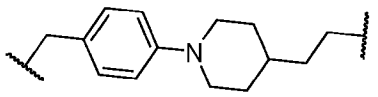
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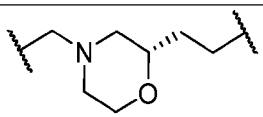
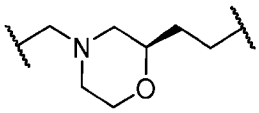
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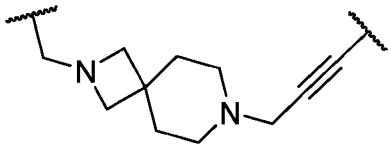
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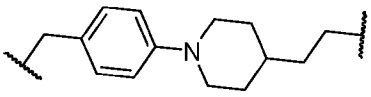
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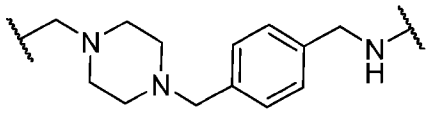
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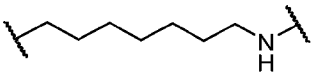
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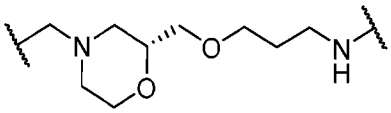
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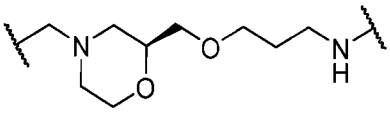
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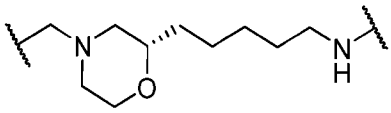
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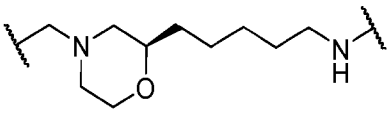
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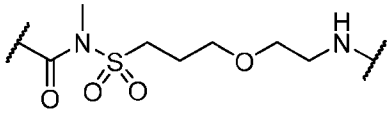
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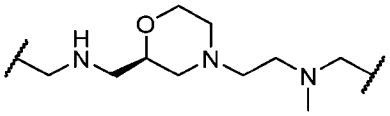
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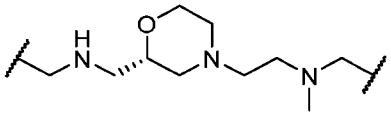
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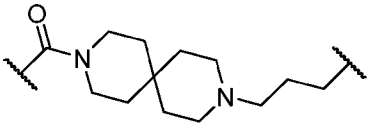
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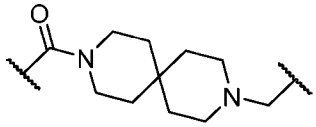
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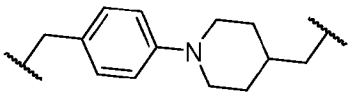
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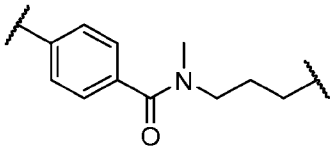
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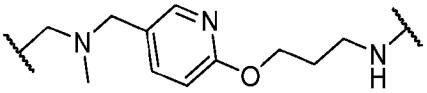
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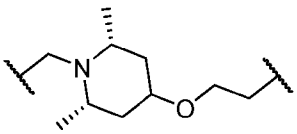
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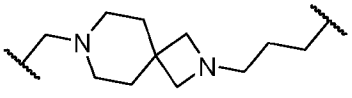
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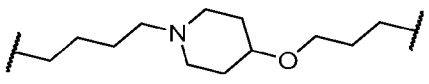
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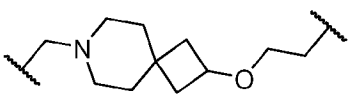
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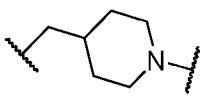
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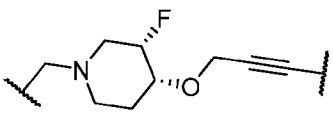
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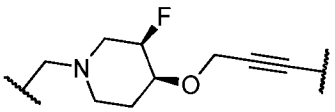
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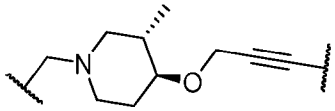
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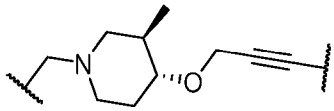
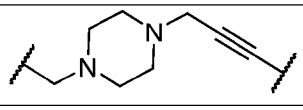


(612),  (613).

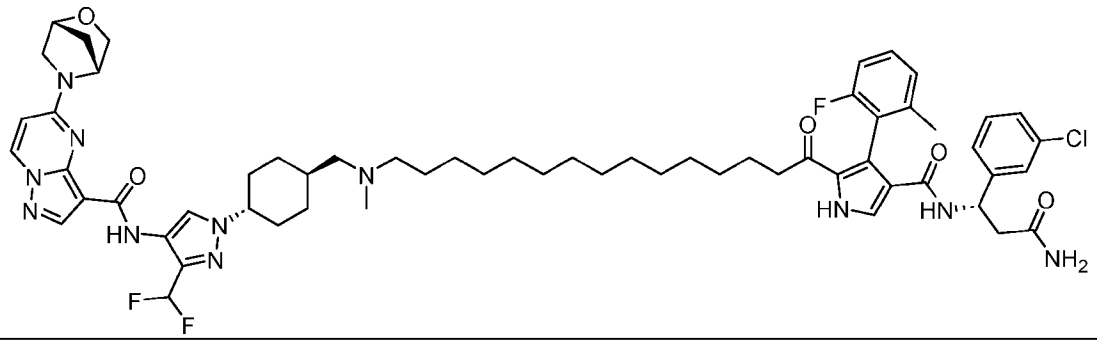
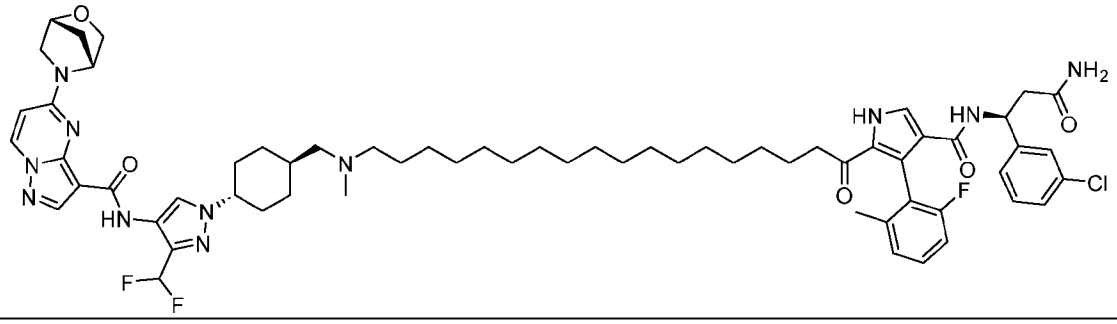
[00527] In some embodiments, the present invention provides a compound having an DBM binding moiety described and disclosed herein, an IRAK described and disclosed herein, and a linker set forth in **Table B** above, or a pharmaceutically acceptable salt thereof.

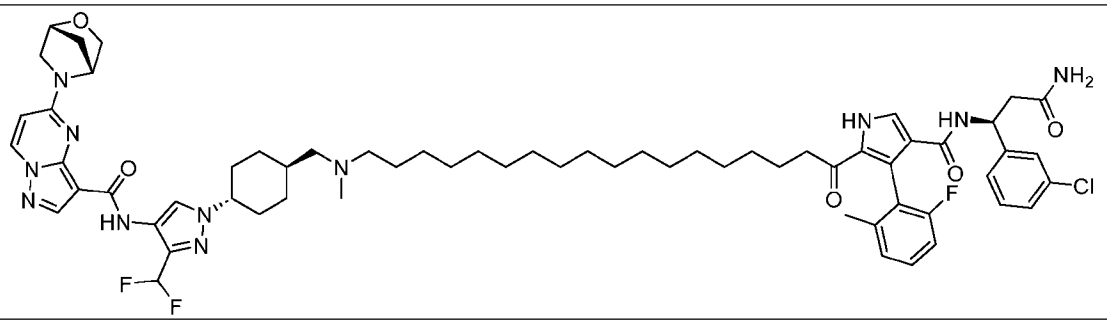
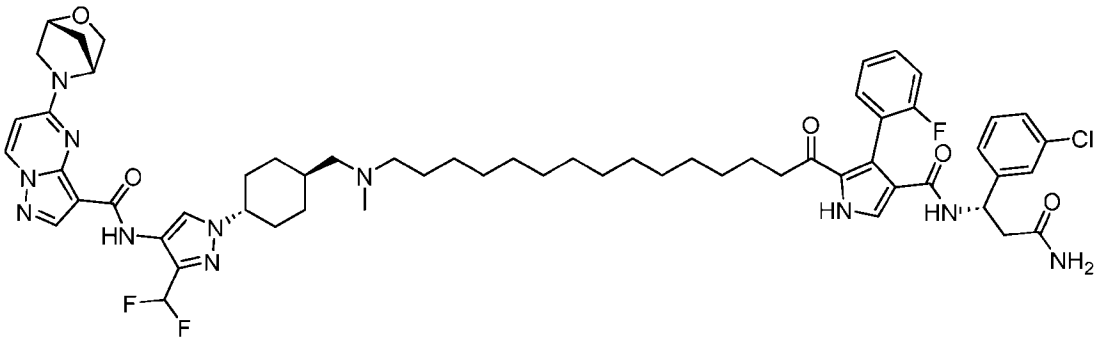
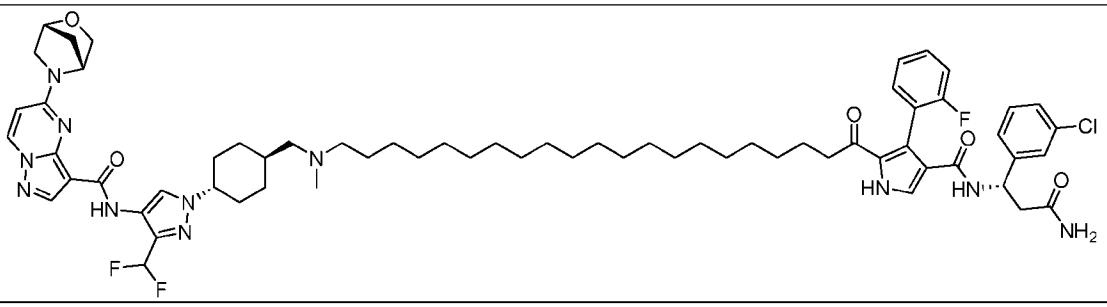
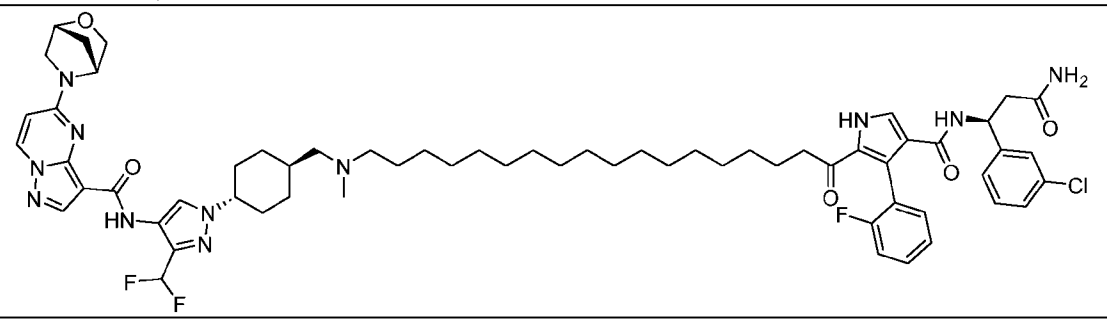
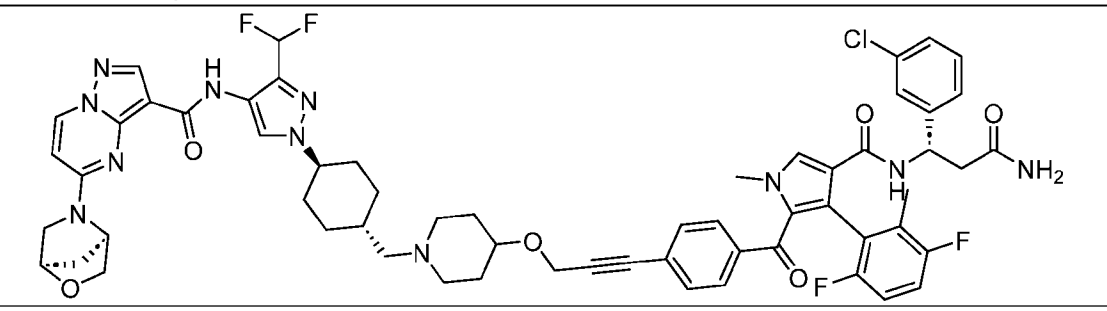
[00528] In some embodiments, the present invention provides a compound having an DBM binding moiety described and disclosed herein, an IRAK set forth in **Table A** above, and a linker described and disclosed herein, or a pharmaceutically acceptable salt thereof.

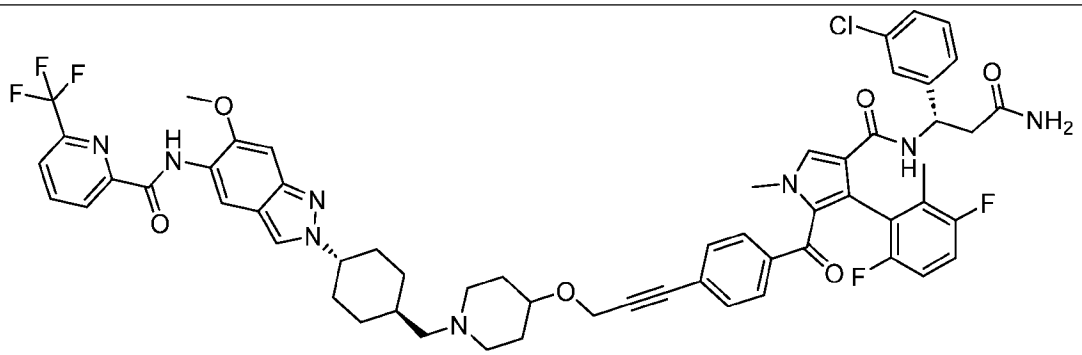
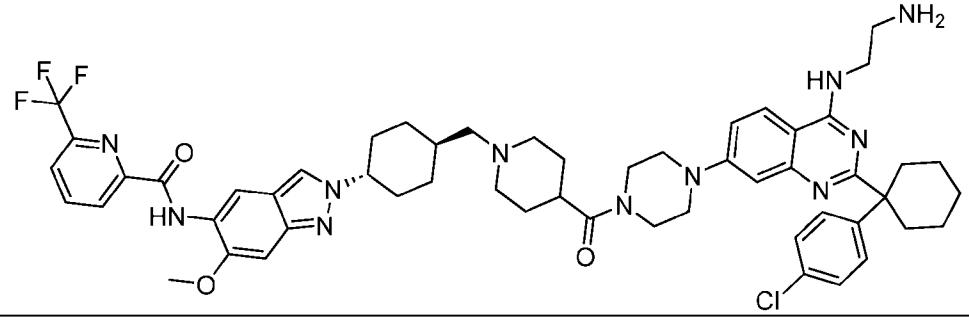
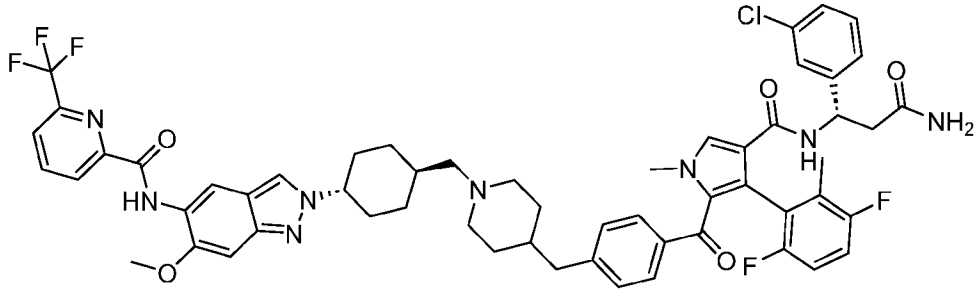
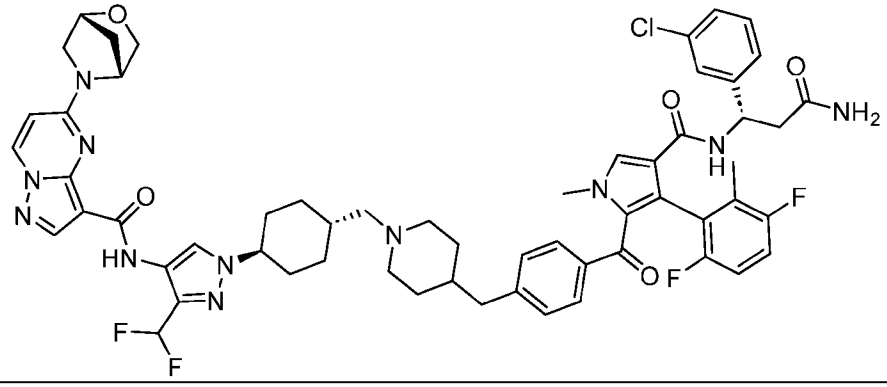
[00529] In some embodiments, the present invention provides a compound having an DBM binding moiety described and disclosed herein, an IRAK set forth in **Table A** above, and a linker set forth in **Table B** above, or a pharmaceutically acceptable salt thereof.

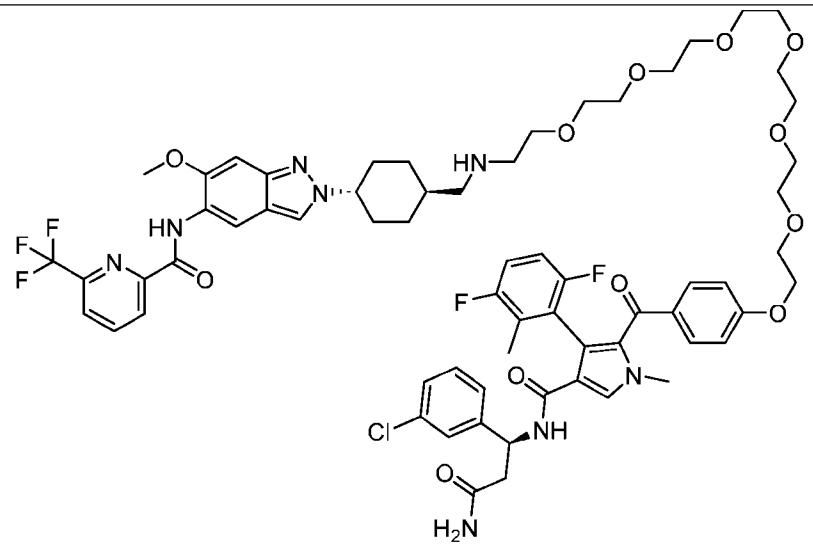
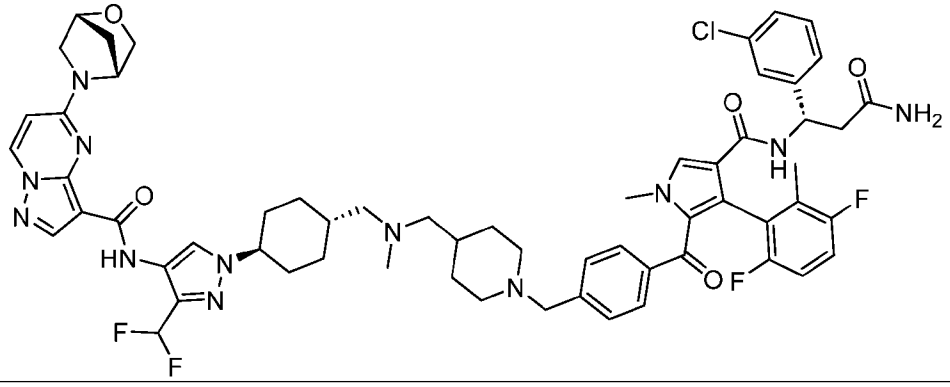
[00530] Exemplary compounds of the invention are set forth in **Table 1**, below.

Table 1. Exemplary Compounds

I-#	Structure
I-1	
I-2	

I-3	
I-4	
I-5	
I-6	
I-7	

I-8	
I-9	
I-10	
I-11	

I-12	
I-13	

[00531] In some embodiments, the present invention provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof.

[00532] In some embodiments, the invention also provides a compound described herein (such as a compound of formulae **I-a**, **I-a'**, **I-b**, or **I-b'**), or pharmaceutical compositions thereof, for use in a method for degrading IRAK4 as described herein and/or in a method for treating an IRAK4-dependent disorder as described herein. In some embodiments, the invention also provides a compound described herein (such as a compound of formulae **I-a**, **I-a'**, **I-b**, or **I-b'**), or pharmaceutical compositions thereof, for use in a method of degrading IRAK4 as described herein. In some embodiments, the invention also provides a compound described herein (such as a compound of formulae **I-a**, **I-a'**, **I-b**, or **I-b'**), or pharmaceutical compositions thereof, for use in a method of treating an IRAK4-dependent disorder as described herein.

[00533] In some embodiments, the present invention provides a compound of formulae **I-a**, **I-a'**, **I-b**, or **I-b'** as defined above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formulae **I-a**, **I-a'**, **I-b**, or **I-b'** as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle for use as a medicament, such as for degrading IRAK4 as described herein and/or for treating an IRAK4-dependent

disorder as described herein.

4. General Methods of Providing the Present Compounds

[00534] The compounds of this invention may be prepared or isolated in general by synthetic and/or semi-synthetic methods known to those skilled in the art for analogous compounds and by methods described in detail in the Examples, herein.

[00535] In the Schemes below, where a particular protecting group, leaving group, or transformation condition is depicted, one of ordinary skill in the art will appreciate that other protecting groups, leaving groups, and transformation conditions are also suitable and are contemplated. Such groups and transformations are described in detail in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, M. B. Smith and J. March, 5th Edition, John Wiley & Sons, 2001, *Comprehensive Organic Transformations*, R. C. Larock, 2nd Edition, John Wiley & Sons, 1999, and *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is hereby incorporated herein by reference.

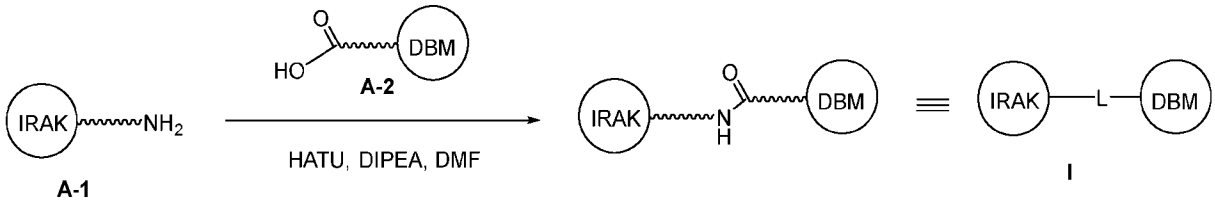
[00536] As used herein, the phrase "oxygen protecting group" includes, for example, carbonyl protecting groups, hydroxyl protecting groups, etc. Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Examples of suitable hydroxyl protecting groups include, but are not limited to, esters, allyl ethers, ethers, silyl ethers, alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of such esters include formates, acetates, carbonates, and sulfonates. Specific examples include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetyl), crotonate, 4-methoxy-crotonate, benzoate, p-benzylbenzoate, 2,4,6-trimethylbenzoate, carbonates such as methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl. Examples of such silyl ethers include trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, and other trialkylsilyl ethers. Alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, allyl, and allyloxycarbonyl ethers or derivatives. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-(trimethylsilyl)ethoxymethyl, and tetrahydropyranyl ethers. Examples of arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, and 2- and 4-picolyl.

[00537] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons,

1999, the entirety of which is incorporated herein by reference. Suitable amino protecting groups include, but are not limited to, aralkylamines, carbamates, cyclic imides, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, phthalimide, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like.

[00538] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 1 set forth below:

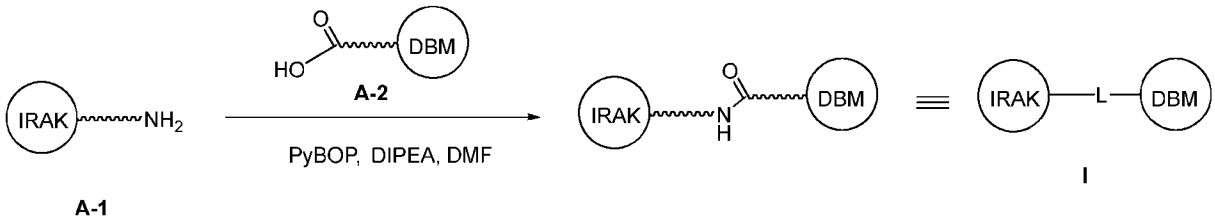
Scheme 1: Synthesis of Compounds of the Invention



[00539] As depicted in Scheme 1, above, amine **A-1** is coupled to acid **A-2** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-1** or the portion of the linker between DBM and the terminal carboxyl group of **A-2**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00540] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 2 set forth below:

Scheme 2: Synthesis of Compounds of the Invention

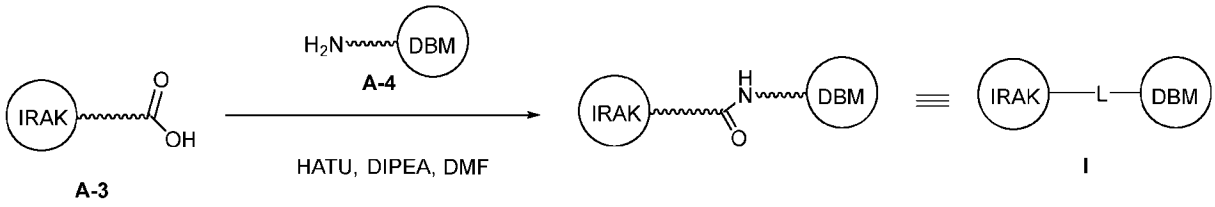


[00541] As depicted in Scheme 2, above, amine **A-1** is coupled to acid **A-2** using the coupling agent PyBOP in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-1** or the portion of the linker between DBM and the terminal carboxyl group of **A-2**, respectively. Additionally, an amide bond can be formed using coupling reagents known in

the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00542] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 3 set forth below:

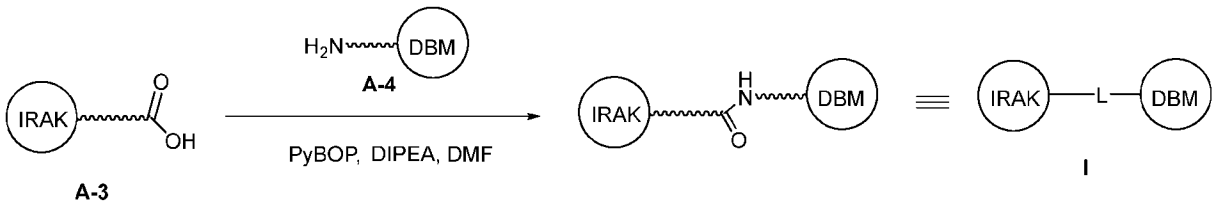
Scheme 3: Synthesis of Compounds of the Invention



[00543] As depicted in Scheme 3, above, acid **A-3** is coupled to amine **A-4** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal carboxyl group of **A-3** or the portion of the linker between DBM and the terminal amino group of **A-4**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00544] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 4 set forth below:

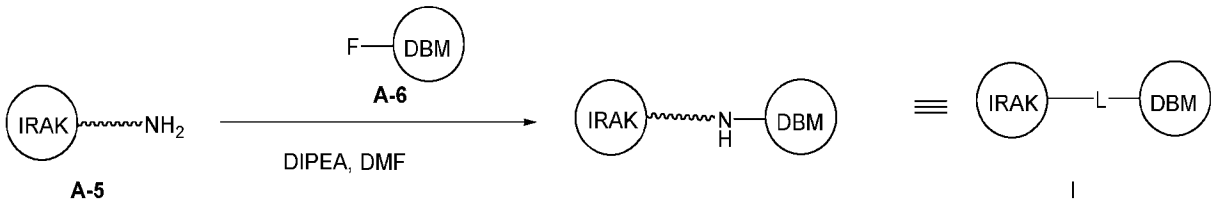
Scheme 4: Synthesis of Compounds of the Invention



[00545] As depicted in Scheme 4, above, acid **A-3** is coupled to amine **A-4** using the coupling agent PyBOP in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal carboxyl group of **A-3** or the portion of the linker between DBM and the terminal amino group of **A-4**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00546] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 5 set forth below:

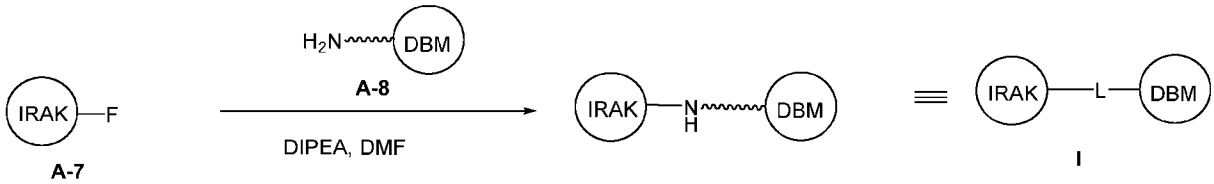
Scheme 5: Synthesis of Compounds of the Invention



[00547] As depicted in Scheme 5, above, an S_NAr displacement of fluoride **A-6** by amine **A-5** is effected in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising a secondary amine. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-5**.

[00548] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 6 set forth below:

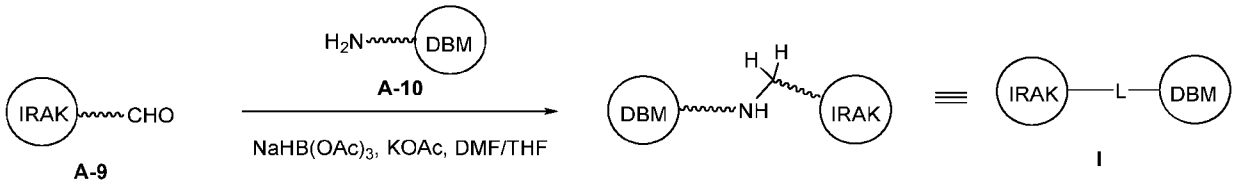
Scheme 6: Synthesis of Compounds of the Invention



[00549] As depicted in Scheme 6, above, an S_NAr displacement of fluoride **A-7** by amine **A-8** is effected in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising a secondary amine. The squiggly bond, ~~~, represents the portion of the linker between DBM and the terminal amino group of **A-8**.

[00550] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 7 set forth below:

Scheme 7: Synthesis of Compounds of the Invention

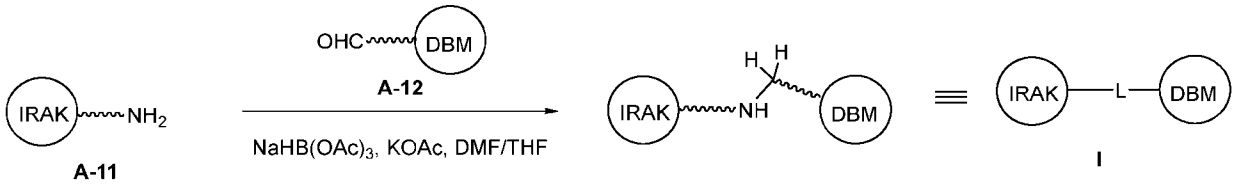


[00551] As depicted in Scheme 7, above, reductive amination of the mixture of aldehyde **A-9** and amine **A-10** is effected in the presence of $NaHB(OAc)_3$ and KOAc in DMF/THF to form a compound of the invention with a linker comprising a secondary amine. A linker comprising a tertiary amine can be prepared similarly using a secondary amine in place of the primary amine **A-10**. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal aldehyde of **A-9** or the portion of the linker between DBM and the terminal amino group of **A-10**, respectively.

[00552] In certain embodiments, compounds of the present invention are generally prepared according

to Scheme 8 set forth below:

Scheme 8: Synthesis of Compounds of the Invention



[00553] As depicted in Scheme 8, above, reductive amination of the mixture of aldehyde **A-12** and amine **A-11** is effected in the presence of $NaHB(OAc)_3$ and KOAc in DMF/THF to form a compound of the invention with a linker comprising a secondary amine. A linker comprising a tertiary amine can be prepared similarily using a secondary amine in place of the primary amine **A-11**. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-11** or the portion of the linker between DBM and the terminal aldehyde of **A-12**, respectively.

[00554] One of skill in the art will appreciate that various functional groups present in compounds of the invention such as aliphatic groups, alcohols, carboxylic acids, esters, amides, aldehydes, halogens and nitriles can be interconverted by techniques well known in the art including, but not limited to reduction, oxidation, esterification, hydrolysis, partial oxidation, partial reduction, halogenation, dehydration, partial hydration, and hydration. See for example, "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of each of which is herein incorporated by reference. Such interconversions may require one or more of the aforementioned techniques, and certain methods for synthesizing compounds of the invention are described below in the Exemplification.

5. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00555] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably degrade and/or inhibit an IRAK protein kinase, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably degrade and/or inhibit an IRAK protein kinase, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00556] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably

a human.

[00557] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00558] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitory or degradatory active metabolite or residue thereof.

[00559] As used herein, the term "inhibitory active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of an IRAK protein kinase, or a mutant thereof.

[00560] As used herein, the term "degratory active metabolite or residue thereof" means that a metabolite or residue thereof is also a degrader of an IRAK protein kinase, or a mutant thereof.

[00561] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00562] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their

polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00563] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00564] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00565] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00566] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00567] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00568] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00569] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00570] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00571] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the compound can be administered to a patient receiving these compositions.

[00572] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00573] Compounds and compositions described herein are generally useful for the degradation and/or inhibition of kinase activity of one or more enzymes.

[00574] Examples of kinases that are degraded and/or inhibited by the compounds and compositions described herein and against which the methods described herein are useful include those of the interleukin-1 receptor-associated kinase (IRAK) family of kinases, the members of which include IRAK-1, IRAK-2, and IRAK-4, or a mutant thereof. Li et al., "IRAK-4: A novel member of the IRAK family with the properties of an IRAK-kinase," *PNAS* 2002, 99(8), 5567-5572, Flannery et al., " The interleukin-1 receptor-

associated kinases: Critical regulators of innate immune signaling" Biochem Pharm 2010, 80(12), 1981-1991 incorporated by reference in its entirety .

[00575] The activity of a compound utilized in this invention as a degrader and/or inhibitor of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity and/or the subsequent functional consequences, or ATPase activity of activated IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to IRAK-1, IRAK-2 and/or IRAK-4. Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/IRAK-1, inhibitor/IRAK-2, or inhibitor/IRAK-4 complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with IRAK-1, IRAK-2, and/or IRAK-4 bound to known radioligands. Representative *in vitro* and *in vivo* assays useful in assaying an IRAK-4 inhibitor include those described and disclosed in, *e.g.*, Kim et al., "A critical role for IRAK4 kinase activity in Toll-like receptor-mediated innate immunity," *J. Exp. Med.* 2007 204(5), 1025-1036; Lebakken et al., "A Fluorescence Lifetime Based Binding Assay to Characterize Kinase Inhibitors," *J. Biomol. Screen.* 2007, 12(6), 828-841; Maschera et al., "Overexpression of an enzymatically inactive interleukin-1-receptor-associated kinase activates nuclear factor-κB," *Biochem. J.* 1999, 339, 227-231; Song et al., "The kinase activities of interleukin-e receptor associated kinase (IRAK)-1 and 4 are redundant in the control of inflammatory cytokine expression in human cells," *Mol. Immunol.* 2009, 46, 1458-1466, each of, the entirety of each of which is herein incorporated by reference. Detailed conditions for assaying a compound utilized in this invention as a degrader and/or inhibitor of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are set forth in the Examples below.

[00576] According to one embodiment, the invention relates to a method of inhibiting protein kinase activity or degrading a protein kinase in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00577] According to another embodiment, the invention relates to a method of inhibiting or degrading IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00578] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00579] Inhibition and/or degradation of a protein kinase, or a protein kinase selected from IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, activity in a biological sample is useful for a variety of

purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[00580] The best characterized member of the IRAK family is the serine/threonine kinase IRAK-4. IRAK-4 is implicated in signaling innate immune responses from Toll-like receptors (TLRs) and Toll/IL-1 receptors (TIRs).

[00581] Innate immunity detects pathogens through the recognition of pathogen-associated molecular patterns by TLRs, when then links to the adaptive immune response. TLRs recognize conserved structures of both microbes and endogenous molecules. TLRs which recognize bacterial and fungal components are located on the cell surface, whereas TLRs which recognize viral or microbial nucleic acids are localized to intracellular membranes such as endosomes and phagosomes. Cell surface TLRs can be targeted by small molecules and antibodies, whereas intracellular TLRs require targeting with oligonucleotides.

[00582] TLRs mediate the innate immune response by upregulating the expression of inflammatory genes in multiple target cells. *See, e.g.*, Sen et al., "Transcriptional signaling by double-stranded RNA: role of TLR3," *Cytokine & Growth Factor Rev.* 2005, 16, 1-14, incorporated by reference in its entirety. While TLR-mediated inflammatory response is critical for innate immunity and host defense against infections, uncontrolled inflammation is detrimental to the host leading to sepsis and chronic inflammatory diseases, such as chronic arthritis, atherosclerosis, multiple sclerosis, cancers, autoimmune disorders such as rheumatoid arthritis, lupus, asthma, psoriasis, and inflammatory bowel diseases.

[00583] Upon binding of a ligand, most TLRs recruit the adaptor molecule MyD88 through the TIR domain, mediating the MyD88-dependent pathway. MyD88 then recruits IRAK-4, which engages with the nuclear factor-κB (NF-κB), mitogen-activated protein (MAP) kinase and interferon-regulatory factor cascades and leads to the induction of pro-inflammatory cytokines. The activation of NF-κB results in the induction of inflammatory cytokines and chemokines, such as TNF-α, IL-1 α, IL-6 and IL-8. The kinase activity of IRAK-4 has been shown to play a critical role in the TLR-mediated immune and inflammatory responses. IRAK4 is a key mediator of the innate immune response orchestrated by interleukin-1 receptor (IL-1R), interleukin-18 receptor (IL-18R), IL-33 receptor (IL-33R), and Toll-like receptors (TLRs). Inactivation of IRAK-1 and/or IRAK-4 activity has been shown to result in diminished production of cytokines and chemokines in response to stimulation of IL-1 and TLR ligands. *See, e.g.*, Picard et al., "Clinical features and outcome of patients with IRAK-4 and MyD88 deficiency," *Medicine (Baltimore)*, 2010, 89(6), 043-25; Li, "IRAK4 in TLR/IL-1R signaling: Possible clinical applications," *Eur. J. Immunology* 2008, 38:614-618; Cohen et al., "Targeting protein kinases for the development of anti-inflammatory drugs," *Curr. Opin. Cell Bio.* 2009, 21:317-324; Flannery et al., "The interleukin-1 receptor-associated kinases: Critical regulators of innate immune signaling," *Biochem. Pharm.* 2010, 80(12), 1981-1991; Gottipati et al., "IRAK1: A critical signaling mediator of innate immunity," *Cellular Signaling* 2008,

20, 269-276; Kim et al., "A critical role for IRAK4 kinase activity in Toll-like receptor-mediated innate immunity," *J. Exp. Med.* 2007 204(5), 1025-1036; Koziczak-Holbro et al., "IRAK-4 Kinase Activity Is Required for Interleukin-1 (IL-1) Receptor- and Toll-like Receptor 7-mediated Signaling and Gene Expression," *J. Biol. Chem.* 2007, 282(18), 13552-13560; Kubo-Murai et al., "IRAK-4-dependent Degradation of IRAK-1 is a Negative Feedback Signal for TLR-mediated NF-κB Activation," *J. Biochem.* 2008, 143, 295-302; Maschera et al., "Overexpression of an enzymatically inactive interleukin-1-receptor-associated kinase activates nuclear factor-κB," *Biochem. J.* 1999, 339, 227-231; Lin et al., "Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR /IL-1R signaling," *Nature* 2010, 465(17), 885-891; Suzuki et al., "IRAK-4 as the central TIR signaling mediator in innate immunity," *TRENDS in Immunol.* 2002, 23(10), 503-506; Suzuki et al., "Severe impairment of interleukin-1 and Toll-like receptor signaling in mice lacking IRAK-4," *Nature* 2002, 416, 750-754; Swantek et al., "IL-1 Receptor-Associated Kinase Modulates Host Responsiveness to Endotoxin," *J. Immunol.* 2000, 164, 4301-4306; Hennessy, E., et al., "Targeting Toll-like receptors: emerging therapeutics?" *Nature Reviews*, vol. 9, pp: 293-307 (2010); Dinarello, C. "Interleukin-18 and the Pathogenesis of Inflammatory Diseases," *Seminars in Nephrology*, vol. 27, no. 1, pp: 98-114 (2007), each of, the entirety of each of which is herein incorporated by reference. In fact, knockdown mice that express a catalytically inactive mutant IRAK-4 protein are completely resistant to septic shock and show impaired IL-1 activity. Moreover, these mice are resistant to joint and bone inflammation/destruction in an arthritis model, suggesting that IRAK-4 may be targeted to treat chronic inflammation. Further, while IRAK-4 appears to be vital for childhood immunity against some pyogenic bacteria, it has been shown to play a redundant role in protective immunity to most infections in adults, as demonstrated by one study in which patients older than 14 lacking IRAK-4 activity exhibited no invasive infections. Cohen et al., "Targeting protein kinases for the development of anti-inflammatory drugs," *Curr. Opin. Cell Bio.* 2009, 21:317-324; Ku et al., "Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity," *J. Exp. Med.* 2007, 204(10), 2407-2422; Picard et al., "Inherited human IRAK-4 deficiency: an update," *Immunol. Res.* 2007, 38, 347-352; Song et al., "The kinase activities of interleukin-e receptor associated kinase (IRAK)-1 and 4 are redundant in the control of inflammatory cytokine expression in human cells," *Mol. Immunol.* 2009, 46, 1458-1466; Rokosz, L. et al., "Kinase inhibitors as drugs for chronic inflammatory and immunological diseases: progress and challenges," *Expert Opinions on Therapeutic Targets*, 12(7), pp: 883-903 (2008); Gearing, A. "Targeting toll-like receptors for drug development: a summary of commercial approaches," *Immunology and Cell Biology*, 85, pp: 490-494 (2007); Dinarello, C. "IL-1: Discoveries, controversies and future directions," *European Journal of Immunology*, 40, pp: 595-653 (2010), each of, the entirety of each of which is herein incorporated by reference. Because TLR activation triggers IRAK-4 kinase activity, IRAK-4 inhibition presents an attractive target for treating the underlying causes of

inflammation in countless diseases.

[00584] Representative IRAK-4 inhibitors include those described and disclosed in *e.g.*, Buckley et al., *Bioorg. Med. Chem. Lett.* 2008, 18, 3211-3214; Buckley et al., *Bioorg. Med. Chem. Lett.* 2008, 18, 3291-3295; Buckley et al., *Bioorg. Med. Chem. Lett.* 2008, 18, 3656-3660; Powers et al., "Discovery and initial SAR of inhibitors of interleukin-1 receptor-associated kinase-4," *Bioorg. Med. Chem. Lett.* 2006, 16, 2842-2845; Wang et al., "IRAK-4 Inhibitors for Inflammation," *Curr. Topics in Med. Chem.* 2009, 9, 724-737, each of, the entirety of each of which is herein incorporated by reference.

[00585] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may 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 may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00586] Provided compounds are degraders and/or inhibitors of one of more of IRAK-1, IRAK-2, and/or IRAK-4 and are therefore useful for treating one or more disorders associated with activity of one or more of IRAK-1, IRAK-2, and/or IRAK-4. Thus, in certain embodiments, the present invention provides a method for treating a IRAK-1-mediated, a IRAK-2-mediated, and/or a IRAK-4-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00587] As used herein, the terms "IRAK-1-mediated", "IRAK-2-mediated", and/or "IRAK-4-mediated" disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are known to play a role.

[00588] According to another embodiment, the invention relates to a method of degrading and/or inhibiting one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00589] In some embodiments, the present invention provides a method for treating one or more disorders, diseases, and/or conditions wherein the disorder, disease, or condition is a cancer, a neurodegenerative disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, or a CNS disorder.

[00590] Diseases and conditions treatable according to the methods of this invention include, but are not limited to, cancer (*see, e.g.*, Ngo, V. et al., "Oncogenically active *MYD88* mutations in human lymphoma," *Nature*, vol. 000, pp: 1-7 (2010); Lust, J. et al., "Induction of a Chronic Disease State in patients With Smoldering of Indolent Multiple Myeloma by Targeting Interleukin 1ß-Induced Interleukin 6 Production and the Myeloma Proliferative Component," *Mayo Clinic Proceedings*, 84(2), pp: 114-122 (2009)), diabetes, cardiovascular disease, viral disease, autoimmune diseases such as lupus (*see, e.g.*, Dinarello, C. " Interleukin-18 and the Pathogenesis of Inflammatory Diseases," *Seminars in Nephrology*, vol. 27, no. 1, pp: 98-114 (2007); Cohen et al., "Targeting protein kinases for the development of anti-inflammatory drugs," *Curr. Opin. Cell Bio*. 2009, 21:317-324) and rheumatoid arthritis (*see, e.g.*, Geyer, M. et al., "Actual status of antiinterleukin-1 therapies in rheumatic diseases," *Current Opinion in Rheumatology*, 22, pp: 246-251 (2010)), autoinflammatory syndromes (*see, e.g.*, Hoffman, H. et al., "Efficacy and Safety of Rilonacept (Interleukin-1 Trap) in Patients with Cryopyrin-Associated Periodic Syndromes," *Arthritis & Rheumatism*, vol. 58, no. 8, pp: 2443-2452 (2008)), atherosclerosis, psoriasis, allergic disorders, inflammatory bowel disease (*see, e.g.*, Cario, E. "Therapeutic Impact of Toll-like Receptors on Inflammatory Bowel Diseases: A Multiple-edged Sword," *Inflamm. Bowel Dis*., 14, pp: 411-421 (2008)), inflammation (*see, e.g.*, Dinarello, C. "Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process, " *The American Journal of Clinical Nutrition*, 83, pp: 447S-455S (2006)), acute and chronic gout and gouty arthritis (*see, e.g.*, Terkeltaub, R. "Update on gout: new therapeutic strategies and options," *Nature*, vol. 6, pp: 30-38 (2010); Weaver, A. "Epidemiology of gout," *Cleveland Clinic Journal of Medicine*, vol. 75, suppl. 5, pp: S9-S12 (2008); Dalbeth, N. et al., "Hyperuricaemia and gout: state of the art and future perspectives," *Annals of Rheumatic Diseases*, 69, pp: 1738-1743 (2010); Martinon, F. et al., "Gout-associated uric acid crystals activate the NALP3 inflammasome," *Nature*, vol. 440, pp: 237-241 (2006); So, A. et al., "A pilot study of IL-1 inhibition by anakinra in acute gout," *Arthritis Research & Therapy*, vol. 9, no. 2, pp: 1-6 (2007); Terkeltaub, R. et al., "The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomized, single-blind pilot study," *Annals of Rheumatic Diseases*, 68, pp: 1613-1617 (2009); Torres, R. et al., "Hyperalgesia, synovitis and multiple biomarkers of

inflammation are suppressed by interleukin 1 inhibition in a novel animal model of gouty arthritis," *Annals of Rheumatic Diseases*, 68, pp: 1602-1608 (2009)), neurological disorders, metabolic syndrome (*see, e.g.*, Troseid, M. "The role of interleukin-18 in the metabolic syndrome," *Cardiovascular Diabetology*, 9:11, pp:1-8 (2010)), immunodeficiency disorders such as AIDS and HIV (*see, e.g.*, Iannello, A. et al., "Role of Interleukin-18 in the Development and Pathogenesis of AIDS," *AIDS Reviews*, 11, pp: 115-125 (2009)), destructive bone disorders (*see, e.g.*, Hennessy, E., et al., "Targeting Toll-like receptors: emerging therapeutics?" *Nature Reviews*, vol. 9, pp: 293-307 (2010)), osteoarthritis, proliferative disorders, Waldenström's Macroglobulinemia (*see, e.g.*, Treon, et al., "Whole genome sequencing reveals a widely expressed mutation (MYD88 L265P) with oncogenic activity in Waldenström's Macroglobulinemia" 53rd ASH Annual Meeting; Xu, et al., "A somatic variant in MYD88 (L256P) revealed by whole genome sequencing differentiates lymphoplasmacytic lymphoma from marginal zone lymphomas" 53rd ASH Annual Meeting; Yang et al., "Disruption of MYD88 pathway signaling leads to loss of constitutive IRAK1, NK-kB and JAK/STAT signaling and induces apoptosis of cells expressing the MYD88 L265P mutation in Waldenström's Macroglobulinemia" 53rd ASH Annual Meeting; Iriyama et al., "Clinical significance of genetic mutations of CD79B, CARD11, MYD88, and EZH2 genes in diffuse large B-cell lymphoma patients" 53rd ASH Annual Meeting; infectious diseases, conditions associated with cell death, pathologic immune conditions involving T cell activation, and CNS disorders in a patient. In one embodiment, a human patient is treated with a compound of the current invention and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound is present in an amount to measurably degrade and/or inhibit IRAK-1 only, IRAK-2-only, IRAK-4-only and/or IRAK1 and IRAK4 kinase activity.

[00591] Compounds of the current invention are useful in the treatment of a proliferative disease selected from a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkin's and Non-Hodgkin's, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, an MyD88 driven disorder, Smoldering of indolent multiple myeloma, or hematological malignancies (including leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone

lymphoma, multiple myeloma, plasmacytoma, intravascular large B-cell lymphoma).

[00592] In some embodiments the proliferative disease which can be treated according to the methods of this invention is an MyD88 driven disorder. In some embodiments, the MyD88 driven disorder which can be treated according to the methods of this invention is selected from ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma and chronic lymphocytic leukemia.

[00593] In some embodiments the proliferative disease which can be treated according to the methods of this invention is an IL-1 driven disorder. In some embodiments the IL-1 driven disorder is Smoldering of indolent multiple myeloma.

[00594] Compounds according to the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics.

[00595] Compounds according to the invention are useful in the treatment of heteroimmune diseases. Examples of such heteroimmune diseases include, but are not limited to, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[00596] Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, such as therapy for or intended to restrict or abort symptomatic attack when it occurs, for example antiinflammatory or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

[00597] Compounds of the current invention can be used for other inflammatory or obstructive airways

diseases and conditions to which the present invention is applicable and include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[00598] With regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil- related disorders of the airways consequential or concomitant to Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

[00599] Compounds of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, and other inflammatory or allergic conditions of the skin.

[00600] Compounds of the invention may also be used for the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis,

Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00601] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is an disease of the skin. In some embodiments, the inflammatory disease of the skin is selected from contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, and other

inflammatory or allergic conditions of the skin.

[00602] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Systemic juvenile idiopathic arthritis (SJIA), Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

[00603] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is a TH17 mediated disease. In some embodiments the TH17 mediated disease is selected from Systemic lupus erythematosus, Multiple sclerosis, and inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[00604] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from Sjogren's syndrome, allergic disorders, osteoarthritis, conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca and vernal conjunctivitis, and diseases affecting the nose such as allergic rhinitis.

[00605] Cardiovascular diseases which can be treated according to the methods of this invention include, but are not limited to, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke, congestive heart failure, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, and deep venous thrombosis.

[00606] In some embodiments, the neurodegenerative disease which can be treated according to the methods of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.

[00607] The loss of IRAK4 function results in decreased Aβ levels in an *in vivo* murine model of Alzheimer's disease and was associated with diminished microgliosis and astrogliosis in aged mice. Analysis of microglia isolated from the adult mouse brain revealed an altered pattern of gene expression associated with changes in microglial phenotype that were associated with expression of IRF transcription factors that govern microglial phenotype. Further, loss of IRAK4 function also promoted amyloid clearance mechanisms, including elevated expression of insulin-degrading enzyme. Finally, blocking IRAK function restored olfactory behavior (Cameron *et al.* "Loss of Interleukin Receptor-Associated Kinase 4 Signaling Suppresses Amyloid Pathology and Alters Microglial Phenotype in a Mouse Model of Alzheimer's Disease" Journal of Neuroscience (2012) 32(43), 15112-15123.

[00608] In some embodiments the invention provides a method of treating, preventing or lessening the severity of Alzheimer's disease comprising administering to a patient in need thereof a provided compound

or a pharmaceutically acceptable salt or composition thereof.

[00609] In some embodiments the invention provides a method of treating a disease or condition commonly occurring in connection with transplantation. In some embodiments, the disease or condition commonly occurring in connection with transplantation is selected from organ transplantation, organ transplant rejection, and graft versus host disease.

[00610] In some embodiments the invention provides a method of treating a metabolic disease. In some embodiments the metabolic disease is selected from Type 1 diabetes, Type 2 diabetes, metabolic syndrome, and obesity.

[00611] In some embodiments the invention provides a method of treating a viral disease. In some embodiments, the viral infection is HIV infection.

[00612] Furthermore, the invention provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof for the preparation of a medicament for the treatment of a proliferative disease, an inflammatory disease, an obstructive respiratory disease, a cardiovascular disease, a metabolic disease, a neurological disease, a neurodegenerative disease, a viral disease, or a disorder commonly occurring in connection with transplantation.

Combination Therapies

[00613] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00614] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00615] 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.

[00616] Examples of agents the combinations of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for HIV

such as ritonavir; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsant, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents that prolong or improve pharmacokinetics such as cytochrome P450 inhibitors (i.e., inhibitors of metabolic breakdown) and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir), and agents for treating immunodeficiency disorders such as gamma globulin.

[00617] In certain embodiments, combination therapies of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00618] Those additional agents may be administered separately from a provided combination therapy, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00619] 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 combination of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

[00620] The amount of additional therapeutic agent present in the compositions of this invention will be 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 additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00621] One or more other therapeutic agent 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 administered as a multiple dosage regimen within greater than 24 hours apart.

[00622] In one embodiment, the present invention provides a composition comprising a provided compound and one or more additional therapeutic agents. The therapeutic agent may be administered together with a provided compound, or may be administered prior to or following administration of a provided compound. Suitable therapeutic agents are described in further detail below. In certain embodiments, a provided compound may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a provided compound may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

[00623] In another embodiment, the present invention provides a method of treating an inflammatory disease, disorder or condition by administering to a patient in need thereof a provided compound and one or more additional therapeutic agents. Such additional therapeutic agents may be small molecules or recombinant biologic agents and include, for example, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol, febuxostat (Uloric®), sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and "anti-TNF" agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), "anti-IL-1" agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), canakinumab (Ilaris®), anti-Jak inhibitors such as tofacitinib, antibodies such as rituximab

(Rituxan®), "anti-T-cell" agents such as abatacept (Orencia®), "anti-IL-6" agents such as tocilizumab (Actemra®), diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®), monoclonal antibodies such as tanezumab, anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot®, anticholinergics or antispasmodics such as dicyclomine (Bentyl®), Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), and flunisolide (Aerobid®), Afviar®, Symbicort®, Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyl®, Theo-24®) and aminophylline, IgE antibodies such as omalizumab (Xolair®), nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevairapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), bortezomib (Velcade®), and dexamethasone (Decadron ®) in combination with lenalidomide (Revlimid ®), or any combination(s) thereof.

[00624] In another embodiment, the present invention provides a method of treating gout comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol and febuxostat (Uloric®).

[00625] In another embodiment, the present invention provides a method of treating rheumatoid arthritis comprising administering to a patient in need thereof a provided compound and one or more

additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and "anti-TNF" agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), "anti-IL-1" agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), antibodies such as rituximab (Rituxan®), "anti-T-cell" agents such as abatacept (Orencia®) and "anti-IL-6" agents such as tocilizumab (Actemra®).

[00626] In some embodiments, the present invention provides a method of treating osteoarthritis comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®) and monoclonal antibodies such as tanezumab.

[00627] In some embodiments, the present invention provides a method of treating lupus comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), cyclophosphamide (Cytoxan®), methotrexate (Rheumatrex®), azathioprine (Imuran®) and anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®).

[00628] In some embodiments, the present invention provides a method of treating inflammatory bowel disease comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from mesalamine (Asacol®) sulfasalazine (Azulfidine®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot® and anticholinergics or antispasmodics such as dicyclomine (Bentyl®), anti-TNF therapies, steroids, and antibiotics such as Flagyl or ciprofloxacin.

[00629] In some embodiments, the present invention provides a method of treating asthma comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA),

levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyl®, Theo-24®) and aminophylline, and IgE antibodies such as omalizumab (Xolair®).

[00630] In some embodiments, the present invention provides a method of treating COPD comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyl®, Theo-24®) and aminophylline, inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®,

[00631] In some embodiments, the present invention provides a method of treating HIV comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevairapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), and combinations thereof.

[00632] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®),

doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00633] In another embodiment, the present invention provides a method of treating a solid tumor comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00634] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a provided compound and a Hedgehog (Hh) signaling pathway inhibitor. In some embodiments, the hematological malignancy is DLBCL (Ramirez *et al* "Defining causative factors contributing in the activation of hedgehog signaling in diffuse large B-cell lymphoma" Leuk. Res. (2012), published online July 17, and incorporated herein by reference in its entirety).

[00635] In another embodiment, the present invention provides a method of treating diffuse large B-cell lymphoma (DLBCL) comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, and combinations thereof.

[00636] In another embodiment, the present invention provides a method of treating multiple myeloma comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from bortezomib (Velcade®), and dexamethasone (Decadron®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor in combination with lenalidomide (Revlimid®).

[00637] In another embodiment, the present invention provides a method of treating Waldenström's macroglobulinemia comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®, Neosar®), fludarabine (Fludara®), cladribine (Leustatin®), rituximab (Rituxan®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, and a SYK inhibitor.

[00638] In some embodiments, one or more other therapeutic 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.

[00639] In some embodiments, one or more other therapeutic 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.).

[00640] In some embodiments, one or more other therapeutic 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).

[00641] In some embodiments, one or more other therapeutic 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).

[00642] In some embodiments, one or more other therapeutic agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present invention include pemetrexed (Alimta®, Eli Lilly).

[00643] In some embodiments, one or more other therapeutic 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).

[00644] In some embodiments, one or more other therapeutic 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).

[00645] In some embodiments, one or more other therapeutic 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).

[00646] In some embodiments, one or more other therapeutic agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present invention include CB-839 (Calithera Biosciences).

[00647] In some embodiments, one or more other therapeutic 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).

[00648] In some embodiments, one or more other therapeutic 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).

[00649] In some embodiments, one or more other therapeutic 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).

[00650] In some embodiments, one or more other therapeutic 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).

[00651] In some embodiments, one or more other therapeutic 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).

[00652] In some embodiments, one or more other therapeutic 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).

[00653] In some embodiments, one or more other therapeutic 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).

[00654] In some embodiments, one or more other therapeutic 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/TGFß 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 TGFß "trap."

[00655] In some embodiments, one or more other therapeutic 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.

[00656] In some embodiments, one or more other therapeutic agent 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, 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_6244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00657] In some embodiments, the present invention provides a method of treating Alzheimer's disease comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from donepezil (Aricept®), rivastigmine (Excelon®), galantamine (Razadyne®), tacrine (Cognex®), and memantine (Namenda®).

[00658] In some embodiments, one or more other therapeutic 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).

[00659] In some embodiments, one or more other therapeutic 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.

[00660] 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).

[00661] In some embodiments, one or more other therapeutic 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).

[00662] 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).

[00663] In another embodiment, the present invention provides a method of treating organ transplant rejection or graft vs. host disease comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from a steroid, cyclosporin, FK506, rapamycin, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, and a SYK inhibitor.

[00664] In another embodiment, the present invention provides a method of treating or lessening the

severity of a disease comprising administering to a patient in need thereof a provided compound and a BTK inhibitor, wherein the disease is selected from inflammatory bowel disease, arthritis, systemic lupus erythematosus (SLE), vasculitis, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease, autoimmune thyroiditis, Sjogren's syndrome, multiple sclerosis, systemic sclerosis, Lyme neuroborreliosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylosis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, autoimmune gastritis, pernicious anemia, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, membranous glomerulonephropathy, endometriosis, interstitial cystitis, pemphigus vulgaris, bullous pemphigoid, neuromyotonia, scleroderma, vulvodynia, a hyperproliferative disease, rejection of transplanted organs or tissues, Acquired Immunodeficiency Syndrome (AIDS, also known as HIV), type 1 diabetes, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis, asthma, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis, B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, multiple myeloma (also known as plasma cell myeloma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, or lymphomatoid granulomatosis, breast cancer, prostate cancer, or cancer of the mast cells (e.g.,

mastocytoma, mast cell leukemia, mast cell sarcoma, systemic mastocytosis), bone cancer, colorectal cancer, pancreatic cancer, diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, bone metastasis, a thromboembolic disorder, (e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, deep venous thrombosis), inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, scleroderma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[00665] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound and a PI3K inhibitor, wherein the disease is selected from a cancer, a neurodegenerative disorder, an angiogenic disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, and a CNS disorder.

[00666] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound and a PI3K inhibitor, wherein the disease is selected from benign or malignant tumor, carcinoma or solid tumor of the

brain, kidney (e.g., renal cell carcinoma (RCC)), liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, endometrium, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, (including, for example, non-Hodgkin's Lymphoma (NHL) and Hodgkin's lymphoma (also termed Hodgkin's or Hodgkin's disease)), a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, or a leukemia, diseases include Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated, asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection, acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy, bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis, pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, pilosis, siderosis, silicosis, tabacosis and byssinosis, Loffler's syndrome, eosinophilic, pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine

ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke and congestive heart failure, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity and hypoxia.

[00667] In some embodiments, one or more other therapeutic 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).

[00668] A compound of the current invention may also be used to advantage in combination with other antiproliferative compounds. 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, 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, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00669] 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, ketoconazole, 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.

[00670] In some embodiments, one or more other therapeutic 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).

[00671] In some embodiments, one or more other therapeutic agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from exemestane (Aromasin®, Pfizer); anastazole (Arimidex®, AstraZeneca) and letrozole (Femara®, Novartis).

[00672] 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.

[00673] 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™.

[00674] 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™.

[00675] 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.

[00676] 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™.

[00677] 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™.

[00678] 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).

[00679] 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™.

[00680] 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™.

[00681] 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.

[00682] 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).

[00683] 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.

[00684] In some embodiments, one or more other therapeutic 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).

[00685] 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.

[00686] 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.

[00687] 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

[00688] 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.

[00689] 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.

[00690] 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.

[00691] 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.

[00692] 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.

[00693] 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.

[00694] 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.

[00695] 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.

[00696] 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.

[00697] 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.

[00698] 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.

[00699] 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.

[00700] 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.

[00701] 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™),); carfilzomib (Kyprolis®, Amgen); and ixazomib (Ninlaro®, Takeda), and MLN 341.

[00702] 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.

[00703] 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.

[00704] 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.

[00705] 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.

[00706] 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.

[00707] 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.

[00708] 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).

[00709] 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.

[00710] 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; ZD6474; 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™).

[00711] 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.

[00712] 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.

[00713] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00714] 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.

[00715] The compounds of the invention are also useful as co-therapeutic compounds for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes

a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

[00716] Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclomethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate; non-steroidal glucocorticoid receptor agonists; LTB4 antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering- Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12- 281 (Asta Medica), CDC-801 (Celgene), SeICID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo); A2a agonists; A2b antagonists; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof. Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate.

[00717] Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine.

[00718] Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1 , CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1 , CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH- 55700 and SCH-D, and Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4- aminium chloride (TAK-770).

[00719] 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).

[00720] A compound of the current invention may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[00721] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or

the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current invention can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[00722] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00723] 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 may be administered with another therapeutic agent 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, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00724] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[00725] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00726] The amount of one or more other therapeutic agent present in the compositions of this invention may be 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 in the presently disclosed compositions will range 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 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.

[00727] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

Exemplary Immuno-Oncology agents

[00728] In some embodiments, one or more other therapeutic 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.

[00729] 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.

[00730] 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.

[00731] 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.

[00732] 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.

[00733] 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.

[00734] In some embodiments, an immuno-oncology agent is an antagonist of inhibitory receptors on NK cells or an agonists of activating receptors on NK cells. In some embodiments, an immuno-oncology agent is an antagonists of KIR, such as lirilumab.

[00735] 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).

[00736] 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.

[00737] 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.

[00738] 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.

[00739] 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).

[00740] 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).

[00741] 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).

[00742] 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).

[00743] 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, Kyn Therapeutics); and NLG-919 (WO09/73620, WO009/1156652, WO11/56652, WO12/142237).

[00744] 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.

[00745] 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).

[00746] 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.

[00747] 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.

[00748] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[00749] 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.

[00750] 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.

[00751] 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).

[00752] 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).

[00753] 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.

[00754] 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.

[00755] 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.

[00756] For example, in some embodiments the CAR-T cell is one of those described in U.S. Patent 8,906,682 (June; 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].

[00757] 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).

[00758] 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).

[00759] Other immuno-oncology agents that may 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.

[00760] 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.

[00761] 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.

[00762] In some embodiments, an immuno-oncology agent is selected from those descripted 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 embodiment, 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.

[00763] 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.

[00764] 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 embodiment, 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

[00765] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[00766] The term "checkpoint inhibitor" as used herein relates 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.

[00767] 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.

[00768] 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.

[00769] In one aspect, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In another aspect, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a fusion protein or a combination thereof. In a further aspect, the checkpoint inhibitor inhibits a checkpoint protein selected from CTLA-4, PDLl, PDL2, PDl, 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 an additional aspect, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from CTLA-4, PDLl, PDL2, PDl, 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 an aspect, the checkpoint inhibitor is an immunostimulatory agent, a T cell growth factor, an interleukin, an antibody, a vaccine or a combination thereof. In a further aspect, the interleukin is IL-7 or IL-15. In a specific aspect, the interleukin is glycosylated IL-7. In an additional aspect, the vaccine is a dendritic cell (DC) vaccine.

[00770] Checkpoint inhibitors include any agent that blocks or inhibits in a statistically significant manner, the inhibitory pathways of the immune system. Such inhibitors may include small molecule inhibitors or may 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 may 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 Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-Ll monoclonal Antibody (Anti-B7-Hl; MEDI4736), MK-3475 (PD-1 blocker), Nivolumab (anti-PDl antibody), CT-011 (anti-PDl antibody), BY55 monoclonal antibody, AMP224 (anti-PDLl antibody), BMS- 936559 (anti-PDLl antibody), MPLDL3280A (anti-PDLl antibody), MSB0010718C (anti-PDLl antibody), and ipilimumab (anti-CTLA-4 checkpoint inhibitor). Checkpoint protein ligands include, but are not limited to PD-Ll, PD-L2, B7-H3, B7-H4, CD28, CD86 and TIM-3.

[00771] 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).

[00772] 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.

[00773] 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).

[00774] 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).

[00775] 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).

[00776] 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).

[00777] Checkpoint inhibitors that may 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).

[00778] Checkpoint inhibitors that may 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).

[00779] Checkpoint inhibitors that may 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).

[00780] Checkpoint inhibitors that may 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 (NCT 02740270); 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).

[00781] Checkpoint inhibitors that may 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).

[00782] Checkpoint inhibitors that may 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 mycloma (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).

[00783] Checkpoint inhibitors that may 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).

[00784] Checkpoint inhibitors that may 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).

[00785] Checkpoint inhibitors that may 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).

[00786] Checkpoint inhibitors that may 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).

[00787] Checkpoint inhibitors that may 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).

[00788] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

[00789] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

EXEMPLIFICATION

[00790] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

General Synthetic Methods

[00791] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

[00792] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

[00793] All reactions are carried out under nitrogen or argon unless otherwise stated.

[00794] Proton NMR (^{1}H NMR) is conducted in deuterated solvent. In certain compounds disclosed herein, one or more ^{1}H shifts overlap with residual proteo solvent signals; these signals have not been reported in the experimental provided hereinafter.

Table 2: Analytical instruments

LCMS	Shimadzu UFLC MS: LCMS-2020 Agilent Technologies 1200 series MS: Agilent Technologies 6110

	Agilent Technologies 1200 series MS: LC/MSD VL
NMR	BRUKER AVANCE III/400; Frequency (MHz) 400.13; Nucleus: 1H; Number of Transients: 8
Prep-HPLC	Gilson GX-281 systems: instruments GX-A, GX-B, GX-C, GX-D, GX-E, GX-F, GX-G and GX-H
GCMS	SHIMADZU GCMS-QP2010 Ultra
Analytical cSFC	Agilent Technologies 1290 Infinity
Prep-cSFC	Waters SFC Prep 80

[00795] For acidic LCMS data: LCMS is recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS2020 equipped with electro-spray ionization and quadruple MS detector [ES+ve to give MH^+] and equipped with Chromolith Flash RP-18e 25*2.0 mm, eluting with 0.0375 vol% TFA in water (solvent A) and 0.01875 vol% TFA in acetonitrile (solvent B). Other LCMS is recorded on an Agilent 1290 Infinity RRLC attached with Agilent 6120 Mass detector. The column used is BEH C18 50*2.1 mm, 1.7 micron. Column flow is 0.55 ml /min and mobile phase used is (A) 2 mM Ammonium Acetate in 0.1% Formic Acid in Water and (B) 0.1 % Formic Acid in Acetonitrile.

[00796] For basic LCMS data: LCMS is recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS 2020 equipped with electro-spray ionization and quadruple MS detector [ES+ve to give MH^+] and equipped with Xbridge C18, 2.1X50 mm columns packed with 5 mm C18-coated silica or Kinetex EVO C18 2.1X30mm columns packed with 5 mm C18-coated silica, eluting with 0.05 vol% $NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B).

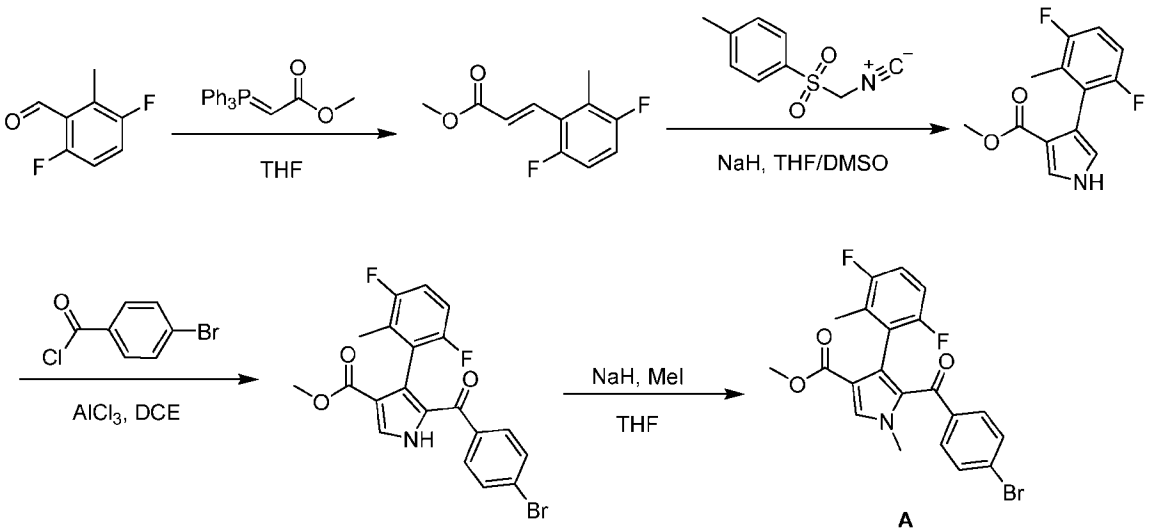
[00797] HPLC Analytical Method: HPLC is carried out on X Bridge C18 150*4.6 mm, 5 micron. Column flow is 1.0 ml /min and mobile phase used is (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile.

[00798] Prep HPLC Analytical Method: The compound is purified on Shimadzu LC-20AP and UV detector. The column used is X-BRIDGE C18 (250*19)mm, 5µ. Column flow is 16.0 ml/min. Mobile phase is (A) 0.1% Formic Acid in Water and (B) Acetonitrile. Basic method used is (A) 5mM ammonium bicarbonate and 0.1% NH_3 in Water and (B) Acetonitrile or (A) 0.1% Ammonium Hydroxide in Water and (B) Acetonitrile. The UV spectra are recorded at 202nm & 254nm.

[00799] NMR Method: The 1H NMR spectra are recorded on a Bruker Ultra Shield Advance 400 MHz/5 mm Probe (BBFO). The chemical shifts are reported in part-per-million.

Intermediates:

[00800] Methyl 5-(4-bromobenzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methyl-1H-pyrrole-3-carboxylate (Intermediate A)



Step 1 - Methyl (*E*)-3-(3,6-difluoro-2-methylphenyl)acrylate

[00801] A solution of 3,6-difluoro-2-methylbenzaldehyde (5.00 g, 32.0 mmol, CAS# 1378525-21-3) and methyl 2-(triphenyl-lambda5-phosphanylidene)acetate (12.85 g, 38.43 mmol) in THF (60 mL) was stirred for 2 h at rt. On completion, the resulting mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 100 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (8:1) to afford the title compound (6.30 g, 93% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, J = 16.3 Hz, 1H), 7.35-7.27 (m, 1H), 7.27-7.11 (m, 1H), 6.49 (dd, J = 16.4, 1.2 Hz, 1H), 3.76 (s, 3H), 2.29 (d, J = 2.3 Hz, 3H).

Step 2 - Methyl 4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate

[00802] To a stirred solution of methyl (*E*)-3-(3,6-difluoro-2-methylphenyl)acrylate (13.00 g, 61.26 mmol) and TosMIC (15.64 g, 80.12 mmol) in THF (70 mL) and DMSO (70 mL) were added NaH (2.31 g, 96.1 mmol) in portions at 0 °C. The resulting mixture was stirred overnight at rt. On completion, the reaction was quenched with water/ice at 0 °C. The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (2 x 100 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1), to afford the title compound (16.00 g, 80% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.58-7.52 (m, 1H), 7.18-7.08 (m, 1H), 7.07-6.97 (m, 1H), 6.86 (t, J = 2.3 Hz, 1H), 3.56 (s, 3H), 2.00 (d, J = 2.6 Hz, 3H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 252.1.

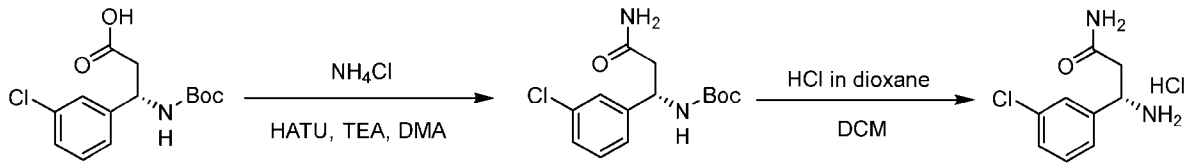
Step 3 - Methyl 5-(4-bromobenzoyl)-4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate

[00803] To a stirred mixture of methyl 4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (2.5 g, 9.9 mmol) and $AlCl_3$ (3.98 g, 29.9 mmol) in DCE (100 mL) were added 4-bromo-benzoyl chloride (2.62 g, 11.9 mmol) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 5 h at 50 °C under air atmosphere. On completion, the mixture was purified by silica gel column chromatography, eluted with PE / EA (15:1), to afford the title compound (3.5 g, 81% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.90-7.85 (m, 1H), 7.45-7.37 (m, 2H), 7.29 (m, 2H), 7.03-6.93 (m, 1H), 6.84-6.73 (m, 1H), 3.60 (s, 3H), 1.85 (d, J = 2.5 Hz, 3H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 434.9.

Step 4 - Methyl 5-(4-bromobenzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methyl-1*H*-pyrrole-3-carboxylate

[00804] To a stirred mixture of methyl 5-(4-bromobenzoyl)-4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (3.4 g, 7.8 mmol) in THF (50 mL) was added NaH (0.63 g, 16 mmol, 60% dispersion in mineral oil) in portions at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 30 min at rt under N_2 atmosphere. To the above mixture was added CH_3I (1.67 g, 11.7 mmol) dropwise over 2 min at rt. The resulting mixture was stirred for additional 2 h at rt. On completion, the mixture was diluted with water (50 mL) and concentrated under reduced pressure. The residue was dissolved in DMF (5 mL). The mixture was purified by reverse phase Flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L, NH_4HCO_3); Eluent B: ACN; Gradient: 25% - 55% B in 25 min; Flow rate: 60mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B) and concentrated under reduced pressure to afford the title compound (800 mg, 23% yield) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.42-7.35 (m, 2H), 7.35-7.27 (m, 2H), 6.96-6.86 (m, J = 9.1, 4.5 Hz, 1H), 6.78-6.61 (m, 1H), 3.94 (s, 3H), 3.59 (s, 3H), 1.86 (d, J = 2.5 Hz, 3H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 447.1.

(*S*)-3-amino-3-(3-chlorophenyl)propanamide hydrochloride (Intermediate B)



B

Step 1 - T*ert*-butyl (*S*)-(3-amino-1-(3-chlorophenyl)-3-oxopropyl)carbamate

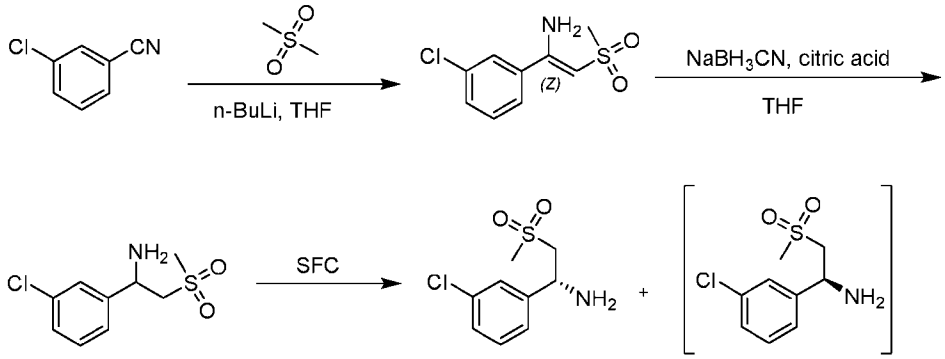
[00805] To a stirred solution of (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-(3-chlorophenyl)propanoic acid (20 g, 67 mmol, CAS# 500770-74-1) and NH_4Cl (17.84 g, 333.6 mmol) in DMA (120 mL) were added DIEA (46.49 mL, 266.9 mmol) and HATU (38.06 g, 100.1 mmol) in portions at rt. The resulting mixture was stirred for 4 h at rt under air atmosphere. On completion, the mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L, NH_4HCO_3), 35% to 65% gradient in 25 min; detector, UV 220/254 nm;

desired fractions were collected at 51% B and concentrated) under reduced pressure to afford the title compound (14 g, 70% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 8.7 Hz, 1H), 7.38 – 7.21 (m, 6H), 6.81 (s, 1H), 4.89 (q, J = 7.8 Hz, 1H), 2.47 (d, J = 7.3 Hz, 2H), 1.36 (s, 9H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 299.1.

Step 2 - (*S*)-3-amino-3-(3-chlorophenyl)propanamide hydrochloride

[00806] To a stirred mixture of *tert*-butyl (*S*)-(3-amino-1-(3-chlorophenyl)-3-oxopropyl)carbamate (13.00 g, 43.51 mmol) in DCM (100 mL) was added HCl (gas) in 1,4-dioxane (20 mL, 80 mmol) at rt. The resulting mixture was stirred for 3 h at rt. On completion, the mixture was concentrated under reduced pressure to give the title compound (8.40 g, 82% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 3H), 7.68-7.59 (m, 2H), 7.54-7.41 (m, 3H), 7.03 (s, 1H), 4.59 (s, 1H), 2.88 (dd, J = 15.6, 6.2 Hz, 1H), 2.79 (dd, J = 15.6, 8.1 Hz, 1H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 199.1.

(R)-1-(3-chlorophenyl)-2-(methylsulfonyl)ethan-1-amine (Intermediate C)



Step 1 - (*Z*)-1-(3-chlorophenyl)-2-(methylsulfonyl)ethen-1-amine

[00807] To a stirred solution of methylsulfonylmethane (6.84 g, 72.7 mmol) in THF (250 mL) was added *n*-BuLi (2.5 M, 21.8 mL, 54.5 mmol) dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at -78 °C under nitrogen atmosphere. To the above mixture was added a solution of 3-chlorobenzonitrile (5 g, 40 mmol,) in THF (30 mL) dropwise at -78 °C. The resulting mixture was stirred for additional 2 h at rt. On completion, the reaction was quenched by addition of water (300 mL), then the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 500 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 30 min; detector, UV 254 nm) to afford the title compound (7.4 g, 88% yield) as a light yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53-7.37 (m, 4H), 5.86 (brs, 2H), 5.06 (s, 1H), 3.05 (s, 3H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 232.0.

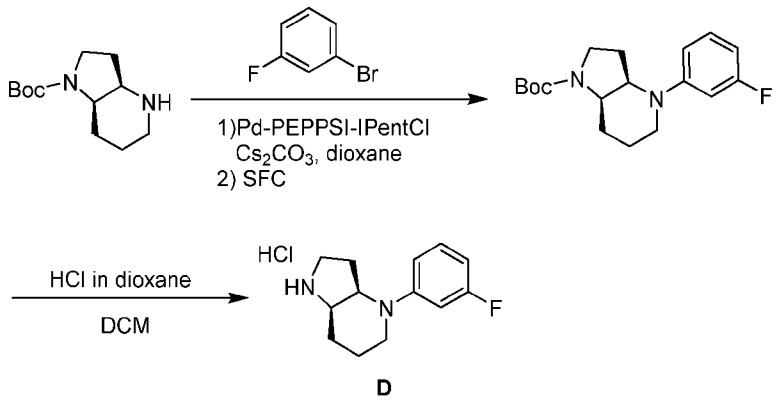
Step 2 - 1-(3-Chlorophenyl)-2-(methylsulfonyl)ethan-1-amine

[00808] To a stirred mixture of (*Z*)-1-(3-chlorophenyl)-2-(methylsulfonyl)ethen-1-amine (7.8 g, 34 mmol) in MeOH (80 mL) was added $NaBH_3CN$ (7.40 g, 118 mmol) and citric acid (12.94 g, 67.33 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the mixture was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 25% - 55% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B) and concentrated under reduced pressure to afford the title compound (4.2 g, 53% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 1H), 7.38-7.25 (m, 3H), 4.70-4.67 (m, 1H), 3.38-3.21 (m, 2H), 3.00 (s, 3H), 1.93 (brs, 2H). LC/MS (ESI, m/z): $[(M + 1)]^+ = 234.0$.

Step 3 - (*R*)-1-(3-chlorophenyl)-2-(methylsulfonyl)ethan-1-amine

[00809] 1-(3-chlorophenyl)-2-(methylsulfonyl)ethan-1-amine (11 g, 47 mmol) was separated by Prep-SFC with the following conditions: Column: CHIRALPAK IF 3*25 cm, 5 um; Mobile Phase A: CO_2, Mobile Phase B: ACN: MeOH = 1:1(1% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 15% B; Column Temperature(°C): 35; RT2(min): 12; Sample Solvent: MeOH; Injection Volume: 2 mL to afford (*R*)-1-(3-chlorophenyl)-2-(methylsulfonyl)ethan-1-amine (3.9 g, 71% yield) (slower peak) as a white solid. The absolute stereochemistry of the enantiomer was assigned arbitrarily. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 (s, 1H), 7.35-7.28 (m, 3H), 4.71-4.68 (m, 1H), 3.41-3.22 (m, 2H), 3.00 (s, 3H), 2.09 (brs, 2H). LC/MS (ESI, m/z): $[(M + 1)]^+ = 234.0$.

(3aR,7aR)-4-(3-fluorophenyl)-octahydropyrrolo[3,2-b]pyridine hydrochloride (Intermediate D)



D

Step 1 - *Tert*-butyl (*3aR,7aR*)-4-(3-fluorophenyl)-hexahydro-2*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate

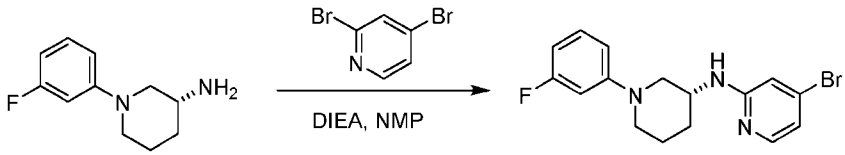
[00810] To a stirred solution of *(cis)-tert*-butyl -octahydropyrrolo[3,2-*b*]pyridine-1-carboxylate (4.7 g, 21 mmol, CAS# 1251010-63-5) and *m*-bromofluorobenzene (4.36 g, 24.920 mmol) in dioxane (70 mL) were added Pd-PEPPSI-IPentCl 2-methylpyridine (*o*-picoline) (0.87 g, 1.04 mmol) and Cs_2CO_3 (13.53 g, 41.53 mmol) at rt. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. On

completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1 - 12:1) to afford crude product. The crude product (6 g) was purified by Prep-SFC (Column: CHIRAL ART Cellulose-SC, 5*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: IPA; Flow rate: 230 mL/min; Gradient: isocratic 15% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 11.5; RT2(min): 14; Sample Solvent: MeOH; Injection Volume: 2 mL; Number Of Runs: 70) to afford the title compound (1.6 g, 24% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24-7.16 (m, 1H), 6.73-6.65 (m, 1H), 6.63-6.57 (m, 1H), 6.54-6.46 (m, 1H), 4.43-4.28 (m, 1H), 4.07-3.79 (m, 1H), 3.60-3.27 (m, 3H), 2.89-2.80 (m, 1H), 2.35-2.13 (m, 1H), 2.03-1.94 (m, 1H), 1.94-1.74 (m, 2H), 1.66-1.53 (m, 1H), 1.50 (d, J = 2.2 Hz, 9H), 1.39 – 1.24 (m, 1H). LC/MS (ESI, m/z): $[(M + H)]^+$ = 321.2.

Step 2 - (*3aR,7aR*)-4-(3-fluorophenyl)-octahydropyrrolo[3,2-*b*]pyridine hydrochloride

[00811] To a stirred solution of *tert*-butyl (*3aR,7aR*)-4-(3-fluorophenyl)-hexahydro-2*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (1.6 g, 4.994 mmol) in DCM (20 mL) was added HCl (gas)in 1,4-dioxane (20 mL, 80 mmol) at rt. The resulting mixture was stirred for 1 h at rt. On completion, the mixture was concentrated under reduced pressure to afford the title compound (1.3 g, 99% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31-7.22 (m, 1H), 6.81-6.73 (m, 2H), 6.63-6.55 (m, 1H), 4.39-4.28 (m, 1H), 3.75-3.63 (m, 1H), 3.41-3.16 (m, 3H), 2.98-2.79 (m, 1H), 2.52-2.50 (m, 2H), 2.07-1.80 (m, 3H), 1.70-1.47 (m, 2H). LC/MS (ESI, m/z): [(M + H)]+ = 221.1.

[00812] (R)-4-Bromo-N-(1-(3-fluorophenyl)piperidin-3-yl)pyridin-2-amine (Intermediate E)

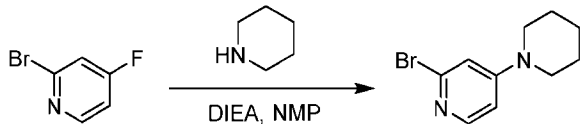


AG E

[00813] To a stirred solution of (R)-1-(3-fluorophenyl)piperidin-3-amine (2.5 g, 13 mmol, Intermediate AG) and 2,4-dibromopyridine (6.71 g, 28.3 mmol, CAS# 58530-53-3) in NMP (30 mL) was added DIEA (5.0 g, 39 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 48 h at 120 °C under nitrogen atmosphere. On completion, the reaction was quenched by the addition of water (300 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 500 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (column, Welflash TM C18-1, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient 40% to 75% B in 30 min; Flow rate: 85 mL/min; Detector: 220/254 nm; desired fractions were collected at 75% B) and concentrated under reduced to afford the title compound (530 mg, 12% yield) as a brown oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93

(d, J = 5.4 Hz, 1H), 7.24 - 7.16 (m, 1H), 6.78 - 6.67 (m, 2H), 6.70 - 6.59 (m, 2H), 6.62-6.50 (m, 1H), 4.89 (d, J = 8.4 Hz, 1H), 4.08 - 3.95 (m, 1H), 3.55 (dd, J = 12.1, 3.4 Hz, 1H), 3.26 (ddd, J = 10.9, 6.6, 3.7 Hz, 1H), 3.15 (ddd, J = 11.6, 7.6, 3.3 Hz, 1H), 3.03 (dd, J = 12.1, 6.9 Hz, 1H), 1.95 - 1.86 (m, 2H), 1.85 - 1.61 (m, 2H); LC/MS (ESI, m/z): $[(M - H)]^-$ = 438.0.

2-Bromo-4-(piperidin-1-yl)pyridine (Intermediate F)



F

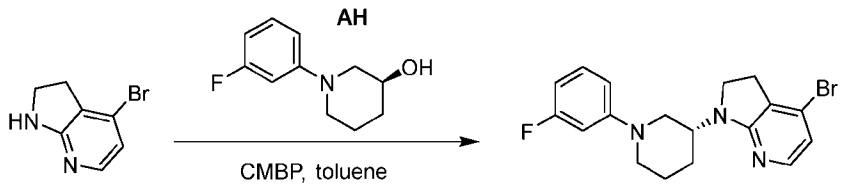
[00814] To a stirred solution of 2-bromo-4-fluoropyridine (500 mg, 2.84 mmol, CAS# 357927-50-5) and piperidine (725.76 mg, 8.523 mmol) in NMP (10 mL) was added DIEA (1101.61 mg, 8.523 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 120 °C under nitrogen atmosphere. On completion, the mixture was allowed to cool down to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford the title compound (580 mg, 85% yield) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.96 (d, J = 6.0 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.59 (s, 1H), 3.35 (d, J = 5.9 Hz, 4H), 1.81 - 1.48 (m, 6H).

3-(6-Bromopyridin-3-yl)-3-azabicyclo[3.1.1]heptane (Intermediate G)

G

[00815] To a stirred mixture of 3-azabicyclo[3.1.1]heptane hydrochloride (2 g, 20 mmol, CAS# 1427380-44-6) and 2-bromo-4-fluoropyridine (4.35 g, 24.7 mmol) in NMP (30 mL) was added DIEA (7.98 g, 61.8 mmol) dropwise at rt under air atmosphere. The resulting mixture was stirred for 1 h at 130 °C under air atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The mixture was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH4HCO3); Eluent B: ACN; Gradient: 40% - 80% B in 40 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B) and concentrated under reduced pressure to afford the title compound (2.748 g, 53% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, J = 6.0 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.53 - 6.39 (m, 1H), 3.58 - 3.44 (m, 4H), 2.72 - 2.57 (m, 2H), 2.34 - 2.23 (m, 2H), 1.49 - 1.37 (m, 2H); LC/MS (ESI, m/z): $[(M + H)]^+$ = 253.2.

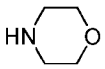
(R)-4-bromo-1-(1-(3-fluorophenyl)piperidin-3-yl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (Intermediate H)



H

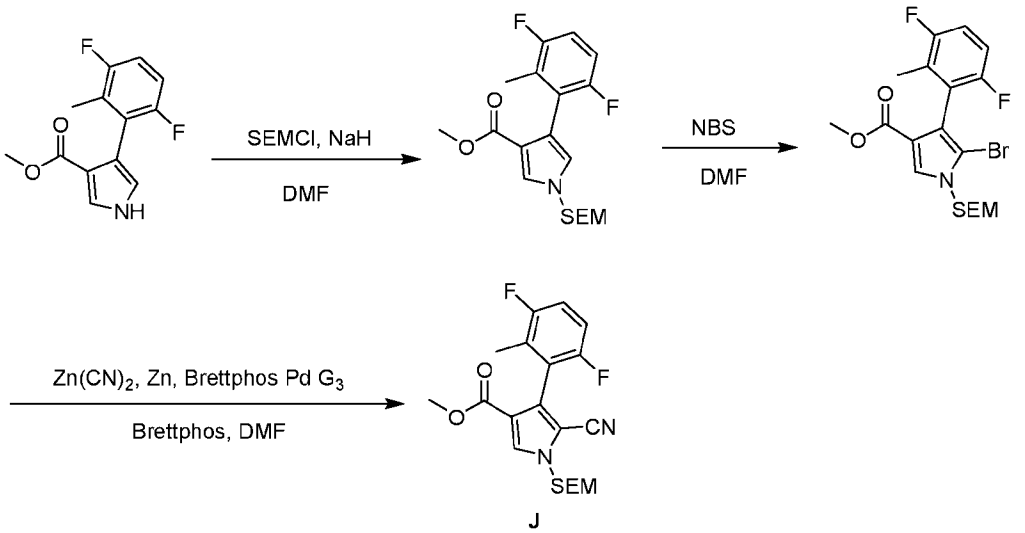
[00816] To a stirred solution of 4-bromo-1*H*,2*H*,3*H*-pyrrolo[2,3-*b*]pyridine (870 mg, 4.37 mmol, CAS# 1393534-35-4) in toluene (20 mL) were added (3*S*)-1-(3-fluorophenyl)piperidin-3-ol (1.71 g, 8.74 mmol, Intermediate AH) and 2-(tributyl-lambda5-phosphanylidene)acetonitrile (3.16 g, 13.1 mmol) in portions at rt under nitrogen atmosphere. The resulting mixture was stirred for 5 h at 110 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and quenched with water (300 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 500 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase Flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 25% - 55% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B) and concentrated under reduced pressure to afford the title compound (140 mg, 9% yield) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.62 (d, *J* = 5.7 Hz, 1H), 7.25 – 7.18 (m, 1H), 6.80 - 6.74 (m, 2H), 6.60 (d, *J* = 5.7 Hz, 1H), 6.54 -6.48 (m, 1H), 3.97-3.92 (m, 1H), 3.74 - 3.59 (m, 4H), 3.02 - 2.87 (m, 3H), 2.72 (td, *J* = 12.4, 2.6 Hz, 1H), 1.87 - 1.65 (m, 4H). LC/MS (ESI, m/z): $[(M + H)]^+$ = 376.0, 378.0.

Morpholine (CAS# 110-91-8) (Intermediate I)



I

[00817] Methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-3-carboxylate (Intermediate J)



J

Step 1 - Methyl 4-(3,6-difluoro-2-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrole-3-carboxylate

[00818] To a stirred solution of methyl 4-(3,6-difluoro-2-methylphenyl)-1H-pyrrole-3-carboxylate (5.00 g, 19.9 mmol, synthesized via Steps 1-2 of Intermediate A) in DMF (50 mL) was added NaH (0.57 g, 24 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at rt. To the above mixture was added SEM-Cl (3.98 g, 23.9 mmol) dropwise at 0 °C. The resulting mixture was stirred for an additional 2 h at rt. On completion, the reaction was quenched with water at 0 °C, then extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1), to afford the title compound (4.70 g, 62% yield) as an orange oil. LC/MS (ESI, m/z): $[(M + H)]^+$= 382.3.

Step 2 - 5-Bromo-4-(3,6-difluoro-2-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrole-3-carboxylate

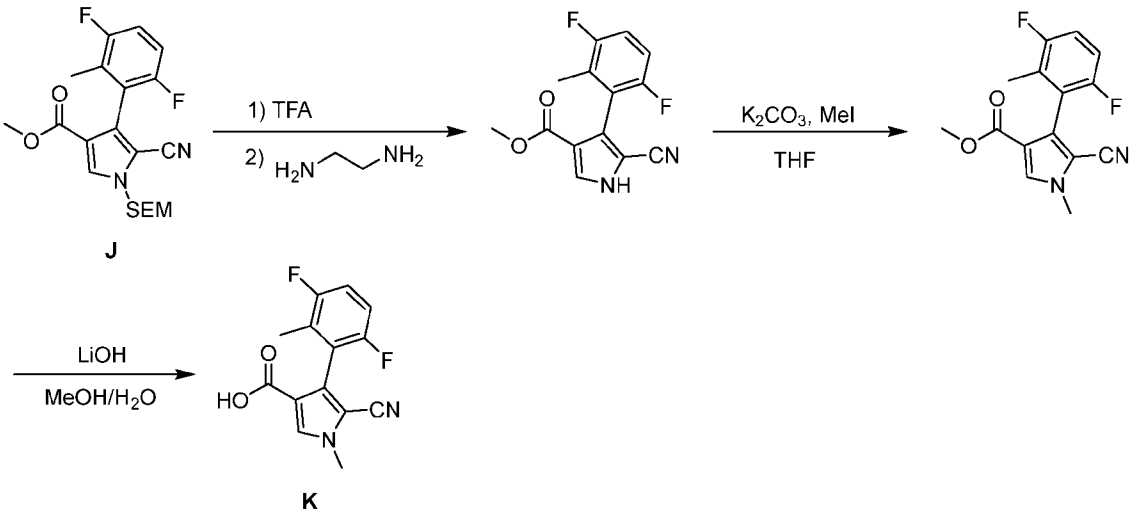
[00819] A solution of methyl 4-(3,6-difluoro-2-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrole-3-carboxylate (2.5 g, 6.6 mmol) and NBS (1.40 g, 7.87 mmol) in THF (25 mL) was stirred for 1 h at rt. The resulting mixture was then stirred for 1 h at 50 °C. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1), to afford the title compound (2 g, 66% yield) as a white solid. LC/MS (ESI, m/z): $[(M + H)]^+$= 460.1, 462.1.

Step 3 - Methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-3-carboxylate

[00820] To a stirred solution of methyl 5-bromo-4-(3,6-difluoro-2-methylphenyl)-1-{[2-

(trimethylsilyl)ethoxy]methyl}pyrrole-3-carboxylate (1.4 g, 0.003 mmol), $Zn(CN)_2$ (0.21 g, 0.002 mmol), Zn (0.02 g) and BrettPhos (0.16 g) in DMF (10 mL) was added BrettPhos Pd G3 (0.28 g) at rt under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (30:1), to afford the title compound (1.1 g, 89% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ7.72 (s, 1H), 7.07 - 7.05 (m, 1H), 6.99 - 7.95 (m, 1H), 5.45 (d, *J* = 1.5 Hz, 2H), 3.72 (s, 3H), 3.65 (dd, *J* = 8.7, 7.5 Hz, 2H), 2.11 (d, *J* = 2.5 Hz, 3H), 0.86 (s, 2H), 0.04 (s, 9H); LC/MS (ESI, m/z): $[(M + H)]^+$= 407.2.

5-Cyano-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (Intermediate K)



Step 1 - Methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate

[00821] A solution of methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-3-carboxylate (270 mg, 0.664 mmol, Intermediate J) in trifluoroacetaldehyde (1 mL) and DCM (2 mL) was stirred for 1 h at rt. The resulting mixture was concentrated under reduced pressure. To the above mixture was added ethane-1,2-diamine (1 mL) and DCM (2 mL) dropwise at rt. The resulting mixture was stirred for an additional 1 h at rt. On completion, the mixture was concentrated under reduced to give the title compound (90 mg, 49% yield) as a white solid. LC/MS (ESI, m/z): $[(M + H)]^-$= 277.1.

Step 2 - Methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate

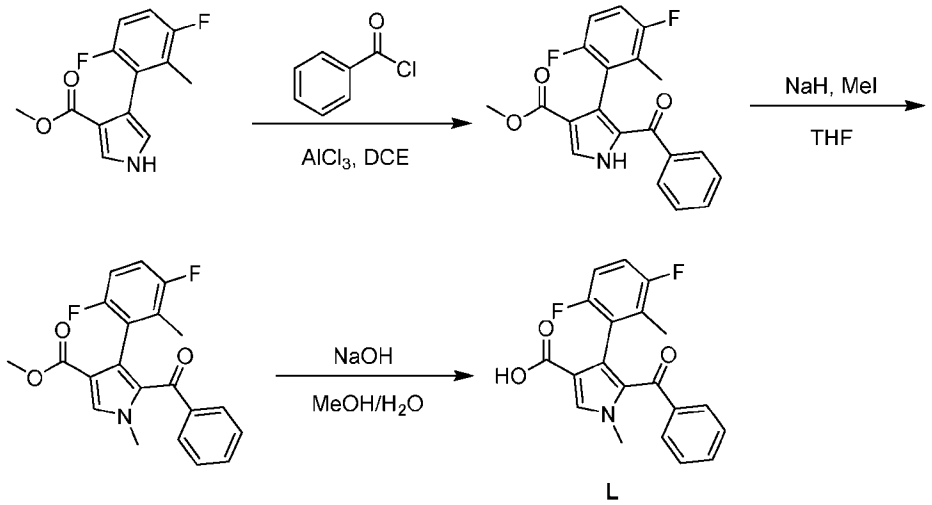
[00822] To a stirred solution of methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (90 mg, 0.33 mmol) and K_2CO_3 (135 mg, 0.977 mmol) in THF (1 mL) was added MeI (69 mg, 0.49 mmol) at rt and the mixture was then stirred for 1 h at rt. On completion, the mixture was acidified to

pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 5:1) to afford the title compound (60 mg, 64% yield) as a white solid. LC/MS (ESI, m/z): $[(M + H)]^+$= 291.2.

Step 3 - 5-Cyano-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid

[00823] A solution of methyl 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate (60 mg, 0.21 mmol) and LiOH (50 mg, 2.1 mmol) in MeOH (1 mL) and H_2O (1 mL) was stirred for 2 h at 80 °C. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (5 x 5mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the title compound (600 mg, 79% yield) as a white solid. LC/MS (ESI, m/z): $[(M + H)]^+$=277.0.

5-Benzoyl-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (Intermediate L)



L

Step 1 - 5-Benzoyl-4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (

[00824] To a stirred mixture of methyl 4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (300 mg, 1.19 mmol, synthesized via Steps 1-2 of Intermediate A) and $AlCl_3$ (477 mg, 3.58 mmol) in DCE (5 mL) was added benzoyl chloride (251 mg, 1.79 mmol) at rt. The resulting mixture was stirred for 2 h at rt. On completion, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1), to afford the title compound (280 mg, 66% yield) as a white solid. LC/MS (ESI, m/z): $[(M + H)]^+$= 356.2.

Step 2 - Methyl 5-benzoyl-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate

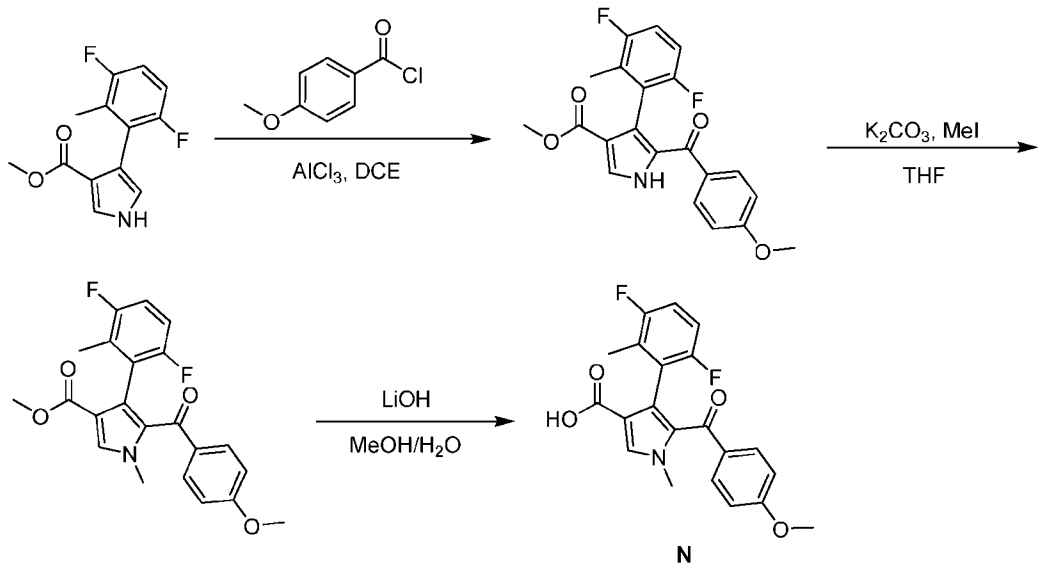
[00825] To a stirred mixture of methyl 5-benzoyl-4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (250 mg, 0.704 mmol) in THF (5 mL) was added NaH (57 mg, 2.4 mmol) in portions at 0 °C

under nitrogen atmosphere. The resulting mixture was stirred for 30 min at rt under nitrogen atmosphere. To the above mixture was added CH_3I (300 mg, 2.11 mmol) dropwise over 2 min at rt. The resulting mixture was stirred for an additional 1 h at rt. On completion, the mixture was quenched with water (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 200mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 10:1) to afford the title compound (233 mg, 90% yield) as a yellow solid. ^1H NMR (300 MHz, Chloroform-d) δ 7.64 (s, 1H), 7.55 - 7.45 (m, 2H), 7.28 - 7.21 (m, 1H), 7.14 (dd, J = 8.2, 6.9 Hz, 2H), 6.65-6.60 (m, 2H), 4.02 (s, 3H), 3.70 (d, J = 7.0 Hz, 3H), 1.92 - 1.83 (m, 3H). LC/MS (ESI, m/z): $[(M + H)]^+$= 370.1.

Step 3 - 5-Benzoyl-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid

[00826] To a stirred mixture of methyl 5-benzoyl-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate (210 mg, 0.57 mmol) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (182 mg, 4.55 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 1 h at 80 °C. On completion, the mixture was cooled to rt and acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give the title compound (200 mg, 99% yield) as a yellow solid. LC/MS (ESI, m/z): $[(M - H)]^-$ = 354.2.

4-(3,6-Difluoro-2-methylphenyl)-5-(4-methoxybenzoyl)-1-methyl-1*H*-pyrrole-3-carboxylic acid (Intermediate N)



N

Step 1 - Methyl 4-(3,6-difluoro-2-methylphenyl)-5-(4-methoxybenzoyl)-1*H*-pyrrole-3-carboxylate

[00827] To a stirred mixture of methyl 4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (1 g, 4 mmol, synthesized via Steps 1-2 of Intermediate A) and 4-methoxy-benzoyl chloride (1.36 g, 7.96

mmol) in (10 mL) was added $AlCl_3$ (1.06 g, 7.96 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 4 h at 50 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 20% - 50% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 35% B) and concentrated under reduced pressure to afford the title compound (1 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.10 (s, 1H), 7.82 (d, *J* = 3.4 Hz, 1H), 7.48 - 7.40 (m, 2H), 6.80 - 6.78 (m, 1H), 6.72 - 6.70 (m, 1H), 6.66 - 6.58 (m, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 1.87 (d, *J* = 2.6 Hz, 3H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 386.2.

Step 2 - Methyl 4-(3,6-difluoro-2-methylphenyl)-5-(4-methoxybenzoyl)-1-methyl-1*H*-pyrrole-3-carboxylate

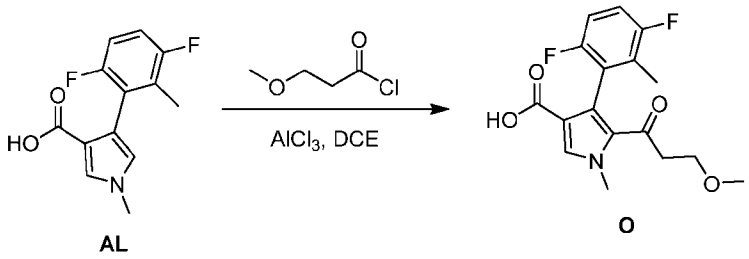
[00828] To a stirred mixture of methyl 4-(3,6-difluoro-2-methylphenyl)-5-(4-methoxybenzoyl)-1*H*-pyrrole-3-carboxylate (500 mg, 1 mmol) in THF (5 mL) was added NaH (77.84 mg, 1.946 mmol, 60% dispersion in mineral oil) in portions at rt under air atmosphere. The resulting mixture was stirred for 0.5 h at rt under nitrogen atmosphere. To the above mixture was added MeI (552.48 mg, 3.891 mmol) dropwise over at rt then the mixture was stirred for additional 16 h at rt. On completion, the mixture was quenched with water (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 200mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography, eluted with PE / EA (5:1), to afford the title compound (500 mg, 97% yield) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (s, 1H), 7.58 - 7.50 (m, 2H), 6.75 - 6.59 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 1H), 3.97 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 1.92 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.46, -117.50, -121.87, -121.91. LC/MS (ESI, m/z): $[(M + 1)]^+$ = 400.1.

Step 3 - 4-(3,6-Difluoro-2-methylphenyl)-5-(4-methoxybenzoyl)-1-methyl-1*H*-pyrrole-3-carboxylic acid

[00829] To a stirred mixture of methyl 4-(3,6-difluoro-2-methylphenyl)-5-(4-methoxybenzoyl)-1-methylpyrrole-3-carboxylate (500 mg, 1 mmol) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (400.58 mg, 10.016 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. On completion, the mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 2 100 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give the title compound (358 mg, 74% yield) as a light yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (s, 1H), 7.58 - 7.49 (m, 2H), 6.65 - 6.62 (m, 4H), 3.96 (s, 3H), 3.77 (s, 3H), 1.91 (d, *J* = 2.6 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.37, -117.42, -121.89, -121.93. LC/MS (ESI, m/z): $[(M + 1)]^+$ = 386.1.

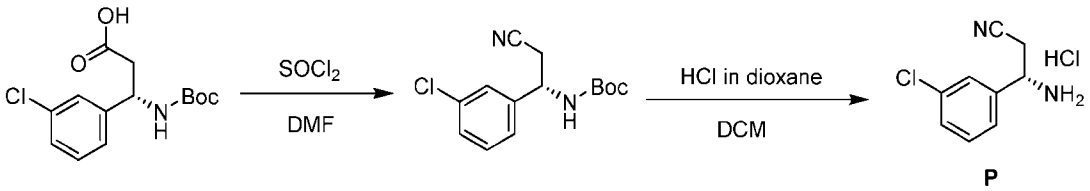
4-(3,6-Difluoro-2-methylphenyl)-5-(3-methoxypropanoyl)-1-methylpyrrole-3-carboxylic acid

(Intermediate O)



[00830] To a stirred mixture of 4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (200 mg, 0.8 mmol, Intermediate AL) and $AlCl_3$ (159.21 mg, 1.194 mmol) in DCE (5 mL) was added 3-methoxypropanoyl chloride (390.24 mg, 3.184 mmol) at rt under air atmosphere. The resulting mixture was stirred for 2 h at 50 °C under nitrogen atmosphere. On completion, the mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector, UV 254 nm) to afford the title compound (10 mg, 4% yield) as a light yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+$ =338.1.

(3*S*)-3-amino-3-(3-chlorophenyl)propanenitrile hydrochloride (Intermediate P)



Step 1 - Tert-butyl *N*-[(1*S*)-1-(3-chlorophenyl)-2-cyanoethyl]carbamate

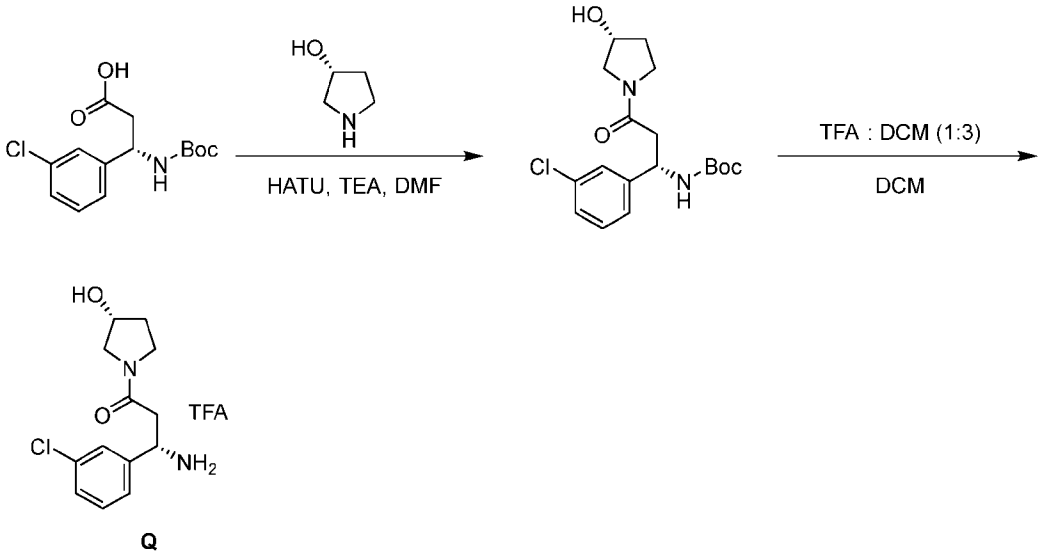
[00831] A solution of *tert*-butyl *N*-[(1*S*)-2-carbamoyl-1-(3-chlorophenyl)ethyl]carbamate (5 g, 20 mmol, CAS# 500770-74-1) and $SOCl_2$ (10 g, 90 mmol) in DMF (100 mL) was stirred for 2 h at rt under air atmosphere. On completion, the reaction was quenched with water at rt and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 45% - 65% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 55% B) and concentrated under reduced pressure to afford the title compound (4 g, 85% yield) as a yellow solid. ^1H NMR (400 MHz, Chloroform-*d*) δ7.78 (d, *J* = 8.9 Hz, 1H), 7.50 - 7.29 (m, 4H), 4.91 (q, *J* = 8.4 Hz, 1H), 3.03 - 2.79 (m, 2H), 1.39 (s, 9H).

Step 2 - (3*S*)-3-amino-3-(3-chlorophenyl)propanenitrile hydrochloride

[00832] A solution of *tert*-butyl *N*-[(1*S*)-1-(3-chlorophenyl)-2-cyanoethyl]carbamate (300 mg, 1.07 mmol) in HCl (gas) in 1,4-dioxane (5 mL) and DCM (5 mL) was stirred for 1 h at rt. On completion, the mixture was concentrated under reduced pressure to give the title compound (182 mg, 94% yield) as a light

yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 181.1$.

(3*S*)-3-amino-3-(3-chlorophenyl)-1-[(3*R*)-3-hydroxypyrrolidin-1-yl]propan-1-one (Intermediate Q)



Q

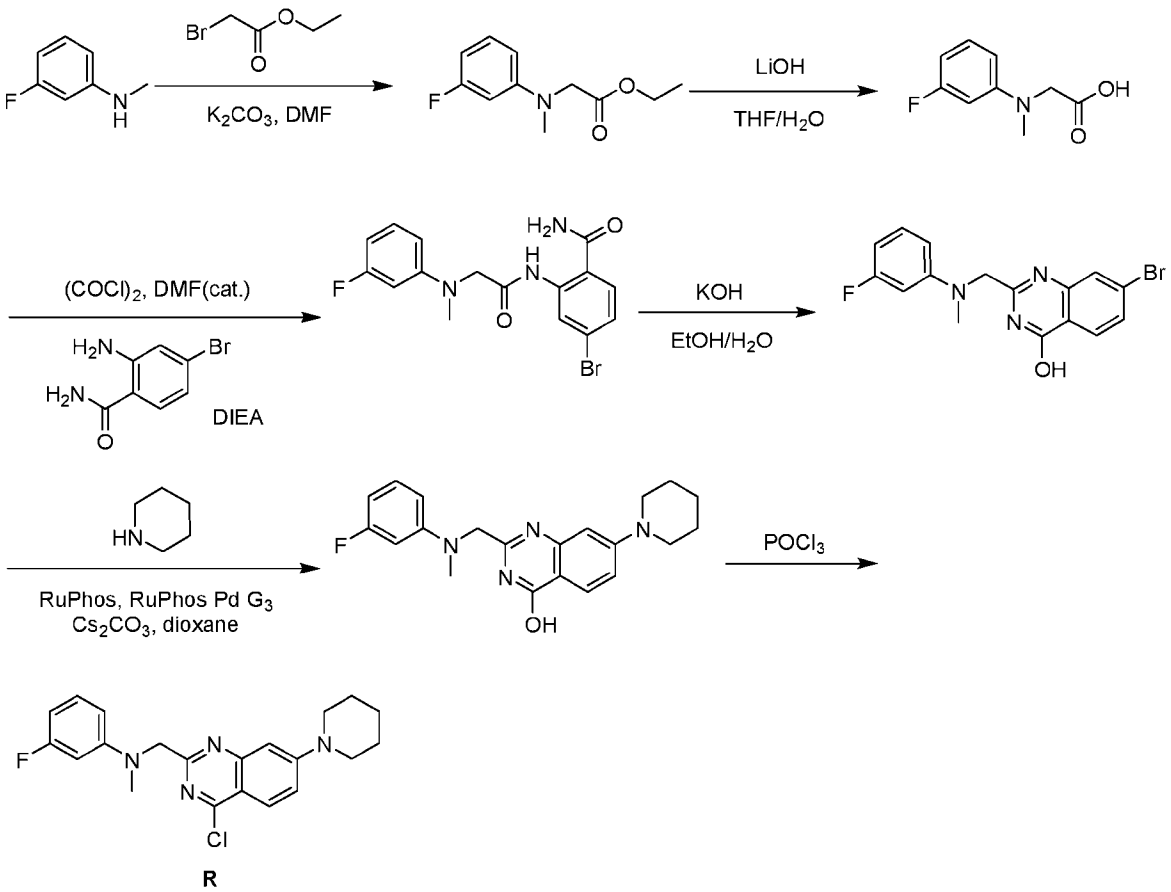
Step 1 - Tert-butyl N-[(1*S*)-1-(3-chlorophenyl)-3-[(3*R*)-3-hydroxypyrrolidin-1-yl]-3-oxopropyl]carbamate

[00833] To a stirred solution of (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-(3-chlorophenyl)propanoic acid (200 mg, 0.667 mmol, CAS# 500770-74-1), (3*R*)-pyrrolidin-3-ol (70 mg, 0.80 mmol) and TEA (135 mg, 1.33 mmol) in DMF (2 mL) was added HATU (304 mg, 0.800 mmol) at rt. The resulting mixture was stirred for 1 h at rt. On completion, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase A: water (5 mmol/L NH_4HCO_3), mobile phase B: ACN, 30% to 50% gradient in 30 min; detector, UV 254 nm; the fractions were collected at 45%) and concentrated under reduced pressure to afford the title compound (250 mg, quant. yield) as a yellow oil. LC/MS (ESI, m/z): $[(M + H)]^+ = 369.2$.

Step 2 - (3*S*)-3-amino-3-(3-chlorophenyl)-1-[(3*R*)-3-hydroxypyrrolidin-1-yl]propan-1-one

[00834] A solution of *tert*-butyl *N*-[(1*S*)-1-(3-chlorophenyl)-3-[(3*R*)-3-hydroxypyrrolidin-1-yl]-3-oxopropyl]carbamate (150 mg, 0.407 mmol) in HCl (gas) in 1,4-dioxane (1 mL) and DCM (1 mL) was stirred for 1 h at rt. On completion, the resulting mixture was concentrated under reduced pressure to give the title compound (120 mg) as a yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 269.2$.

N-((4-chloro-7-(piperidin-1-yl)quinazolin-2-yl)methyl)-3-fluoro-N-methylaniline (Intermediate R)



R

Step 1 - Ethyl 2-[(3-fluorophenyl)(methyl)amino]acetate

[00835] To a stirred solution of 3-fluoro-*N*-methylaniline (10 g, 80 mmol) and ethyl bromoacetate (40.03 g, 239.7 mmol) in DMF (50 mL) was added K_2CO_3 (16.57 g, 119.9 mmol) at rt under air atmosphere. The resulting mixture was stirred for 1 h at 80 °C under air atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 30% - 60% B in 30 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 51% B) and concentrated under reduced pressure to afford the title compound (13 g, 77% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 - 7.11 (m, 1H), 6.50 - 6.43 (m, 2H), 6.43 - 6.35 (m, 1H), 4.30 - 4.16 (m, 2H), 4.06 (s, 2H), 3.08 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); LC/MS (ESI, m/z): $[(M + H)]^+$ = 212.1.

Step 2 - [(3-Fluorophenyl)(methyl)amino]acetic acid

[00836] To a stirred solution of ethyl 2-[(3-fluorophenyl)(methyl)amino]acetate (13 g, 62 mmol) in THF (100 mL)/H_2O (100 mL) was added LiOH (14.74 g, 615.4 mmol) at rt under air atmosphere. The resulting mixture was stirred for 4 h at rt under air atmosphere. On completion, the mixture was concentrated under

reduced pressure. The mixture was acidified to pH 5 with conc. HCl. The aqueous layer was extracted with EtOAc (5x50 mL). The resulting mixture was concentrated under reduced pressure to afford the title compound (10 g, 89% yield) as a purple solid. LC/MS (ESI, m/z): $[(M + H)]^+$= 184.2.

Step 3 - 4-Bromo-2-{2-[(3-fluorophenyl)(methyl)amino]acetamido}benzamide

[00837] To a stirred solution of [(3-fluorophenyl)(methyl)amino]acetic acid (4 g, 20 mmol) in DCM (80 mL) were added $(COCl)_2$ (3.72 mL, 43.7 mmol) and DMF (319.22 mg, 4.367 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt under nitrogen atmosphere. Then the mixture was concentrated under reduced pressure. The residue was dissolved in THF (80 mL). To a stirred solution of 2-amino-4-bromobenzamide (4.70 g, 21.8 mmol) and DIEA (0.57 mL, 3.276 mmol) in THF (40 mL) was added the rt temperature under air atmosphere. On completion, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase Flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 30% - 60% B in 30 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 47% B) and concentrated under reduced pressure to afford the title compound (3.1 g, 37% yield) as a reddish solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.89 (s, 1H), 9.02 (d, *J* = 1.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.30 - 7.15 (m, 4H), 6.55 - 6.47 (m, 2H), 6.02 (s, 1H), 4.04 (s, 2H), 3.18 (s, 3H). LC/MS (ESI, m/z): $[(M + H)]^+$= 380.0, 382.0.

Step 4 - 7-Bromo-2-{[(3-fluorophenyl)(methyl)amino]methyl}quinazolin-4-ol

[00838] To a stirred solution of 4-bromo-2-{2-[(3-fluorophenyl)(methyl)amino]acetamido}benzamide (3 g, 8 mmol) in EtOH (30 mL)/H_2O (30 mL) was added KOH (2.21 g, 39.5 mmol) at rt under air atmosphere. The resulting mixture was stirred for 1 h at 80 °C under air atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The aqueous layer was extracted with EtOAc (5x50 mL). The resulting mixture was concentrated under reduced pressure to afford the title compound (2.6 g) as a brown yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 - 7.81 (m, 1H), 7.52 - 7.46 (m, 1H), 7.32 - 7.24 (m, 1H), 7.14 - 7.03 (m, 1H), 6.56 - 6.43 (m, 2H), 6.35 - 6.25 (m, 1H), 4.34 - 4.29 (m, 2H), 4.09 - 3.99 (m, 1H), 3.14 (s, 3H). LC/MS (ESI, m/z): $[(M + H)]^+$= 362.0, 364.0.

Step 5 - 2-{[(3-Fluorophenyl)(methyl)amino]methyl}-7-(piperidin-1-yl)quinazolin-4-ol

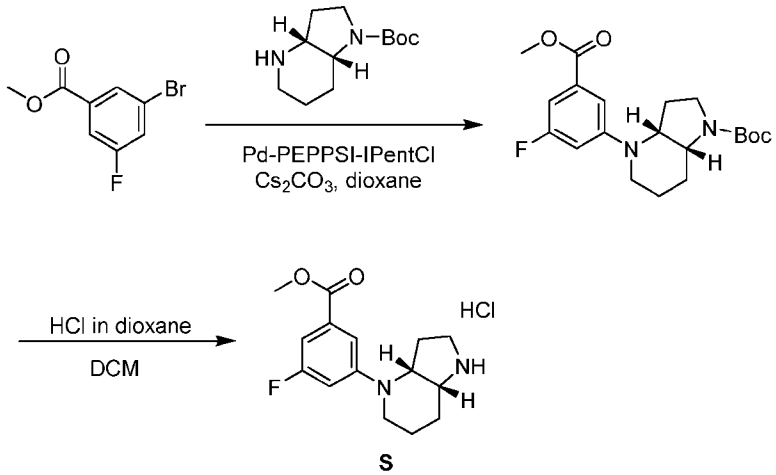
[00839] To a stirred solution of 7-bromo-2-{[(3-fluorophenyl)(methyl)amino]methyl}quinazolin-4-ol (3.2 g, 8.835 mmol) and piperidine (1.50 g, 17.7 mmol) in 1,4-dioxane (32 mL) were added Cs_2CO_3 (5.76 g, 17.7 mmol) and RuPhos (412.27 mg, 0.884 mmol) at rt under air atmosphere. To the above mixture was added RuPhos Palladacycle Gen.3 (738.93 mg, 0.884 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for an additional 16 h at 80 °C. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1), to afford the title compound (1.4 g, 43% yield) as a yellow solid. ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 9.40 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.26 - 7.15 (m, 1H), 7.11 - 7.05 (m, 1H), 7.03 (s, 1H), 6.63 - 6.48 (m, 3H), 4.50 - 4.46 (m, 1H), 3.51 - 3.44 (m, 3H), 3.12 (s, 3H), 1.76 - 1.69 (m, 5H), 1.33 - 1.22 (m, 2H), 0.89 - 0.84 (m, 1H); LC/MS (ESI, m/z): $[(M + H)]^+$= 367.2.

Step 6 - *N*-{[4-chloro-7-(piperidin-1-yl)quinazolin-2-yl]methyl}-3-fluoro-*N*-methylaniline

[00840] Into a 40 mL vial were added 2-{[(3-fluorophenyl)(methyl)amino]methyl}-7-(piperidin-1-yl)quinazolin-4-ol (1.4 g, 3.821 mmol) and $POCl_3$ (14 mL) at rt. The resulting mixture was stirred for 1 h at 90 °C under air atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and quenched with Water/Ice at 0 °C. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure to afford the title compound (1.8 g) as a red solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 - 7.97 (m, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.23 - 7.13 (m, 1H), 6.75 - 6.68 (m, 1H), 6.63 - 6.52 (m, 1H), 6.51 - 6.43 (m, 1H), 5.06 (s, 1H), 3.72 (s, 2H), 3.30 (s, 2H), 1.79 (s, 5H), 1.28 (s, 3H), 0.94 - 0.86 (m, 1H), 0.87 (s, 1H); LC/MS (ESI, m/z): $[(M + H)]^+$= 385.1.

Methyl 3-fluoro-5-((3aR,7aR)-octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)benzoate hydrochloride (Intermediate S)



S

Step 1 - Tert-butyl (3aR,7aR)-4-(3-fluoro-5-(methoxycarbonyl)phenyl)octahydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate

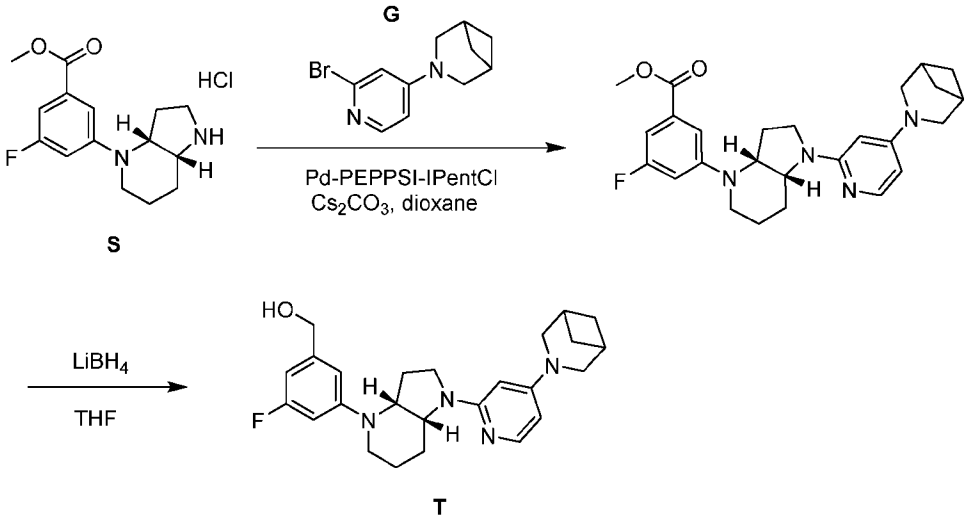
[00841] To a stirred solution of methyl 3-bromo-5-fluorobenzoate (1 g, 4 mmol, CAS# 334792-52-8) and *tert*-butyl (3*aR*,7*aR*)-octahydropyrrolo[3,2-*b*]pyridine-1-carboxylate (48.56 mg, 0.215 mmol, CAS# 1251010-63-5) in dioxane (15 mL) were added Pd-PEPPSI-IPentCl 2-methylpyridine (o-picoline) (18.05 mg, 0.022 mmol) and Cs_2CO_3 (2.80 g, 8.58 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (60:1- 5:1), to afford the title compound (1 g, 62% yield) as a yellow oil. LC/MS (ESI, m/z):

$[(M + H)]^+ = 379.2$.

Step 2 - methyl 3-fluoro-5-((3aR,7aR)-octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)benzoate hydrochloride

[00842] To a stirred solution of *tert*-butyl (3*aR*,7*aR*)-4-[3-fluoro-5-(methoxycarbonyl)phenyl]-hexahydro-2*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (1 g, 3 mmol) in DCM (10 mL) was added HCl (gas)in 1,4-dioxane (10 mL, 40.000 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt under nitrogen atmosphere. On completion, the mixture was concentrated under reduced pressure to give the title compound (1.5 g, 96% yield) as a yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 279.2$.

(3-((3aR,7aR)-1-(4-(3-Azabicyclo[3.1.1]heptan-3-yl)pyridin-2-yl)octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)-5-fluorophenyl)methanol (Intermediate T)



Step 1 - Methyl 3-((3aR,7aR)-1-(4-(3-azabicyclo[3.1.1]heptan-3-yl)pyridin-2-yl)octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)-5-fluorobenzoate

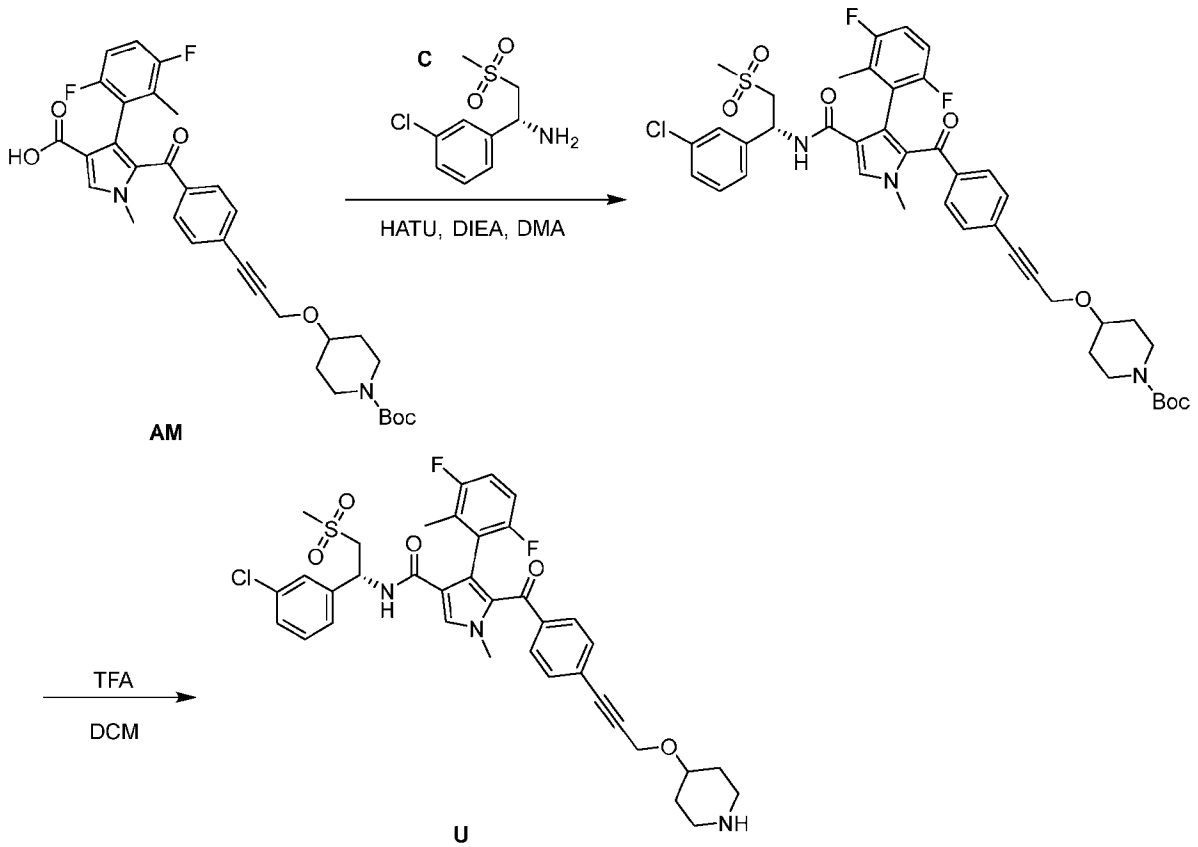
[00843] To a stirred solution of methyl 3-[(3*aR*,7*aR*)-octahydropyrrolo[3,2-*b*]pyridin-4-yl]-5-fluorobenzoate hydrochloride (1.5 g, 4.8 mmol, Intermediate S) and 3-(2-bromopyridin-4-yl)-3-azabicyclo[3.1.1]heptane (1.21 g, 4.77 mmol, Intermediate G) in dioxane (25 mL) were added Pd-PEPPSI-IPentCl 2-methylpyridine (*o*-picoline) (26.72 mg, 0.032 mmol) and Cs_2CO_3 (4.66 g, 14.3 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (100:1 - 8:1), to afford the title compound (1.2 g, 56% yield) as a yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 451.4$.

Step 2 - (3-((3aR,7aR)-1-(4-(3-Azabicyclo[3.1.1]heptan-3-yl)pyridin-2-yl)octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)-5-fluorophenyl)methanol

[00844] To a stirred solution of methyl 3-[(3*aR*,7*aR*)-1-(4-{3-azabicyclo[3.1.1]heptan-3-yl}pyridin-2-yl)-hexahydro-2*H*-pyrrolo[3,2-*b*]pyridin-4-yl]-5-fluorobenzoate (1.2 g, 2.7 mmol) in THF (20 mL) was

added $LiBH_4$ (174.02 mg, 7.989 mmol) at rt under nitrogen atmosphere. The resulting mixture was then stirred for 2 h at rt under nitrogen atmosphere. On completion, the mixture was diluted with water (200 mL), then extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with water (3x100 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: MeOH; Gradient: 45% - 95% B in 40 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 83% B) and concentrated under reduced pressure to afford the title compound (1 g, 89% yield) as a yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 423.3$.

(R)-N-(1-(3-chlorophenyl)-2-(methylsulfonyl)ethyl)-4-(3,6-difluoro-2-methylphenyl)-1-methyl-5-(4-(3-(piperidin-4-yloxy)prop-1-yn-1-yl)benzoyl)-1H-pyrrole-3-carboxamide 2,2,2-trifluoroacetate (Intermediate U)



Step 1 - *Tert*-butyl 4-({3-[4-(4-{[(1*R*)-1-(3-chlorophenyl)-2-methanesulfonylethyl]carbamoyl}-3-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-2-carbonyl)phenyl]prop-2-yn-1-yl}oxy)piperidine-1-carboxylate

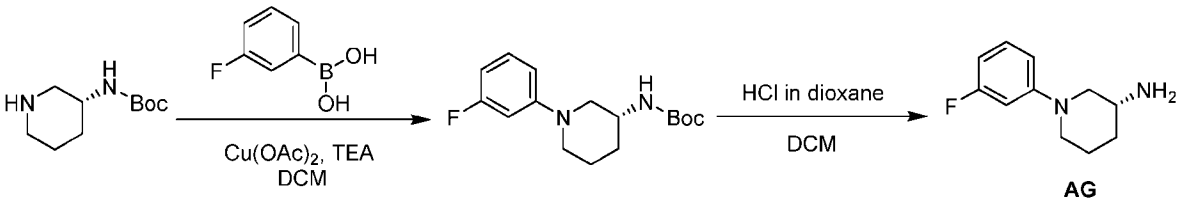
[00845] To a stirred solution of 5-[4-(3-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}prop-1-yn-1-

yl)benzoyl]-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (1.2 g, 2.0 mmol, Intermediate AM) and DIEA (0.8 g, 6.2 mmol) in DMA (10 mL) were added (1*R*)-1-(3-chlorophenyl)-2-methanesulfonylethanamine (0.7 g, 3.0 mmol, Intermediate C) and HATU (1.2 g, 3.2 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under air atmosphere. On completion, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C_{18}-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 40% - 70% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 60% B) and concentrated under reduced pressure to afford the title compound (900 mg, 55% yield) as a yellow solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 808.5$.

Step 2 - *N*-[(1*R*)-1-(3-chlorophenyl)-2-methanesulfonylethyl]-4-(3,6-difluoro-2-methylphenyl)-1-methyl-5-{4-[3-(piperidin-4-yloxy)prop-1-yn-1-yl]benzoyl}pyrrole-3-carboxamide

[00846] A solution of *tert*-butyl 4-({3-[4-(4-{[(1*R*)-1-(3-chlorophenyl)-2-methanesulfonylethyl]carbamoyl}-3-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-2-carbonyl)phenyl]prop-2-yn-1-yl}oxy)piperidine-1-carboxylate (50 mg, 0.062 mmol) and TFA (1 mL, 10 mmol) in DCM (5 mL) was stirred for 1 h at rt under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C_{18}-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 50% - 70% B in 25 min; Flow rate: 60mL/min; Detector: 220/254 nm; desired fractions were collected at 60% B) and concentrated under reduced pressure to afford the title compound (8.5 mg, 19% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (m, J = 20.1, 8.3 Hz, 1H), 7.90 (d, J = 10.0 Hz, 1H), 7.44 (m, J = 7.5, 2.0 Hz, 1H), 7.39 - 7.27 (m, 5H), 7.24 - 7.17 (m, 2H), 6.79 (td, J = 9.1, 4.5 Hz, 1H), 6.60 (m, J = 17.7, 8.9, 4.5 Hz, 1H), 5.42 (m, J = 17.5, 8.9, 4.4 Hz, 1H), 4.39 (s, 2H), 3.94 (s, 3H), 3.73 - 3.59 (m, 2H), 3.49 (s, 1H), 3.01 - 2.87 (m, 5H), 2.45 (t, J = 11.3 Hz, 2H), 1.91 – 1.80 (m, 4H), 1.75 (d, J = 2.5 Hz, 1H), 1.28 (m, J = 9.8 Hz, 2H); LC/MS (ESI, m/z): $[(M + H)]^+$ =708.2.

(*R*)-1-(3-fluorophenyl)piperidin-3-amine (Intermediate AG)



AG

Step 1 - *Tert*-butyl (*R*)-(1-(3-fluorophenyl)piperidin-3-yl)carbamate

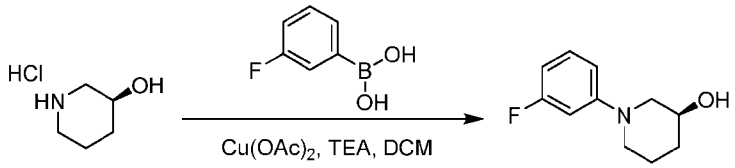
[00847] To a stirred solution of 3-fluorophenylboronic acid (74 g, 530 mmol, CAS# 768-35-4) and $Cu(OAc)_2$ (96.06 g, 528.9 mmol) in DCM (140 mL) were added TEA (107.04 g, 1057.8 mmol) and tert-butyl *N*-[(3*R*)-piperidin-3-yl]carbamate (127.11 g, 634.65 mmol, CAS# 309956-78-3) at rt under nitrogen

atmosphere. The resulting mixture was stirred for 16 h at rt under oxygen atmosphere. On completion, the resulting mixture was filtered, and the filter cake was washed with DCM (3 x 400 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1), to afford the title compound (71 g, 46% yield) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.37 - 7.13 (m, 1H), 6.82 - 6.41 (m, 3H), 4.86 (s, 1H), 3.86 (s, 1H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.33 - 2.85 (m, 4H), 1.62 - 0.90 (m, 12H); LC/MS (ESI, m/z): $[(M + 1)]^+ = 295.2$.

Step 2 - (*R*)-1-(3-fluorophenyl)piperidin-3-amine

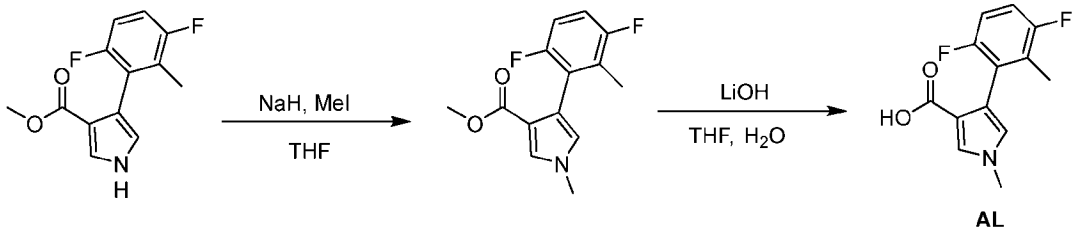
[00848] To a stirred solution of tert-butyl *N*-[(3*R*)-1-(3-fluorophenyl)piperidin-3-yl]carbamate (16.3 g, 55.4 mmol) in DCM (150 mL) was added HCl (gas) in 1,4-dioxane (150 mL) at rt under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt under nitrogen. On completion, the resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with Et_2O (100 mL) to give (10.7 g, quant. yield) as a brown yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (s, 1H), 6.79 - 6.18 (m, 3H), 3.66 - 3.47 (m, 1H), 3.41 (d, *J* = 12.3, 4.5 Hz, 1H), 3.09 - 2.90 (m, 1H), 2.86 (s, 1H), 2.75 - 2.58 (m, 1H), 2.54 - 2.31(m, 3H), 2.05 - 1.85 (m, 2H), 1.69 (d, *J* = 13.8, 7.1, 3.9 Hz, 1H). LC/MS (ESI, m/z): $[(M + H)]^+ = 195.1$.

(3*S*)-1-(3-fluorophenyl)piperidin-3-ol (Intermediate AH)



[00849] To a stirred mixture of 3-fluorophenylboronic acid (10 g, 70 mmol), (3*S*)-piperidin-3-ol hydrochloride (11.80 g, 85.76 mmol, CAS# 475058-41-4), and $Cu(OAc)_2$ (1.30 g, 7.15 mmol) in DCM (100 mL) was added TEA (43.39 g, 428.8 mmol) dropwise at rt under air atmosphere. The resulting mixture was stirred for 16 h at rt. On completion, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1), to afford the title compound (440 mg, 3.15% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ7.21 - 7.26 (m, 7.0 Hz, 1H), 6.76 - 6.73 (m, 1H), 6.66 - 6.64 (m, 1H), 6.58 - 6.55 (m, 1H), 3.95 (s, 1H), 3.37 - 3.40 (m, 1H), 3.21 - 3.01 (m, 3H), 2.07 (s, 1H), 1.94 - 1.90 (m, 2H), 1.69 - 1.65 (m, 2H).

4-(3,6-Difluoro-2-methylphenyl)-1-methyl-1*H*-pyrrole-3-carboxylic acid (Intermediate AL)



AL

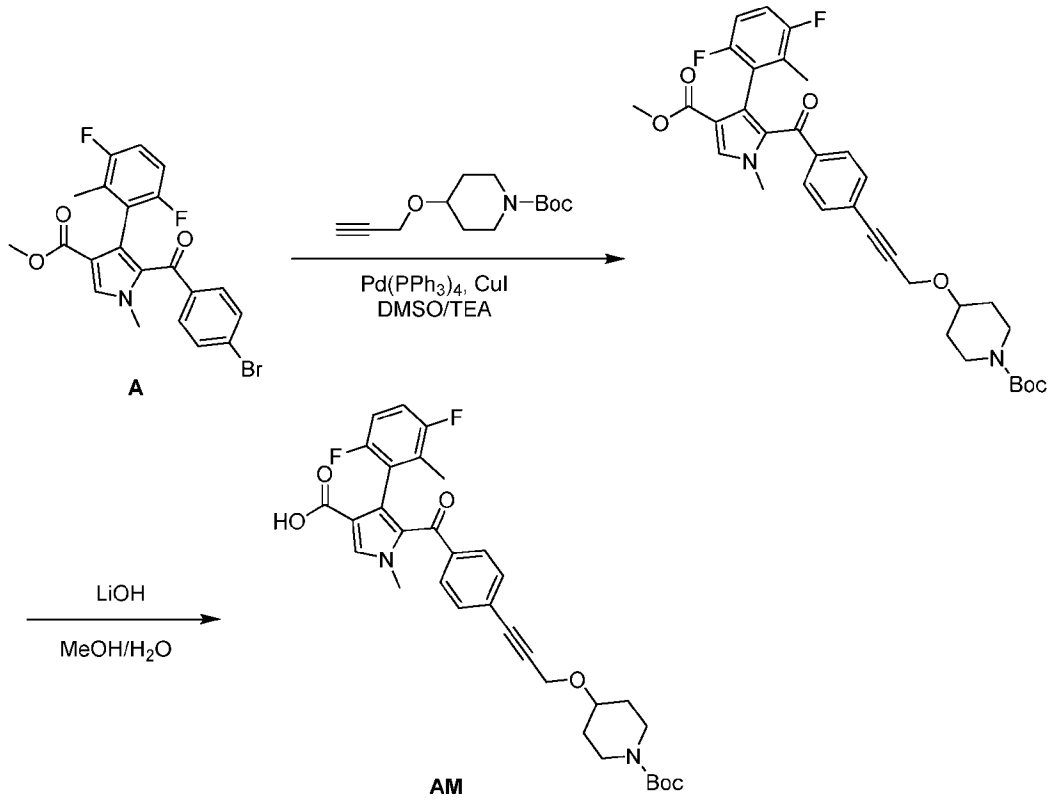
Step 1 - Methyl 4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate

[00850] A solution of methyl 4-(3,6-difluoro-2-methylphenyl)-1*H*-pyrrole-3-carboxylate (500 mg, 2 mmol, synthesized via Steps 1-2 of Intermediate A) and NaH (58 mg, 2.4 mmol) in THF (5 mL) was stirred for 30 min at 0 °C. To the above mixture was added CH_3I (565 mg, 3.98 mmol) dropwise at 0 °C. The resulting mixture was stirred for an additional 2 h at rt. On completion, the reaction was quenched with Water/Ice at 0 °C. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1), to afford the title compound (500 mg, 95% yield) as a light yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 (d, J = 2.4 Hz, 1H), 6.98 - 6.85 (m, 2H), 6.53 (d, J = 2.4 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.10 (d, J = 2.6 Hz, 3H); LC/MS (ESI, m/z): $[(M + 1)]^+$ = 266.0.

Step 2 - 4-(3,6-Difluoro-2-methylphenyl)-1-methyl-1*H*-pyrrole-3-carboxylic acid

[00851] A solution of methyl 4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate (500 mg, 2 mmol) in LiOH (2 mL) and THF (2 mL) was stirred for 2 h at 80 °C. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was acidified to pH 3 with HCl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give the title compound (400 mg, 85% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.54 (s, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.10 (td, J = 9.1, 4.5 Hz, 1H), 7.02 (td, J = 8.8, 4.7 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 3.70 (s, 3H), 2.01 (d, J = 2.6 Hz, 3H). LC/MS (ESI, m/z): $[(M + H)]^+$ =252.2.

5-(4-(3-((1-(Tert-butoxycarbonyl)piperidin-4-yl)oxy)prop-1-yn-1-yl)benzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methyl-1H-pyrrole-3-carboxylic acid (Intermediate AM)



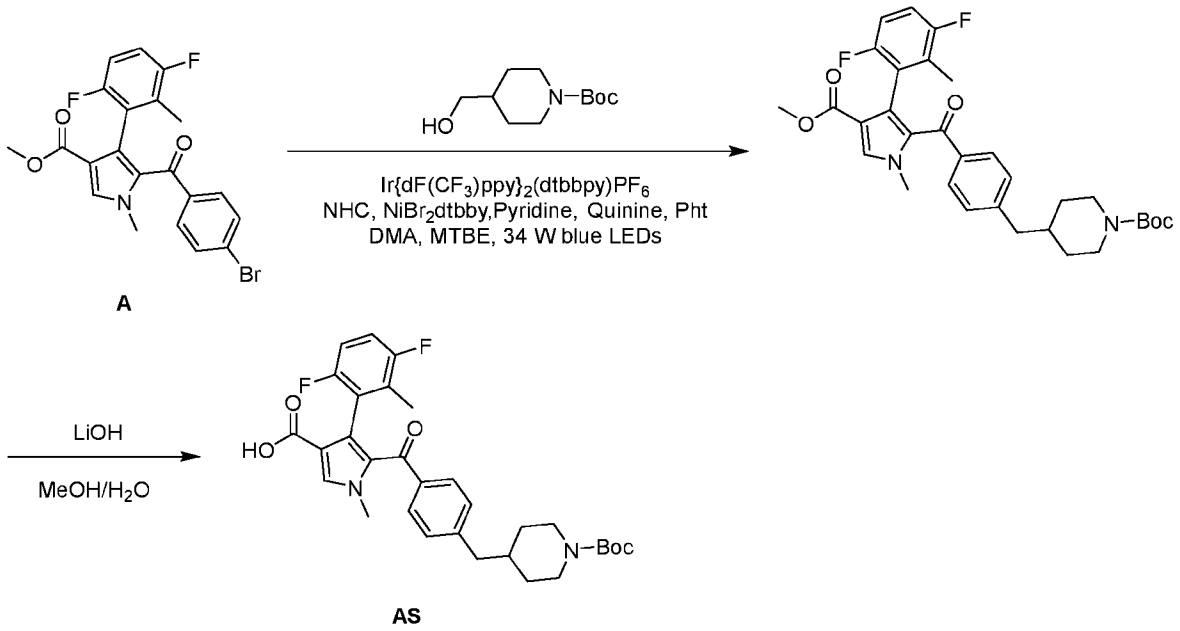
Step 1 - *Tert*-butyl 4-[(3-{4-[3-(3,6-difluoro-2-methylphenyl)-4-(methoxycarbonyl)-1-methylpyrrole-2-carbonyl]phenyl}prop-2-yn-1-yl)oxy]piperidine-1-carboxylate

[00852] To a stirred solution of methyl 5-(4-bromobenzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate (17.8 g, 39.7 mmol, Intermediate A) and *tert*-butyl 4-(prop-2-yn-1-yloxy)piperidine-1-carboxylate (19.01 g, 79.42 mmol, CAS# 1219827-56-1) in DMSO (300 mL) were added TEA (60 mL) and CuI (1.51 g, 7.94 mmol) in portions at rt under nitrogen atmosphere. To the above mixture was added $Pd(PPh_3)_4$ (4.59 g, 3.97 mmol) in portions at rt. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The mixture was diluted with water (200 mL), then extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1), to afford the title compound (20.2 g, 84% yield) as a brown oil. ^1H NMR (400 MHz, DMSO-*d*) δ 8.05 (s, 1H), 7.42 - 7.36 (m, 2H), 7.28 - 7.22 (m, 2H), 6.90 - 6.86 (m, 1H), 6.73 - 6.70 (m, 1H), 4.43 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.93 (s, 2H), 3.65 (ddd, J = 13.3, 8.2, 4.6 Hz, 3H), 3.59 (s, 2H), 1.99 (s, 3H), 1.87 (d, J = 2.6 Hz, 3H), 1.40 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H).

Step 2 - 5-[4-(3-{[1-(Tert-butoxycarbonyl)piperidin-4-yl]oxy}prop-1-yn-1-yl)benzoyl]-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid

[00853] To a stirred solution of tert-butyl 4-[(3-{4-[3-(3,6-difluoro-2-methylphenyl)-4-(methoxycarbonyl)-1-methylpyrrole-2-carbonyl]phenyl}prop-2-yn-1-yl)oxy]piperidine-1-carboxylate (20.7 g, 34.1 mmol) in MeOH (200 mL) was added $LiOH.H_2O$ (200 mL, 400 mmol) in portions at rt under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The mixture was acidified to pH 4 with conc. HCl and diluted with water (200 mL), then extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the title compound (16 g, 79% yield) as a yellow solid. LC/MS (ESI, m/z): $[(M - 1)]^- = 591.4$.

5-(4-{[1-(Tert-butoxycarbonyl)piperidin-4-yl]methyl}benzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (Intermediate AS)



Step 1 - *Tert*-butyl 4-({4-[3-(3,6-difluoro-2-methylphenyl)-4-(methoxycarbonyl)-1-methylpyrrole-2-carbonyl]phenyl}methyl)piperidine-1-carboxylate

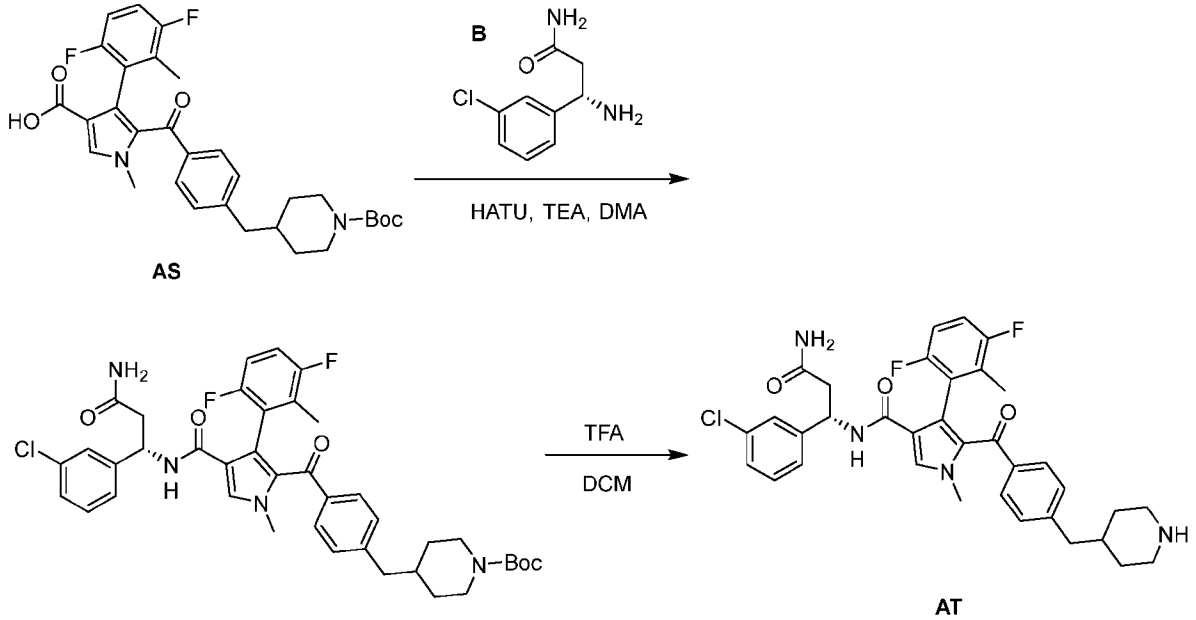
[00854] To a stirred mixture of *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (192.11 mg, 0.892 mmol, CAS# 123855-51-6) in 2-methoxy-2-methylpropane (10 mL) were added 5,7-di-*tert*-butyl-3-phenyl-1,3lambda5-benzoxazol-3-ylium boron trifluoride fluoride (1.69 g, 4.28 mmol, CAS# 1207294-92-5) and pyridine (338.80 mg, 4.283 mmol) at rt under nitrogen atmosphere. The mixture was stirred for 20 min at rt under nitrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with 2-methoxy-2-methylpropane (2 mL) to give the filtrate which was used directly. Next, to a stirred mixture of methyl 5-(4-bromobenzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylate

(1.2 g, 2.7 mmol, Intermediate A) and photocatalyst Ir{dF(CF_3)ppy}2(dtbbpy)PF_6 (367.00 mg, 0.402 mmol, CAS# 676525-77-2) in DMA (10 mL) were added (Dtpby)$NiBr_2$ (13),2 (65.17 mg, 0.134 mmol, CAS# 1894189-67-3), quinazoline (609.70 mg, 4.685 mmol) and 2,3-dihydro-1H-isoindole-1,3-dione (78.77 mg, 0.535 mmol, CAS# 85-41-6) at rt under nitrogen atmosphere. To the above mixture was added the previous filtrate at rt. The vial was stirred at 1500 rpm stir rate and irradiated under 450 nm LED modules at 100% light intensity in a PennOC Integrated Photoreactor for 2 h. On completion, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1), to afford the title compound (1.2 g, 79% yield) as a light yellow solid. LC/MS (ESI, m/z): $[(M + 1)]^+$ = 567.2.

Step 2 - 5-(4-{[1-(Tert-butoxycarbonyl)piperidin-4-yl]methyl}benzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid

[00855] To a stirred mixture of *tert*-butyl 4-({4-[3-(3,6-difluoro-2-methylphenyl)-4-(methoxycarbonyl)-1-methylpyrrole-2-carbonyl]phenyl}methyl)piperidine-1-carboxylate (880 mg, 1.55 mmol) in MeOH (10 mL) was added LiOH.H_2O (10 mL, 20 mmol) dropwise at rt under air atmosphere. The resulting mixture was stirred for 2 h at 80 °C under air atmosphere. On completion, the mixture was cooled to rt and was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and the mixture was acidified to pH 6 with conc. HCl. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in DMF (4 mL). The mixture was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 70% - 90% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 80 % B) and concentrated under reduced pressure to afford the title compound (480 mg, 56% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.98 (s, 1H), 7.92 (s, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.75 - 6.70 (m, 2H), 3.91 (s, 4H), 2.65 (s, 2H), 2.48 - 2.40 (m, 2H), 2.08 (d, *J* = 0.7 Hz, 2H), 1.88 (d, J = 2.5 Hz, 3H), 1.41 (s, 11H), 0.92 (tq, J = 13.1, 9.2, 6.4 Hz, 2H).

(S)-N-(3-amino-1-(3-chlorophenyl)-3-oxopropyl)-4-(3,6-difluoro-2-methylphenyl)-1-methyl-5-(4-(piperidin-4-ylmethyl)benzoyl)-1H-pyrrole-3-carboxamide (Intermediate AT)



Step 1 - Tert-butyl (S)-4-(4-(4-((3-amino-1-(3-chlorophenyl)-3-oxopropyl)carbamoyl)-3-(3,6-difluoro-2-methylphenyl)-1-methyl-1H-pyrrole-2-carbonyl)benzyl)piperidine-1-carboxylate

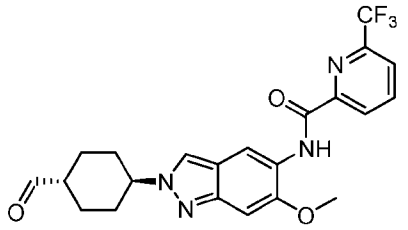
[00856] To a stirred mixture of 5-(4-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methyl}benzoyl)-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (450 mg, 0.814 mmol, Intermediate AS) and (3*S*)-3-amino-3-(3-chlorophenyl)propanamide hydrochloride (287.18 mg, 1.221 mmol, Intermediate B) in DMA (5 mL) were added TEA (247.21 mg, 2.442 mmol) and HATU (464.44 mg, 1.221 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 3 h at rt under air atmosphere. On completion, the mixture was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 25% - 55% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 48% B) and concentrated under reduced pressure to afford the title compound (540 mg, 90% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.22 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 2.5 Hz, 1H), 7.52 - 7.13 (m, 8H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.83 (s, 1H), 6.69 - 6.62 (m, 2H), 5.19 (dq, *J* = 14.9, 7.2 Hz, 1H), 3.91 (s, 3H), 2.59 (d, *J* = 42.6 Hz, 5H), 2.48 - 2.32 (m, 2H), 2.08 (s, 2H), 1.82 (dd, *J* = 44.3, 2.5 Hz, 3H), 1.40 (s, 12H); LC/MS (ESI, m/z): $[(M + 1)]^+$ = 733.2.

Step 2 - (S)-N-(3-amino-1-(3-chlorophenyl)-3-oxopropyl)-4-(3,6-difluoro-2-methylphenyl)-1-methyl-5-(4-(piperidin-4-ylmethyl)benzoyl)-1H-pyrrole-3-carboxamide

[00857] To a stirred mixture of *tert*-butyl 4-{[4-(4-{[(1*S*)-2-carbamoyl-1-(3-chlorophenyl)ethyl]carbamoyl}-3-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-2-carbonyl)phenyl]methyl}piperidine-1-carboxylate (540 mg, 0.736 mmol) in DCM (9 mL) was added TFA (3 mL, 40 mmol) dropwise at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under

air atmosphere. On completion, the resulting mixture was concentrated under reduced pressure, then the residue was dissolved in DMF (3 mL). The mixture was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 25% - 55% B in 25 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 48% B) and concentrated under reduced pressure to afford the title compound (400 mg, 85% yield) as a white solid. LC/MS (ESI, m/z): $[(M + 1)]^- = 633.1$.

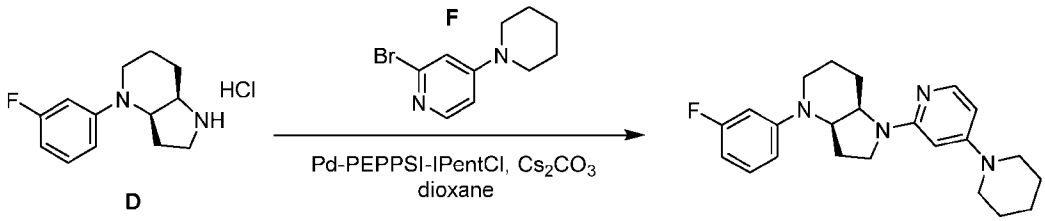
N-(2-((1r,4r)-4-formylcyclohexyl)-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)picolinamide (Intermediate AU)



AU

[00858] N-(2-((1r,4r)-4-formylcyclohexyl)-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)picolinamide was synthesized, for example, as described in WO 2022/147465.

Example 1 (Method 1): Synthesis of (3aR,7aR)-4-(3-fluorophenyl)-1-(4-(piperidin-1-yl)pyridin-2-yl)octahydro-1H-pyrrolo[3,2-b]pyridine

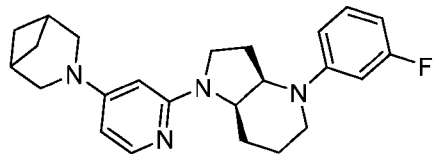
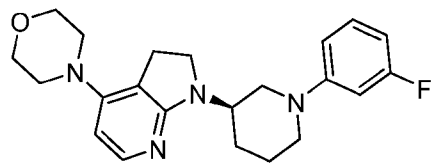


D

[00859] To a stirred solution of 2-bromo-4-(piperidin-1-yl)pyridine (150 mg, 0.622 mmol, Intermediate F) and {1,3-bis[2,6-bis(pentan-3-yl)phenyl]-4,5-dichloro-2,3-dihydro-1*H*-imidazol-2-yl}dichloro(2-methyl-1lambda4-pyridin-1-yl)palladium (52.33 mg, 0.062 mmol) in dioxane (3 mL) were added Cs_2CO_3 (405.36 mg, 1.244 mmol) and (3aR,7aR)-4-(3-fluorophenyl)octahydro-1H-pyrrolo[3,2-b]pyridine (137.04 mg, 0.622 mmol, Intermediate D) at rt under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 100 °C under nitrogen atmosphere. On completion, the mixture was allowed to cool down to rt and the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 30% - 80% B in 50 min; Flow rate: 60 mL/min; Detector: 220/254 nm; desired fractions were collected at 66% B) and concentrated under reduced pressure. The product (150

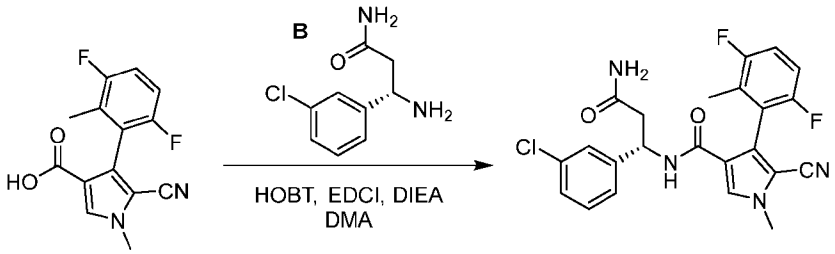
mg) was then purified by CHIRA-HPLC (Column: CHIRALPAKIG3; Mobile Phase A: Hex(0.2%DEA): (MeOH: DCM=1:1) = 80: 20; Flow rate: 1.0mL/min mL/min; Gradient: isocratic; Injection Volume: 3µL mL) to afford the title compound (12.5 mg, 5% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.71 (d, *J* = 6.0 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 6.93 - 6.70 (m, 2H), 6.47 (d, *J* = 8.3 Hz, 1H), 6.16 (d, *J* = 6.2 Hz, 1H), 5.69 (d, *J* = 2.2 Hz, 1H), 4.46 (d, *J* = 12.8, 1H), 4.15 (d, *J* = 11.8, 1H), 3.51 (d, *J* = 11.9 Hz, 1H), 3.41 (d, *J* = 9.5 Hz, 1H), 3.27 (s, 4H), 2.84 - 2.72 (m, 1H), 2.43 - 2.15 (m, 2H), 2.11 - 1.83 (m, 2H), 1.76 (d, J = 13.7 Hz, 1H), 1.57 (s, 7H), 1.23 (d, *J* = 10.6 Hz, 1H). LC/MS (ESI, m/z): $[(M + 1)]^+$ = 381.5.

Table 1: Compounds synthesized via Method 1, the cross coupling of the corresponding amines and bromides.

Compound[a]	Amine	Bro-mide	LCMS (ESI+) m/z $(M+H)^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ
	D	G	393.3	7.73 (d, *J* = 5.9 Hz, 1H), 7.27 - 7.13 (m, 1H), 6.85 - 6.70 (m, 2H), 6.54 - 6.40 (m, 1H), 6.11 - 5.91 (m, 1H), 5.49 (d, *J* = 2.1 Hz, 1H), 4.55 - 4.36 (m, 1H), 4.25 - 4.09 (m, 1H), 3.60 - 3.33 (m, 7H), 2.89 - 2.75 (m, 1H), 2.62 - 2.53 (m, 2H), 2.30 - 2.23 (m, 1H), 2.21 - 2.12 (m, 2H), 2.10 - 2.01 (m, 1H), 1.99 - 1.86 (m, 1H), 1.82 - 1.71 (m, 1H), 1.61 - 1.44 (m, 1H), 1.39 - 1.30 (m, 2H), 1.29 - 1.13 (m, 1H)
	I	H	383.2	7.65 (d, *J* = 5.9 Hz, 1H), 7.19 (q, *J* = 8.0 Hz, 1H), 6.81 - 6.74 (m, 2H), 6.49 (td, *J* = 8.3, 2.2 Hz, 1H), 6.11 (d, *J* = 6.0 Hz, 1H), 3.98-3.90 (m, 1H), 3.76 (d, *J* = 13.0 Hz, 1H), 3.69 (d, *J* = 9.4 Hz, 5H), 3.47 (t, *J* = 8.4 Hz, 2H), 3.11 (t, *J* = 4.7 Hz, 4H), 2.94 (t, *J* = 8.3 Hz, 2H), 2.84 (t, *J* = 11.5 Hz, 1H), 2.72 - 6.65 (m, 1H), 1.84 - 1.74 (m, 2H), 1.71 - 1.54 (m, 2H)

[a]The reaction was run at 100 °C for 1-16 h. The final products were purified under a variety of conditions including prep-HPLC and reverse phase flash chromatography.

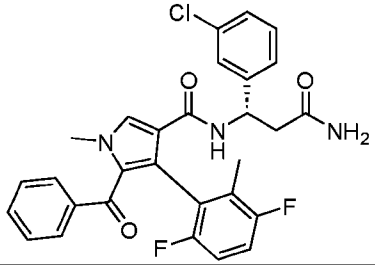
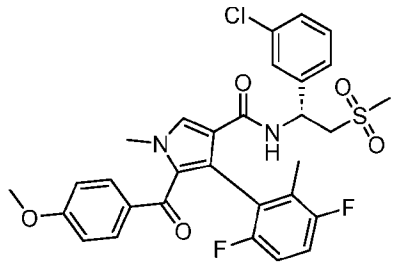
Example 2 (Method 2): Synthesis of (S)-N-(3-amino-1-(3-chlorophenyl)-3-oxopropyl)-5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-methyl-1H-pyrrole-3-carboxamide

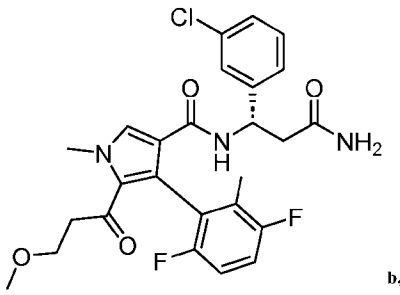
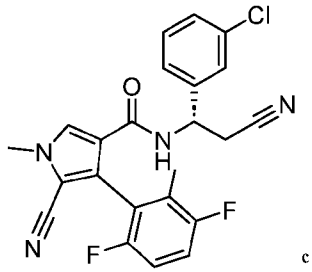
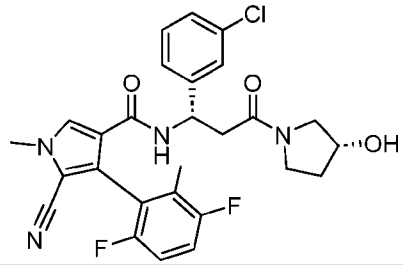


K

[00860] To a stirred solution of 5-cyano-4-(3,6-difluoro-2-methylphenyl)-1-methylpyrrole-3-carboxylic acid (50 mg, 0.18 mmol, Intermediate K), HOBT (29 mg, 0.22 mmol), EDCI (42 mg, 0.22 mmol) and (*S*)-3-amino-3-(3-chlorophenyl)propenamide (43 mg, 0.22 mmol, Intermediate B) in DMA (1 mL) was added DIEA (70 mg, 0.54 mmol) dropwise at rt. The resulting mixture was stirred for 1 h at rt. On completion, the mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 40% to 60% gradient in 25 min; detector, UV 254 nm; the fractions were collected at 45%) and concentrated under reduced pressure to afford the title compound (15 mg, 18% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 2.9 Hz, 1H), 7.36 (s, 1H), 7.36 - 7.18 (m, 5H), 7.12 (m, J = 8.7, 4.5 Hz, 1H), 6.85 (s, 1H), 5.22 (m, 1H), 3.87 (s, 3H), 2.54 (d, J = 7.9 Hz, 2H), 1.91 - 1.84 (m, 3H). LC/MS (ESI, m/z): $[(M + H)]^+$ = 457.1.

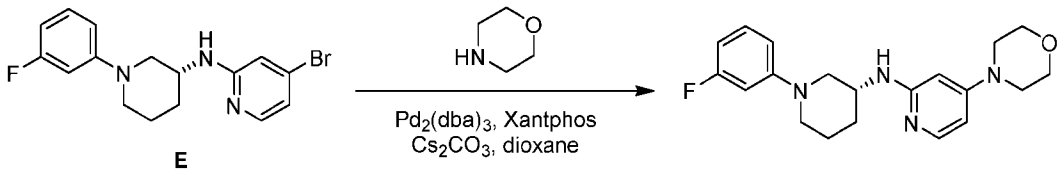
Table 2: Compounds synthesized via Method 2, the coupling of the corresponding amines and acids.

Compound[a]	Amine	Acid	LCMS (ESI+) m/z $(M+H)^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ
	B	L	536.1	8.24 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.46 – 7.08 (m, 10H), 6.84 (d, J = 4.0 Hz, 1H), 6.75 (td, J = 9.0, 4.4 Hz, 1H), 6.60 - 6.65 (m, 1H), 5.19 (dq, J = 15.0, 7.3 Hz, 1H), 3.91 (s, 3H), 2.53 (s, 2H), 1.82 - 1.80 (m, 3H).
	C	N	601.2	8.61 – 8.49 (m, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.48 - 7.28 (m, 6H), 6.82 - 6.78 (m, 4.4 Hz, 1H), 6.76 - 6.68 (m, 2H), 6.67 - 6.63 (m, 1H), 5.50 - 5.33 (m, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.69 - 3.55 (m, 2H), 2.97 (d, J = 8.6 Hz, 3H), 1.89 (d, 3H)

 b,c	B	O	518.1	7.68 (d, J = 5.6 Hz, 1H), 7.31 - 7.20 (m, 2H), 7.20 - 7.10 (m, 2H), 7.06 (dd, J = 4.5, 2.3 Hz, 1H), 5.28 (d, J = 6.5 Hz, 1H), 3.99 (s, 2H), 3.66 (d, J = 2.1 Hz, 1H), 3.59 - 3.43 (m, 2H), 3.19 (s, 2H), 2.65 (d, J = 6.8 Hz, 2H), 2.32 (dd, J = 6.1, 1.2 Hz, 1H), 2.01 (d, J = 2.4 Hz, 3H), 1.32 (d, J = 4.9 Hz, 3H).
 c	P	K	439.0	8.76 - 8.74 (m, 1H), 7.95 - 7.93 (m, 1H), 7.50 - 7.41 (m, 1H), 7.41 - 7.27 (m, 3H), 7.22 (t, J = 9.1, 4.6, 1.3 Hz, 1H), 7.11 (t, J = 8.8, 4.1Hz, 1H), 5.27 - 5.23 (m, 1H), 3.89 (s, 3H), 3.14 - 2.93 (m, 2H), 1.94 (t, J = 34.7, 2.4 Hz, 3H)
	Q	K	527.1	8.37 - 8.22 (m, 1H), 7.90 - 7.84 (m, 1H), 7.36 - 7.23 (m, 5H), 7.23 (d, J = 3.4 Hz, 1H), 5.25 (m, 1H), 4.96 (m, 1H), 4.27 (s, 1H), 3.87 (s, 3H), 3.49 - 3.38 (m, 2H), 3.28 - 3.19 (m, 2H), 2.89 - 2.76 (m, 2H), 2.11 - 1.88 (m, 5H)

[a]The reaction was run at 25-50 °C for 1-16 h. The final products were purified under a variety of conditions including prep-HPLC and reverse phase flash chromatography. [b]MeOD-d4 used as the solvent for ^{1}H NMR data. [c]HATU was used in place of HOBt and EDCI for the coupling.

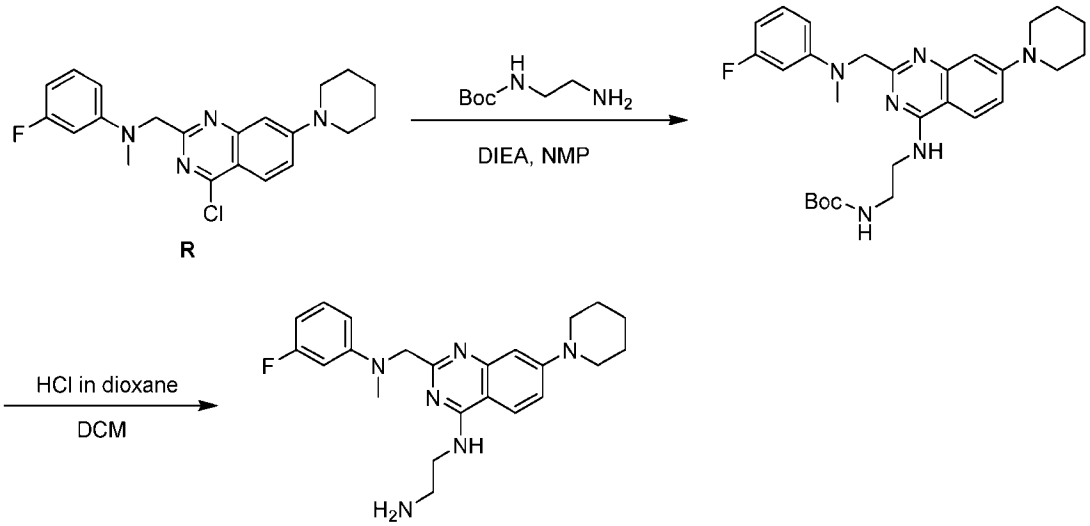
Example 3: Synthesis of (R)-N-(1-(3-fluorophenyl)piperidin-3-yl)-4-morpholinopyridin-2-amine



[00861] To a stirred solution of (R)-4-Bromo-N-(1-(3-fluorophenyl)piperidin-3-yl)pyridin-2-amine (530 mg, 1.5 mmol, Intermediate E) and morpholine (791.03 mg, 9.078 mmol) in dioxane (6 mL) were added Cs_2CO_3 (986.10 mg, 3.026 mmol), XantPhos (175.13 mg, 0.303 mmol) and $Pd_2(dba)_3$ (138.57 mg, 0.151 mmol) in turns at rt under nitrogen atmosphere. The resulting mixture was stirred overnight at 110 °C under nitrogen atmosphere. On completion, the reaction was quenched with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was

purified by reverse flash chromatography (column, Welflash TM C18-1, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient 25% to 55% B in 30 min; Flow rate: 85 mL/min; Detector: 220/254 nm; desired fractions were collected at 55% B) and concentrated under reduced to afford the title compound (157.8 mg, 28% yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 - 7.69 (m, 1H), 7.24 - 7.13 (m, 1H), 6.81 - 6.71 (m, 2H), 6.52 - 6.43 (m, 1H), 6.21 - 6.15 (m, 1H), 6.10 - 6.04 (m, 1H), 5.91 - 5.86 (m, 1H), 3.93 - 3.76 (m, 2H), 3.74 - 3.67 (m, 4H), 3.66 - 3.56 (m, 1H), 3.16 - 3.10 (m, 4H), 2.90 - 2.79 (m, 1H), 2.67 - 2.57 (m, 1H), 1.96 - 1.86 (m, 1H), 1.80 - 1.70 (m, 1H), 1.65 - 1.52 (m, 1H), 1.52 - 1.38 (m, 1H); LC/MS (ESI, m/z): $[(M + H)]^+ = 357.1$.

Example 4: Synthesis of N1-(2-(((3-fluorophenyl)(methyl)amino)methyl)-7-(piperidin-1-yl)quinazolin-4-yl)ethane-1,2-diamine



[00862] Step 1 - Tert-butyl (2-((2-(((3-fluorophenyl)(methyl)amino)methyl)-7-(piperidin-1-yl)quinazolin-4-yl)amino)ethyl)carbamate

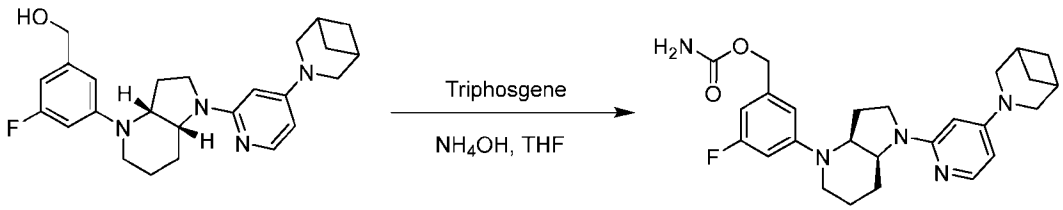
[00863] To a stirred solution of *N*-{[4-chloro-7-(piperidin-1-yl)quinazolin-2-yl]methyl}-3-fluoro-*N*-methylaniline (400 mg, 1.04 mmol, Intermediate R) and *tert*-butyl *N*-(2-aminoethyl)carbamate (499.53 mg, 3.117 mmol, CAS# 57260-73-8) in NMP (5 mL) was added DIEA (0.54 mL, 3.12 mmol) at rt under air atmosphere. The resulting mixture was stirred for 1 h at 100 °C under air atmosphere. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 50% - 95% B in 30 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 95% B) and concentrated under reduced pressure to afford the title compound (270 mg, 51% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, J = 9.2 Hz, 1H), 7.17 - 7.05 (m, 3H), 6.66 - 6.55 (m, 2H), 6.41 - 6.32 (m, 1H), 4.91 (s, 1H), 4.66 (s, 1H), 3.56

- 3.48 (m, 2H), 3.42 - 3.37 (m, 3H), 3.31 (s, 1H), 3.20 (s, 3H), 2.03 (s, 4H), 1.76 - 1.67 (m, 6H), 1.42 (s, 9H). LC/MS (ESI, m/z): $[(M + H)]^+ = 509.4$.

[00864] Step 2 - N^1-(2-{[(3-fluorophenyl)(methyl)amino]methyl}-7-(piperidin-1-yl)quinazolin-4-yl)ethane-1,2-diamine

[00865] To a stirred solution of tert-butyl (2-((2-(((3-fluorophenyl)(methyl)amino)methyl)-7-(piperidin-1-yl)quinazolin-4-yl)amino)ethyl)carbamate (270 mg, 0.531 mmol) in DCM (4 mL) was added 4 M HCl (gas) in 1,4-dioxane (4 mL, 16 mmol) at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under air atmosphere. On completion, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 120 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: ACN; Gradient: 30% - 60% B in 30 min; Flow rate: 80mL/min; Detector: 220/254 nm; desired fractions were collected at 43% B) and concentrated under reduced pressure to afford the title compound (69.4 mg, 32% yield) as a yellow green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 - 7.80 (m, 2H), 7.20 - 7.13 (m, 1H), 7.13 - 7.03 (m, 1H), 6.84 - 6.79 (m, 1H), 6.58 - 6.45 (m, 2H), 6.35 - 6.26 (m, 1H), 4.48 - 4.43 (m, 2H), 3.43 - 3.35 (m, 2H), 3.34 (s, 1H), 3.33 (s, 2H), 3.31 (s, 1H), 3.17 (s, 3H), 2.71 - 2.62 (m, 2H), 1.63 - 1.57 (m, 6H). LC/MS (ESI, m/z): $[(M + H)]^+$= 409.2.

Example 5: Synthesis of 3-((3aS,7aS)-1-(4-(3-azabicyclo[3.1.1]heptan-3-yl)pyridin-2-yl)octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)-5-fluorobenzyl carbamate



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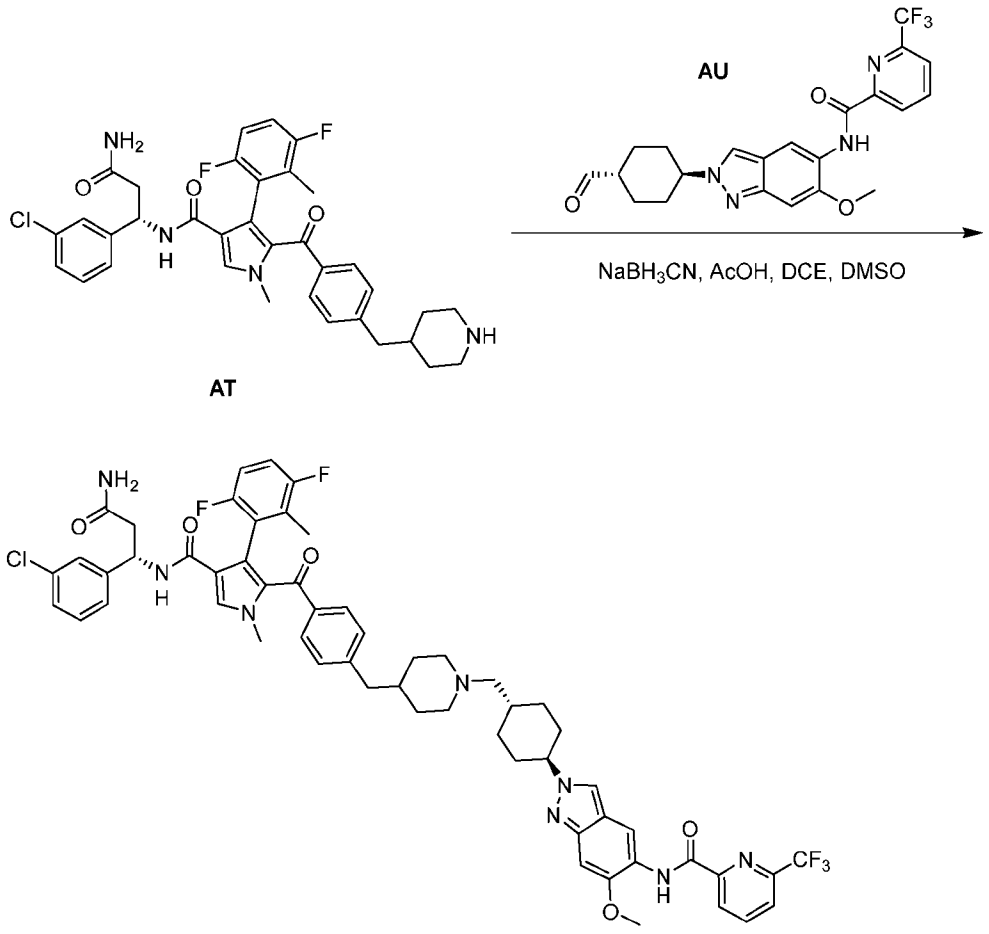
[00866] To a stirred solution of {3-[(3*aR*,7*aR*)-1-(4-{3-azabicyclo[3.1.1]heptan-3-yl}pyridin-2-yl)-hexahydro-2*H*-pyrrolo[3,2-*b*]pyridin-4-yl]-5-fluorophenyl}methanol (500 mg, 1.18 mmol, Intermediate T) in THF (5 mL) was added ditrichloromethyl carbonate (140.46 mg, 0.473 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 30 min at rt under nitrogen atmosphere. To the above mixture was added $NH_3.H_2O$ (5 mL, 200 mmol) at rt. The resulting mixture was stirred for an additional 1 h at 60 °C. On completion, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 um, 330 g; Eluent A: Water (plus 10 mmol/L NH_4HCO_3); Eluent B: MeOH; Gradient: 45% - 95% B in 40 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 83% B) and concentrated under reduced pressure to afford the crude product. The crude product (300 mg) was purified by Prep-HPLC

(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1-HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 30 min; Wave Length: 220/254 nm; RT1(min): 12.188; RT2(min): 23.353; Sample Solvent: EtOH: DCM=1: 1-HPLC; Injection Volume: 1.5 mL; Number Of Runs: 4) to afford the title compound (88.9 mg, 16% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 6.0 Hz, 1H), 6.81 - 6.53 (m, 4H), 6.44 (d, J = 9.0 Hz, 1H), 6.03 - 5.94 (m, 1H), 5.49 (d, J = 2.1 Hz, 1H), 4.92 (s, 2H), 4.54 - 4.35 (m, 1H), 4.22 - 4.07 (m, 1H), 3.55 - 3.48 (m, 1H), 3.43 - 3.33 (m, 6H), 2.85 - 2.72 (m, 1H), 2.55 (d, J = 6.3 Hz, 2H), 2.30 - 2.11 (m, 3H), 2.11 - 2.00 (m, 1H), 1.97 - 1.83 (m, 1H), 1.76 (d, J = 13.4 Hz, 1H), 1.59 - 1.44 (m, 1H), 1.38 - 1.30 (m, 2H), 1.28 - 1.14 (m, 1H). LC/MS (ESI, m/z): $[(M + H)]^+$ = 466.3.

Example 6: Synthesis of N-(2-((1r,4r)-4-((4-(4-(4-(((S)-3-amino-1-(3-chlorophenyl)-3-oxopropyl)carbamoyl)-3-(3,6-difluoro-2-methylphenyl)-1-methyl-1H-pyrrole-2-carbonyl)benzyl)piperidin-1-yl)methyl)cyclohexyl)-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)picolinamide (I-10)



[00867] To a stirred mixture of (3*S*)-3-(3-chlorophenyl)-3-{[4-(3,6-difluoro-2-methylphenyl)-1-methyl-5-[4-(piperidin-4-ylmethyl)benzoyl]pyrrol-3-yl]formamido}propanamide (70 mg, 0.111 mmol, Intermediate AT) and AcOH (0.66 mL, 0.011 mmol) in DCE (1 mL) and DMSO (1 mL) were added $NaBH_3CN$ (13.90 mg, 0.222 mmol) in portions at rt under air atmosphere. The resulting mixture was stirred for 0.5 h at rt under air atmosphere. To the above mixture was added *N*-{6-methoxy-2-[(1*r*,4*r*)-4-formylcyclohexyl]indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide (49.36 mg, 0.111 mmol, Intermediate AU) in portions over 3 min at rt. The resulting mixture was stirred for an additional 3 h at rt. On completion, the mixture was diluted with DCM (10 mL) and H_2O (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), dried over anhydrous Na_2SO_4. filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford the title compound (22.3 mg, 17% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.69 (s, 1H), 8.47 (d, J = 7.8 Hz, 1H), 8.42 (d, J = 7.7 Hz, 1H), 8.41 - 8.27 (m, 4H), 8.22 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 3.6 Hz, 1H), 7.37 (s, 1H), 7.36 - 7.20 (m, 5H), 7.23 - 7.16 (m, 1H), 7.16 (d, J = 3.1 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 4.6 Hz, 1H), 6.71 (td, J = 9.0, 4.5 Hz, 1H), 6.66 - 6.60 (m, 1H), 5.20 - 5.17 (m, 1H), 4.37 (s, 1H), 3.94 (d, J = 28.6 Hz, 4H), 2.84 (s, 2H), 2.54 (d, J = 4.0 Hz, 1H), 2.39 (d, J = 6.3 Hz, 2H), 2.16 - 2.05 (m, 4H), 1.94 - 1.89 (m, 3H), 1.84 - 1.73 (m, 3H), 1.67 - 1.56 (m, 2H), 1.35 (d, J = 11.7 Hz, 2H), 1.23 (s, 1H), 1.20 - 1.02 (m, 4H). LC/MS (ESI, m/z): $[(M + H)]^+$ =1063.4.

Example 7. DCAF1 Binding Assays

[00868] The affinities of compound binding to DCAF1 WD40 domain (residues 1077 – 1390) were measured by SPR at 25 °C on a Biacore 8K+ instrument. Purified His-tagged DCAF1 WD40 domain was diluted in running buffer (10 mM HEPES (pH 7.4), 150 mM NaCl, 0.05% (v/v) Tween 20, 1 mM tris(carboxyethyl)phosphine, 2% (v/v) DMSO) and immobilized to a density of 2700 resonance units (RU) on Series S Sensor Chip NTA (Cytiva Cat# 28994951) using His capture, amine coupling (HCAC) methodology (Kimple, A.J., Muller, R.E., Siderovski, D.P., Willard, F.S. (2010). A Capture Coupling Method for the Covalent Immobilization of Hexahistidine Tagged Proteins for Surface Plasmon Resonance. In: Mol, N., Fischer, M. (eds) Surface Plasmon Resonance. Methods in Molecular Biology, vol 627. Humana Press. doi.org/10.1007/978-1-60761-670-2_5). The system was equilibrated with running buffer for 1 h at a flow rate of 70 μL min^{-1} followed by 30 start up cycles (contact time = 30 s, dissociation time = 120 s, flow rate = 70 μL min^{-1}) before injecting 22 point, 1.5-fold dilution series of the compounds in running buffer (contact time = 30 s, dissociation time = 240 s, flow rate = 70 μL min^{-1}). Solvent correction cycles were run at the start and end of each experiment, and the system performance was evaluated with a 10 μM DCAF1 binder and negative (running buffer) controls run before and after each compound series.

Data were analyzed using Biacore Insights Evaluation software. SPR traces were solvent corrected, double referenced, and fit in the multi-cycle kinetics (MCK) mode using the steady state affinity and, when applicable, the 1:1 binding kinetic affinity models. From this analysis, K_Ds were extracted from the fits and for compounds fit with both models, the K_D from the 1:1 binding kinetic model is reported.

[00869] DCAF1-3 binding results for compounds of the invention are presented in **Table 3**. The letter codes for DCAF1-3 KD include: A (<10 μM); B (10 – 100 μM); C (>100 – 200 μM); D (>200 μM); and E (not tested).

Table 3. DCAF1-3 SPR

I-#	DCAF1-3 SPR (KD) (μM)
I-1	B
I-2	D
I-3	D
I-4	B
I-5	D

I-#	DCAF1-3 SPR (KD) (μM)
I-6	D
I-7	A
I-8	A
I-9	E
I-10	A

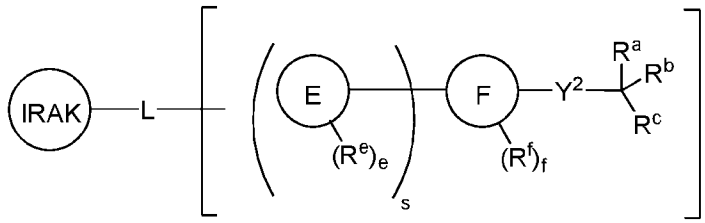
I-#	DCAF1-3 SPR (KD) (μM)
I-11	A
I-12	A
I-13	A

* * * * *

[00870] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of examples.

CLAIMS

1. A compound of formula **I-a'**



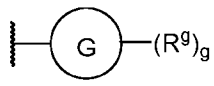
I-a'

or a pharmaceutically acceptable salt thereof, wherein:

Ring E is phenyl, naphthyl, a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring F is phenyl, a 4-11 membered partially unsaturated monocyclic or bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Y^2 is a C_{1-4} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, -S(O)-, $-S(O)_2-$, -C(OR)=N-, $-N(R^d)-$, or -O-;

R^a is hydrogen, an optionally substituted C_{1-6} aliphatic, or 

;

Ring G is phenyl, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^b is hydrogen, an optionally substituted C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur, or:

R^a and R^b are taken together with their intervening atoms to form an optionally substituted 9-10 membered saturated or partially unsaturated bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

when Y^2 is -C(NR)-, R^b is taken together with R of -C(NR)- with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 heteroatoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur;

R^c is halogen, -CN, -CFR_2, -CF_2R, -CF_3, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)(NR)R, -S(O)R, -C(O)R, -CR=NOR, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, -$P(O)R_2$, -$P(O)(OR)_2$, -$P(O)(OR)NR_2$, -$P(O)(NR_2)_2$, -CR_2CN, -CR_2CFR_2, -CR_2CF_2R, -CR_2CF_3, -CR_2NO_2, -CR_2OR, -CR_2SR, -CR_2NR_2, -CR_2SiR_3, -$CR_2S(O)_2R$, -$CR_2S(O)_2NR_2$, -$CR_2S(O)(NR)R$, -$CR_2S(O)R$, -$CR_2C(O)R$, -CR_2CR=NOR, -$CR_2C(O)OR$, -$CR_2C(O)NR_2$, -$CR_2C(O)NROR$, -$CR_2C(NOR)R$, -$CR_2OC(O)R$, -$CR_2OC(O)NR_2$, -$CR_2OP(O)R_2$, -$CR_2OP(O)(OR)_2$, -$CR_2OP(O)(OR)NR_2$, -$CR_2OP(O)(NR_2)_2$, -$CR_2NRC(O)OR$, -$CR_2NRC(O)R$, -$CR_2NRC(O)N(R)_2$, -$CR_2NRS(O)_2R$, -$CR_2NP(O)R_2$, -$CR_2NRP(O)(OR)_2$, -$CR_2NRP(O)(OR)NR_2$, -$CR_2NRP(O)(NR_2)_2$, -$CR_2P(O)R_2$, -$CR_2P(O)(OR)_2$, -$CR_2P(O)(OR)NR_2$, -$CR_2P(O)(NR_2)_2$, -CR_2CR_2CN, -$CR_2CR_2CFR_2$, -$CR_2CR_2CF_2R$, -$CR_2CR_2CF_3$, -$CR_2CR_2NO_2$, -CR_2CR_2OR, -CR_2CR_2SR, -$CR_2CR_2NR_2$, -$CR_2CR_2SiR_3$, -$CR_2CR_2S(O)_2R$, -$CR_2CR_2S(O)_2NR_2$, -$CR_2CR_2S(O)(NR)R$, -$CR_2CR_2S(O)R$, -$CR_2CRC(O)R$, -CR_2CR_2CR=NOR, -$CR_2CR_2C(O)OR$, -$CR_2CR_2C(O)NR_2$, -$CR_2CR_2C(O)NROR$, -$CR_2CR_2C(NOR)R$, -$CR_2CR_2OC(O)R$, -$CR_2CR_2OC(O)NR_2$, -$CR_2CR_2OP(O)R_2$, -$CR_2CR_2OP(O)(OR)_2$, -$CR_2CR_2OP(O)(OR)NR_2$, -$CR_2CR_2OP(O)(NR_2)_2$, -$CR_2CR_2NRC(O)OR$, -$CR_2CR_2NRC(O)R$, -$CR_2CR_2NRC(O)N(R)_2$, -$CR_2CR_2NRS(O)_2R$, -$CR_2CR_2NP(O)R_2$, -$CR_2CR_2NRP(O)(OR)_2$, -$CR_2CR_2NRP(O)(OR)NR_2$, -$CR_2CR_2NRP(O)(NR_2)_2$, -$CR_2CR_2P(O)R_2$, -$CR_2CR_2P(O)(OR)_2$, -$CR_2CR_2P(O)(OR)NR_2$, -$CR_2CR_2P(O)(NR_2)_2$, -$CR_2CR(OR)CR_2OR$, or an optionally substituted group selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or:

–$(CR_2)_{1-2}$-X^a, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or:

-$(CR_2)_{0-2}C(O)R^{cc}$ or -$(CR_2)_{0-2}S(O)_{0-2}R^{cc}$; or:

R^b and R^c are taken together with their intervening atoms to form an optionally substituted 4-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or:

R^a is absent and R^b and R^c are taken together with their intervening atoms to form an optionally substituted phenyl;

R^d is hydrogen or an optionally substituted C_{1-6} aliphatic, or:

when R^c is $-CR_2CONR_2$, R^d is taken together with a single R of $-CR_2CONR_2$ with their intervening atoms to form a 5-7 membered saturated or partially unsaturated heterocyclyl with 0-3 heteroatoms, in addition to the nitrogen atom to which R^d is attached, independently selected from nitrogen, oxygen, and sulfur;

R^e, R^f, and R^g are each independently selected from hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{cc} is R^A, halogen, -CN, -OR, -SR, $-NR_2$, -NROR, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$;

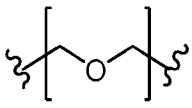
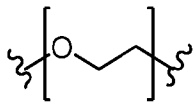
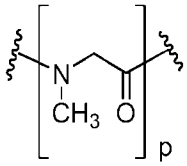
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, naphthyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom, or on different atoms, are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

s is 0 or 1;

each of e, f, and g are independently 0, 1, 2, 3, or 4;

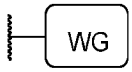
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, $-CF_2-$, -O-, -N(R)-, $-Si(R)_2-$, -Si(OH)(R)-, $-Si(OH)_2-$, -P(O)(OR)-, -P(O)(R)-, $-P(O)(NR_2)-$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -

N(R)C(O)O-,  ,  , or  ;

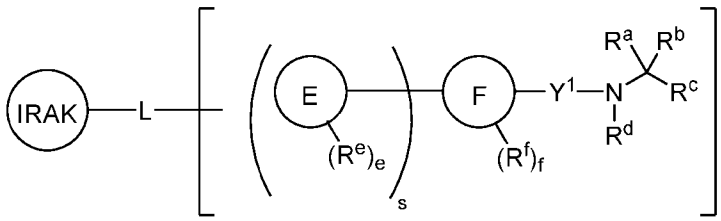
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 3-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

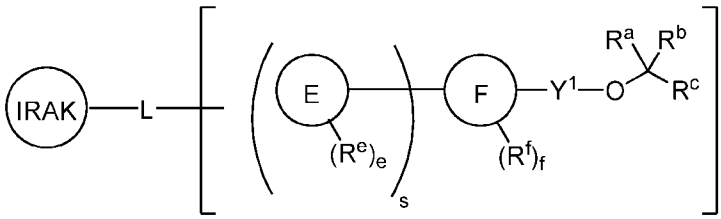
IRAK is an IRAK4 binding moiety;

wherein said compound of formula **I-a'** is optionally substituted with  , and wherein is a warhead group.

2. The compound of claim 1, wherein the compound is any one of the following formulae:



I-a-1'



I-a-2'

or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, $-S(O)-$, $-S(O)_2-$; or:

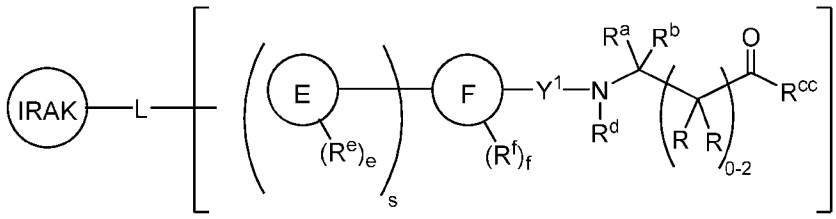
Y^1 is -C(OR)= in formula **I-a-1**, R^d is absent, and R^c is optionally taken together with R of -C(OR)=, and with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 heteroatoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur.

3. The compound of claim 2, wherein Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, $-S(O)-$, or $-S(O)_2-$.

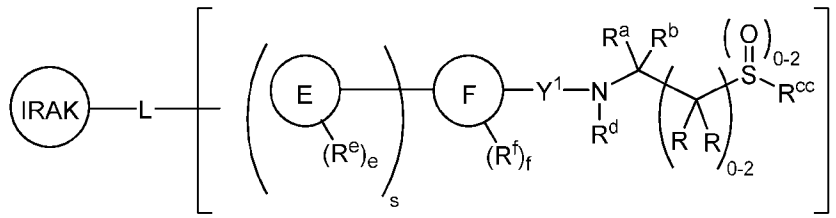
4. The compound of claim 2 or claim 3, wherein Y^1 is $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, $-S(O)-$, or $-S(O)_2-$.

5. The compound of any one of claims 2-4, wherein Y^1 is -C(O)-.

6. The compound of any one of claims 1-5, wherein the compound is any one of the following formulae:



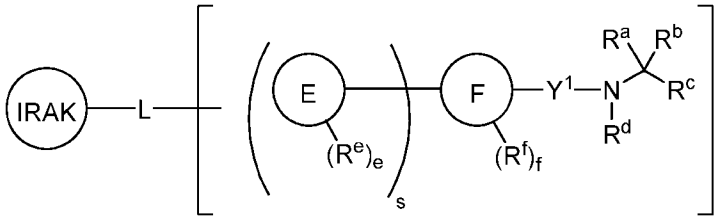
I-a-3'



I-a-4'

or a pharmaceutically acceptable salt thereof.

7. A compound of formula **I-a**:



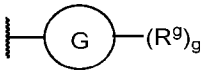
I-a

or a pharmaceutically acceptable salt thereof, wherein:

Ring E is phenyl, a 4-7 membered partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring F is phenylenyl, a 4-10 membered partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Y^1 is a C_{1-3} hydrocarbon chain wherein each methylene is optionally substituted with $-CR_2-$, -CR(OR)-, -C(O)-, -C(NR)-, -C(NOR)-, -S(O)-, or $-S(O)_2-$;

R^a is an optionally substituted C_{1-6} aliphatic or  ;

Ring G is phenyl, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^b is hydrogen, an optionally substituted C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur, or:

R^a and R^b are optionally taken together with their intervening atoms to form an optionally substituted 9-10 membered saturated or partially unsaturated bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

when Y^1 is -C(NR)-, R^b is optionally taken together with R of -C(NR)- with their intervening atoms to form a 5-7 membered partially unsaturated heterocyclyl with 0-1 heteroatoms, in addition to the 2 nitrogen atoms within the heterocyclyl, independently selected from nitrogen, oxygen, and sulfur;

R^c is $-CR_2CONR_2$, a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^d is hydrogen, or:

when R^c is $-CR_2CONR_2$, R^d is optionally taken together with a single R of $-CR_2CONR_2$ with their intervening atoms to form a 5-7 membered saturated or partially unsaturated heterocyclyl with 0-3 heteroatoms, in addition to the nitrogen atom to which R^d is attached, independently selected from nitrogen, oxygen, and sulfur;

R^e, R^f, and R^g are each independently selected from hydrogen, oxo, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$;

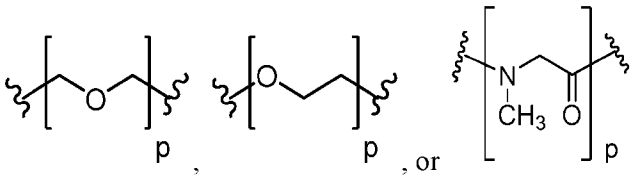
each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

s is 0 or 1; and

each of e, f, and g are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, $-CF_2-$, -O-, -N(R)-, $-Si(R)_2-$, -Si(OH)(R)-, $-Si(OH)_2-$, -P(O)(OR)-, -P(O)(R)-, $-P(O)(NR_2)-$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-, 

, or ;

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 3-7 membered saturated or partially unsaturated carbocyclylenyl, a

4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

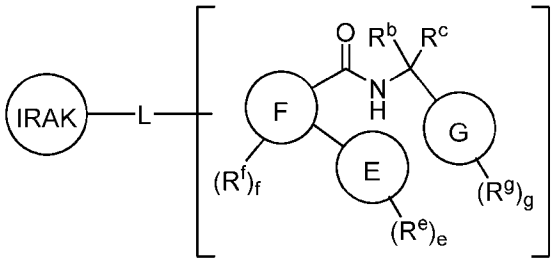
IRAK is an IRAK4 binding moiety;

wherein said compound of formula **I-a** is optionally substituted with

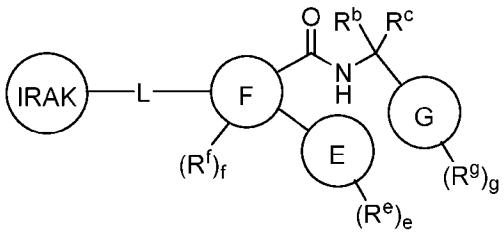
, and wherein

is a warhead group.

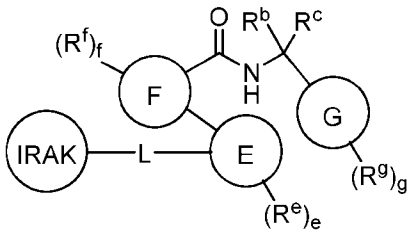
8. The compound of any one of claims 1-7, wherein the compound is any one of the following formulae:



I-a-5'



I-a-6'



I-a-7'

or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-8, wherein Ring E is phenyl, naphthyl, or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and

sulfur.

10. The compound of any one of claims 1-9, wherein Ring E is phenyl or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

11. The compound of any one of claims 1-10, wherein Ring E is phenyl or a 5-6 membered monocyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

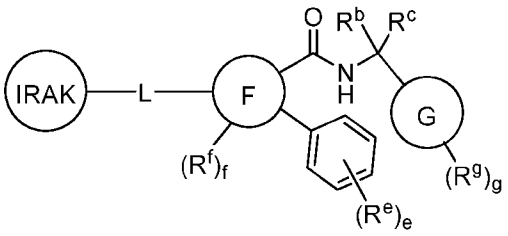
12. The compound of any one of claims 1-11, wherein Ring E is phenyl or a 5-6-membered heteroaryl with 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur.

13. The compound of any one of claims 1-12, Ring E is phenyl.

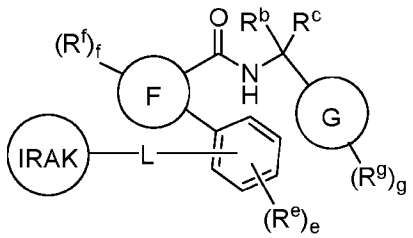
14. The compound of any one of claims 1-8, wherein Ring E is a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic carbocyclyl.

15. The compound of any one of claims 1-8, wherein Ring E is a 4-9 membered partially unsaturated monocyclic, bicyclic, or bridged bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

16. The compound of any one of claims 1-13, wherein the compound is any one of the following formulae:



I-a-8'



I-a-9'

or a pharmaceutically acceptable salt thereof.

17. The compound of any one of claims 1-16, wherein Ring F is phenyl or a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

18. The compound of any one of claims 1-17, wherein Ring F is phenyl or a 5-6 membered heteroaryl

with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

19. The compound of any one of claims 1-18, Ring F is a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

20. The compound of any one of claims 1-19, Ring F is a 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

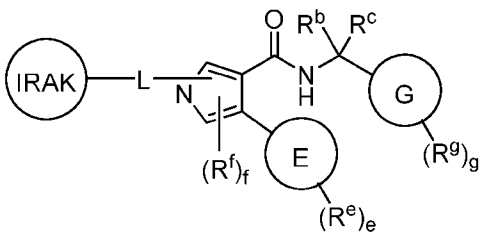
21. The compound of any one of claims 1-20, Ring F is a 5-membered heteroaryl with 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur.

22. The compound of any one of claims 1-21, Ring F is a 5-membered heteroaryl with 1-2 nitrogen heteroatoms.

23. The compound of any one of claims 1-16, wherein Ring F is a 4-11 membered partially unsaturated monocyclic or bicyclic carbocyclylenyl.

24. The compound of any one of claims 1-16, wherein Ring F is a 4-11 membered partially unsaturated monocyclic or bicyclic heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

25. The compound of any one of claims 1-24, wherein the compound is any one of the following formulae:



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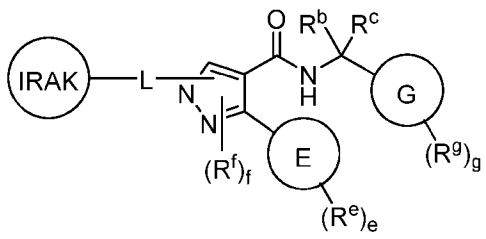

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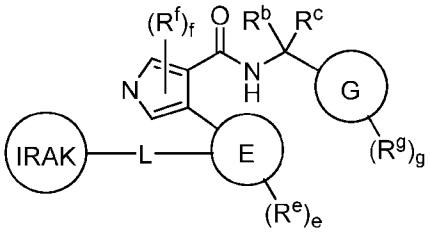

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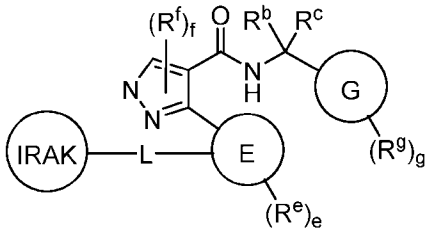


I-a-13'

or a pharmaceutically acceptable salt thereof.

26. The compound of any one of claims 1-25, wherein Ring G is phenyl or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

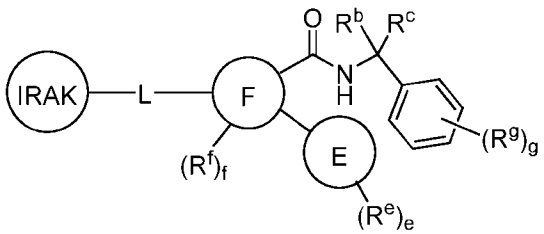
27. The compound of any one of claims 1-26, wherein Ring G is phenyl or a 6-membered heteroaryl with 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur.

28. The compound of any one of claims 1-27, wherein Ring G is phenyl.

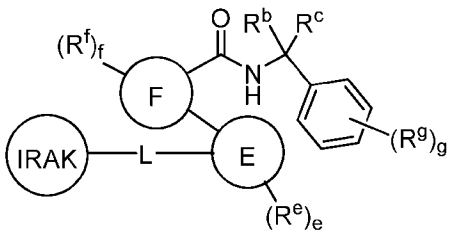
29. The compound of any one of claims 1-25, wherein Ring G is a 5-7 membered saturated or partially unsaturated carbocyclyl.

30. The compound of any one of claims 1-25, wherein Ring G is a 5-7 membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

31. The compound of any one of claims 1-30, wherein the compound is any one of the following formulae:



I-a-14'



I-a-15'

or a pharmaceutically acceptable salt thereof.

32. The compound of any one of claims 1-31, wherein e is 1, 2, or 3.

33. The compound of any one of claims 1-32, wherein e is 1 or 2.

34. The compound of any one of claims 1-33, wherein e is 1.

35. The compound of any one of claims 1-31, wherein e is 0.

36. The compound of any one of claims 1-34, wherein R^e is R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

37. The compound of any one of claims 1-34, wherein R^e is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

38. The compound of any one of claims 1-34, wherein R^e is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, $-NR_2$, -C(O)R, -C(O)OR, or $-C(O)NR_2$.

39. The compound of any one of claims 1-38, wherein f is 1, 2, or 3.

40. The compound of any one of claims 1-39, wherein f is 1 or 2.

41. The compound of any one of claims 1-40, wherein f is 1.

42. The compound of any one of claims 1-38, wherein f is 0.

43. The compound of any one of claims 1-41, wherein R^f is R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

44. The compound of any one of claims 1-41, wherein R^f is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or

-$NRS(O)_2R$.

45. The compound of any one of claims 1-41, wherein R^f is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, $-NR_2$, -C(O)R, -C(O)OR, or $-C(O)NR_2$.

46. The compound of any one of claims 1-45, wherein g is 1, 2, or 3.

47. The compound of any one of claims 1-46, wherein g is 1 or 2.

48. The compound of any one of claims 1-47, wherein g is 1.

49. The compound of any one of claims 1-45, wherein g is 0.

50. The compound of any one of claims 1-48, wherein R^g is R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

51. The compound of any one of claims 1-48, wherein R^g is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, or $-NRS(O)_2R$.

52. The compound of any one of claims 1-48, wherein R^g is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, $-NR_2$, -C(O)R, -C(O)OR, or $-C(O)NR_2$.

53. The compound of any one of claims 1-52, wherein R^b is hydrogen, an optionally substituted C_{1-6} aliphatic, phenyl, or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

54. The compound of any one of claims 1-53, wherein R^b is hydrogen or an optionally substituted C_{1-6} aliphatic.

55. The compound of any one of claims 1-54, wherein R^b is hydrogen or C_{1-6} alkyl.

56. The compound of any one of claims 1-55, wherein R^b is hydrogen.

57. The compound of any one of claims 1-56, wherein R^c is halogen, -CN, -CFR_2, -CF_2R, -CF_3, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)(NR)R, -S(O)R, -C(O)R, -CR=NOR, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -$OC(O)R$, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, -$P(O)R_2$, -$P(O)(OR)_2$, -$P(O)(OR)NR_2$, -$P(O)(NR_2)_2$, -CR_2CN, -CR_2CFR_2, -CR_2CF_2R, -CR_2CF_3, -CR_2NO_2, -CR_2OR, -CR_2SR, -CR_2NR_2, -CR_2SiR_3, -$CR_2S(O)_2R$, -$CR_2S(O)_2NR_2$, -$CR_2S(O)(NR)R$, -$CR_2S(O)R$, -$CR_2C(O)R$, -CR_2CR=NOR, -$CR_2C(O)OR$, -$CR_2C(O)NR_2$, -$CR_2C(O)NROR$, -$CR_2C(NOR)R$, -$CR_2OC(O)R$, -$CR_2OC(O)NR_2$, -$CR_2OP(O)R_2$, -$CR_2OP(O)(OR)_2$, -$CR_2OP(O)(OR)NR_2$, -$CR_2OP(O)(NR_2)_2$, -$CR_2NRC(O)OR$, -$CR_2NRC(O)R$, -$CR_2NRC(O)N(R)_2$, -$CR_2NRS(O)_2R$, -$CR_2NP(O)R_2$, -$CR_2NRP(O)(OR)_2$, -$CR_2NRP(O)(OR)NR_2$, -$CR_2NRP(O)(NR_2)_2$, -$CR_2P(O)R_2$, -$CR_2P(O)(OR)_2$, -$CR_2P(O)(OR)NR_2$, -$CR_2P(O)(NR_2)_2$, -CR_2CR_2CN, -$CR_2CR_2CFR_2$, -$CR_2CR_2CF_2R$, -$CR_2CR_2CF_3$, -$CR_2CR_2NO_2$, -CR_2CR_2OR, -CR_2CR_2SR, -$CR_2CR_2NR_2$, -$CR_2CR_2SiR_3$, -$CR_2CR_2S(O)_2R$, -$CR_2CR_2S(O)_2NR_2$, -$CR_2CR_2S(O)(NR)R$, -$CR_2CR_2S(O)R$, -$CR_2CRC(O)R$, -CR_2CR_2CR=NOR, -$CR_2CR_2C(O)OR$, -$CR_2CR_2C(O)NR_2$, -$CR_2CR_2C(O)NROR$, -$CR_2CR_2C(NOR)R$, -$CR_2CR_2OC(O)R$, -$CR_2CR_2OC(O)NR_2$, -$CR_2CR_2OP(O)R_2$, -$CR_2CR_2OP(O)(OR)_2$, -$CR_2CR_2OP(O)(OR)NR_2$, -$CR_2CR_2OP(O)(NR_2)_2$, -$CR_2CR_2NRC(O)OR$, -$CR_2CR_2NRC(O)R$, -$CR_2CR_2NRC(O)N(R)_2$, -$CR_2CR_2NRS(O)_2R$, -$CR_2CR_2NP(O)R_2$, -$CR_2CR_2NRP(O)(OR)_2$, -$CR_2CR_2NRP(O)(OR)NR_2$, -$CR_2CR_2NRP(O)(NR_2)_2$, -$CR_2CR_2P(O)R_2$, -$CR_2CR_2P(O)(OR)_2$, -$CR_2CR_2P(O)(OR)NR_2$, -$CR_2CR_2P(O)(NR_2)_2$, -$CR_2CR(OR)CR_2OR$, , or an optionally substituted group selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; or: –$(CR_2)_{1-2}$-X^a, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

58. The compound of any one of claims 1-57, wherein R^c is -CO_2R, -$CONR_2$, -CR_2CN, -CR_2CFR_2, -CR_2CF_2R, -CR_2CF_3, -CR_2NO_2, -CR_2OR, -CR_2SR, -CR_2NR_2, -CR_2SiR_3, -$CR_2S(O)_2R$, -$CR_2S(O)_2NR_2$, -$CR_2S(O)(NR)R$, -$CR_2S(O)R$, -$CR_2C(O)R$, -CR_2CR=NOR, -$CR_2C(O)OR$, -$CR_2C(O)NR_2$, -$CR_2C(O)NROR$, -$CR_2C(NOR)R$, -$CR_2OC(O)R$, -$CR_2OC(O)NR_2$, -$CR_2NRC(O)OR$, -$CR_2NRC(O)R$, -$CR_2NRC(O)N(R)_2$, -$CR_2NRS(O)_2R$, -CR_2CR_2CN, -$CR_2CR_2CFR_2$, -$CR_2CR_2CF_2R$, -$CR_2CR_2CF_3$, -$CR_2CR_2NO_2$, -CR_2CR_2OR, -

CR_2CR_2SR, $-CR_2CR_2NR_2$, $-CR_2CR_2SiR_3$, $-CR_2CR_2S(O)_2R$, $-CR_2CR_2S(O)_2NR_2$, $-CR_2CR_2S(O)(NR)R$, $-CR_2CR_2S(O)R$, $-CR_2CRC(O)R$, $-CR_2CR_2CR{=}NOR$, $-CR_2CR_2C(O)OR$, $-CR_2CR_2C(O)NR_2$, $-CR_2CR_2C(O)NROR$, $-CR_2CR_2C(NOR)R$, $-CR_2CR_2OC(O)R$, $-CR_2CR_2OC(O)NR_2$, $-CR_2CR_2NRC(O)OR$, $-CR_2CR_2NRC(O)R$, $-CR_2CR_2NRC(O)N(R)_2$, $-CR_2CR_2NRS(O)_2R$, $-CR_2CR(OR)CR_2OR$; or: $-(CR_2)_{1\text{-}2}\text{-}X^a$, wherein X^a is halogen or an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

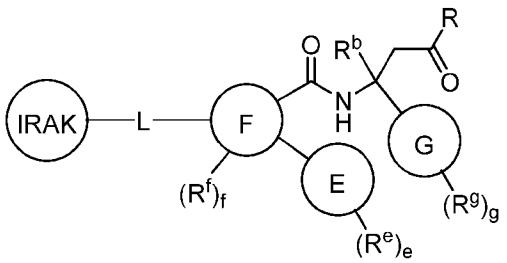
59. The compound of any one of claims 1-58, wherein R^c is $-CO_2R$, $-CONR_2$, $-CR_2CN$, $-CR_2CF_2R$, $-CR_2OR$, $-CR_2SR$, $-CR_2NR_2$, $-CR_2S(O)_2R$, $-CR_2S(O)_2NR_2$, $-CR_2S(O)(NR)R$, $-CR_2S(O)R$, $-CR_2C(O)R$, $-CR_2CR{=}NOR$, $-CR_2C(O)OR$, $-CR_2C(O)NR_2$, $-CR_2CR_2CN$, $-CR_2CR_2CF_2R$, $-CR_2CR_2OR$, $-CR_2CR_2SR$, $-CR_2CR_2NR_2$, $-CR_2CR_2S(O)_2R$, $-CR_2CR_2S(O)_2NR_2$, $-CR_2CR_2S(O)(NR)R$, $-CR_2CR_2S(O)R$, $-CR_2CRC(O)R$, $-CR_2CR_2CR{=}NOR$, $-CR_2CR_2C(O)OR$, $-CR_2CR_2C(O)NR_2$, $-CR_2CR_2C(O)NROR$, $-CR_2CR_2C(NOR)R$, $-CR_2CR(OR)CR_2OR$; or: $-(CR_2)_{1\text{-}2}\text{-}X^a$, wherein X^a is an optionally substituted ring selected from phenyl; a 4-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 5-9 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

60. The compound of any one of claims 1-59, wherein R^c is $-CO_2R$, $-CONR_2$, $-CR_2CN$, $-CR_2CF_2R$, $-CR_2CONR_2$, $-CR_2C(O)R$, $-CR_2CO_2R$, $-CR_2NR_2$, $-CR_2OR$, $-CR_2S(O)NR_2$, $-CR_2SO_2NR_2$, $-CR_2S(O)R$, $-CR_2SO_2R$, $-CR_2S(O)(NR)R$, $-CR_2CN$, $-CR_2CR_2NR_2$, $-CR_2CR_2OR$, $-CR_2CR{=}NOR$, $-CR_2CR(OR)CR_2OR$.

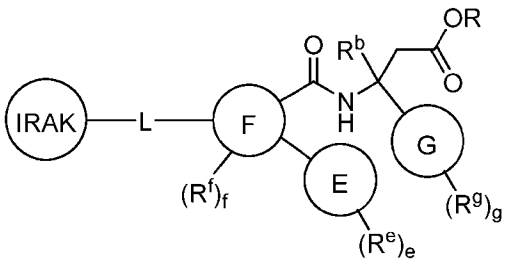
61. The compound of any one of claims 1-60, wherein R^c is $-CR_2CN$, $-CR_2CF_2R$, $-CR_2CONR_2$, $-CR_2C(O)R$, $-CR_2CO_2R$, $-CR_2NR_2$, $-CR_2OR$, $-CR_2SONR_2$, $-CR_2SO_2NR_2$, $-CR_2S(O)R$, $-CR_2SO_2R$, $-CR_2S(O)(NR)R$, or $-CR_2CN$.

62. The compound of any one of claims 1-61, wherein R^c is $-CR_2CN$, $-CR_2CONR_2$, $-CR_2C(O)R$, $-CR_2CO_2R$, $-CR_2S(O)NR_2$, $-CR_2SO_2NR_2$, $-CR_2S(O)R$, $-CR_2SO_2R$, or $-CR_2CR_2NR_2$.

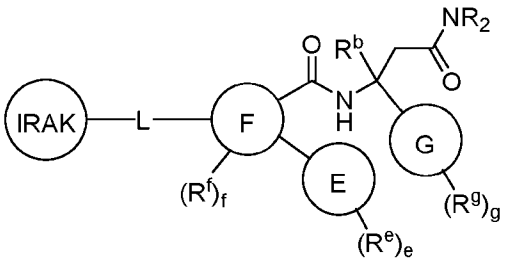
63. The compound of any one of claims 1-62, wherein the compound of any one of the following formulae:



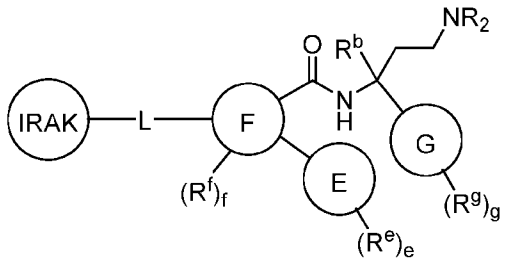
I-a-16'



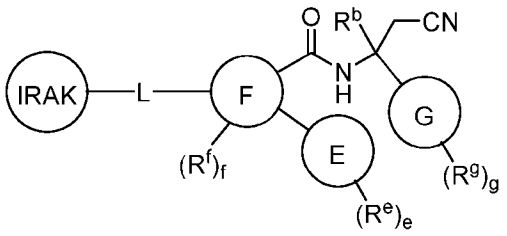
I-a-17



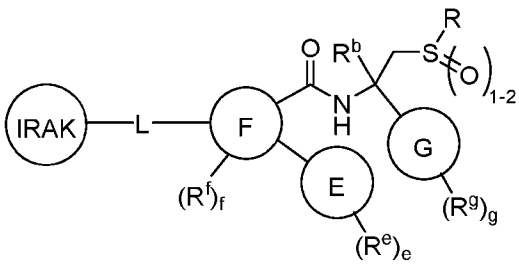
I-a-18



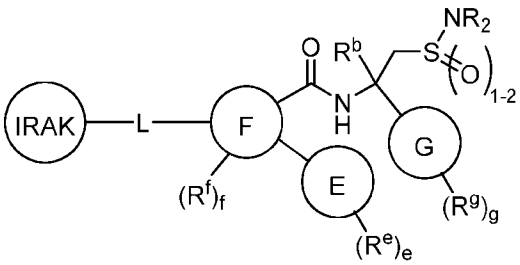
I-a-19



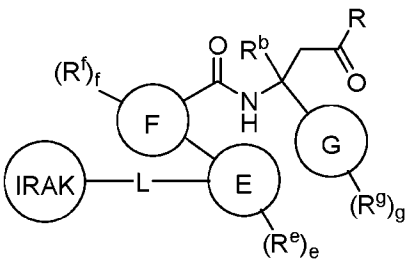
I-a-20



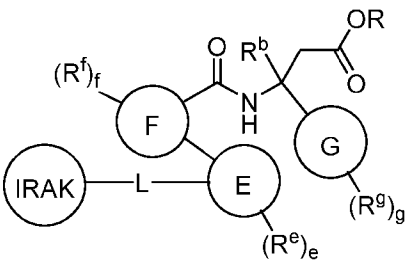
I-a-21



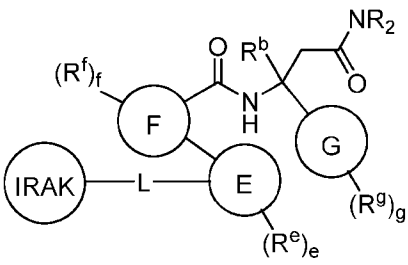
I-a-22



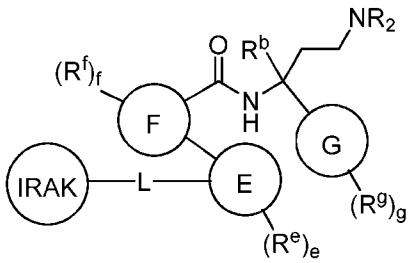
I-a-23



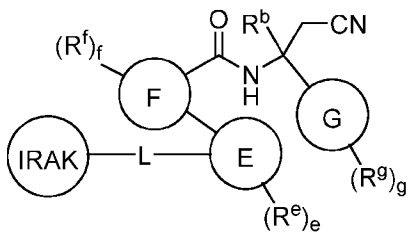
I-a-24



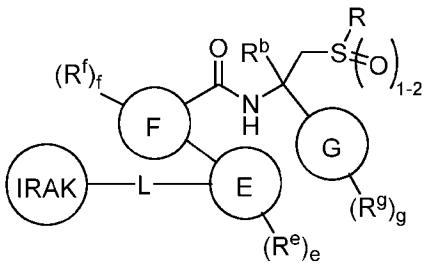
I-a-25



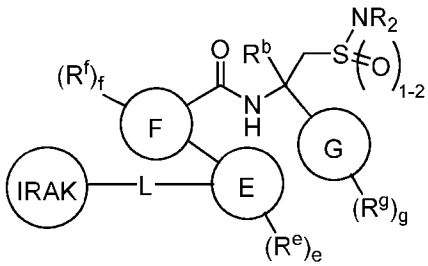
I-a-26



I-a-27



I-a-28



I-a-29

or a pharmaceutically acceptable salt thereof.

64. The compound of any one of claims 1-63, wherein R^c is $-CH_2CONH_2$, $-CH_2CONHMe$, $-CH_2CONHEt$, $-CH_2CON(Me)CH_2CH_2NH_2$, $-CH_2CONHCONH_2$, $-CH_2CONHCH_2Ph$, $-CH_2CONHcyclopropyl$, $-CH_2SO_2Me$, $-CH_2SO_2Et$, $-CH_2SO_2iPr$, $-CH_2CH_2NH_2$, or $-CH_2CH_2NMe_2$.

65. The compound of any one of claims 1-64, wherein R^c is $-CH_2CONH_2$, $-CH_2SO_2Me$, or $-CH_2CH_2NH_2$.

66. The compound of any one of claims 1-65, wherein R^c is $-CH_2CONH_2$.

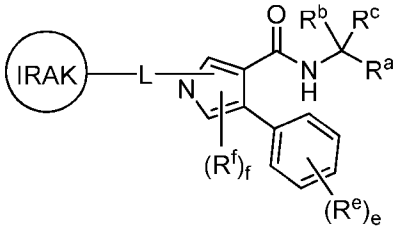
67. The compound of any one of claims 1-65, wherein R^c is $-CH_2SO_2Me$.

68. The compound of any one of claims 1-65, wherein R^c is $-CH_2CH_2NH_2$.

69. The compound of any one of claims 1-68, wherein Ring E is phenyl or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; Ring F is phenyl or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; and Ring G is phenyl or a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

70. The compound of any one of claims 1-69, wherein Ring E is phenyl or a 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; Ring F is phenyl or a 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur; and Ring G is phenyl or a 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

71. The compound of any one of claims 1-5 and 7, wherein the compound of any one of the following formulae:



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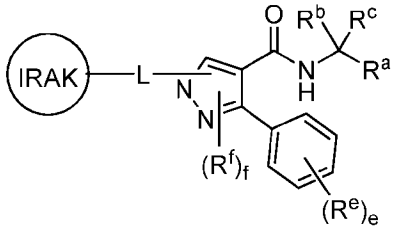

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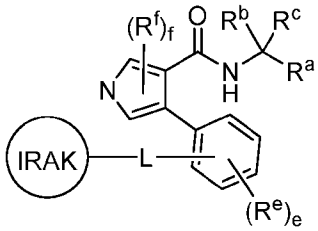

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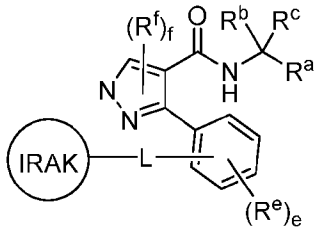

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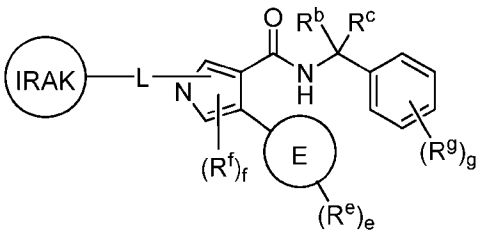

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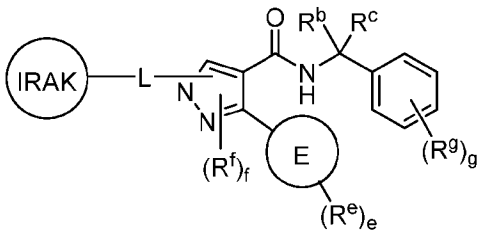

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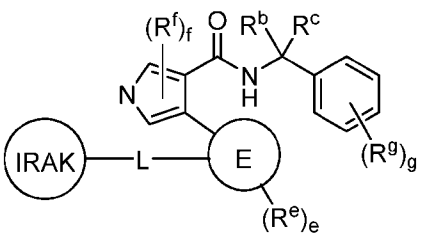

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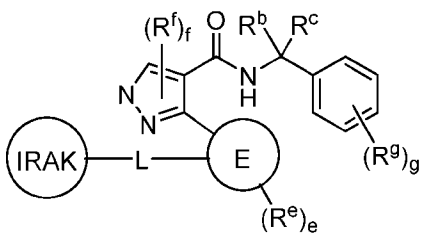

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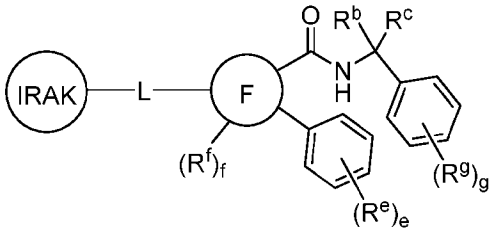

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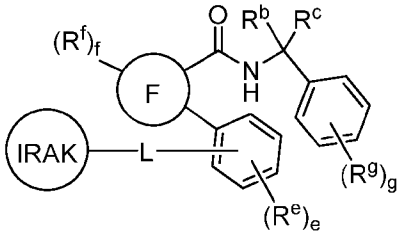

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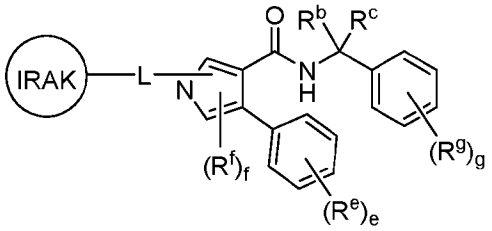

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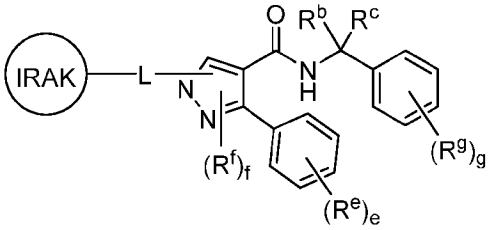

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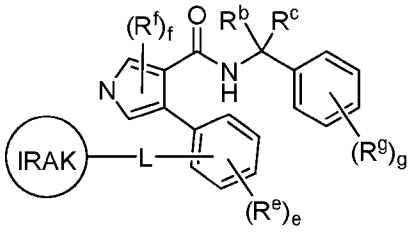

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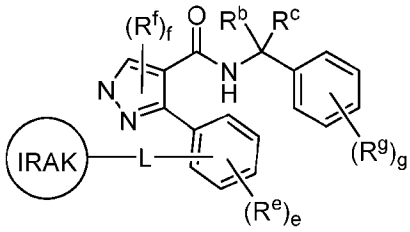
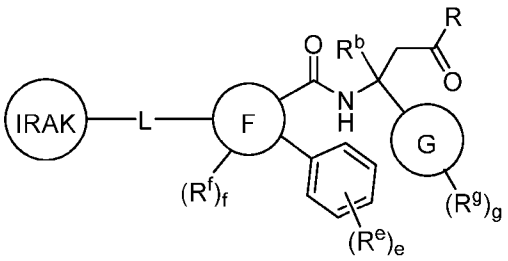


I-a-43

or a pharmaceutically acceptable salt thereof.

72. The compound of any one of claims 1-5 and 7, wherein the compound of any one of the following formulae:



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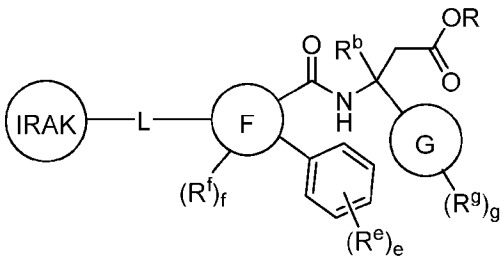

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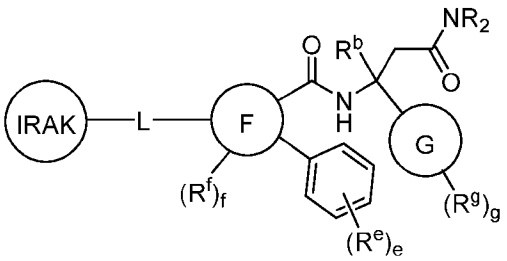

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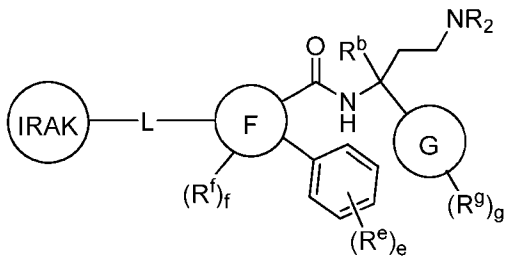

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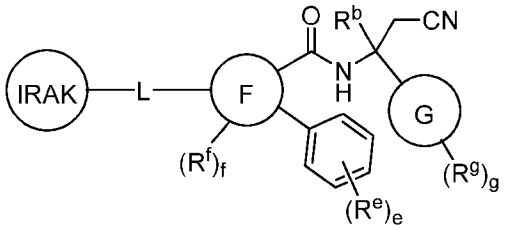

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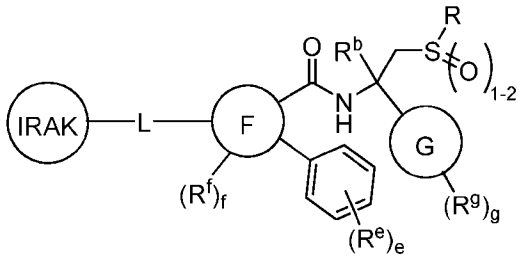

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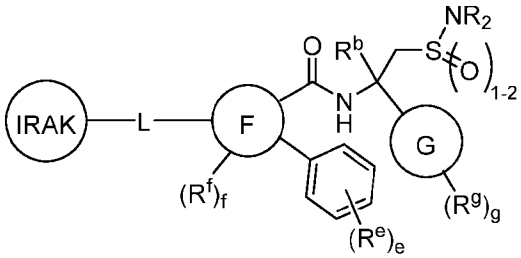

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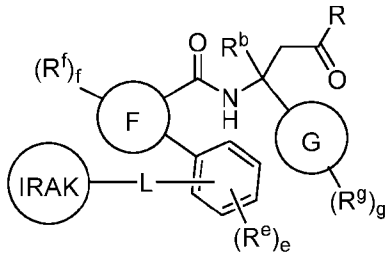

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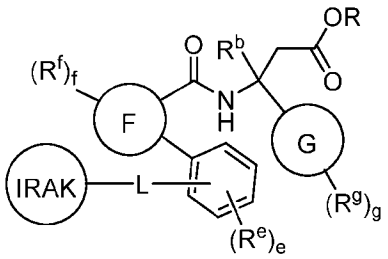

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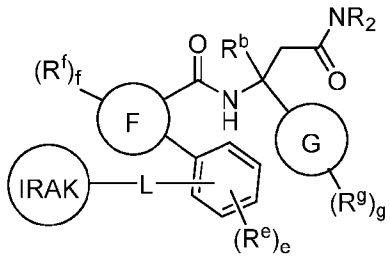

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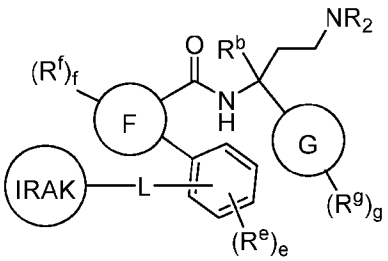

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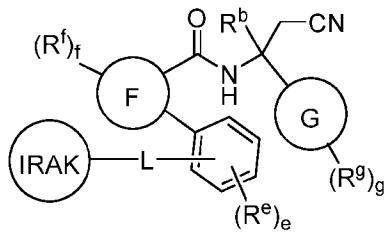

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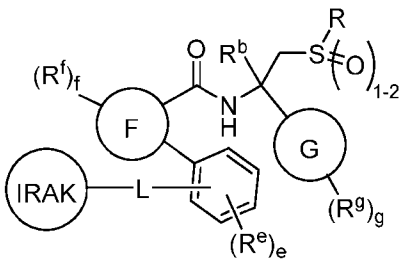

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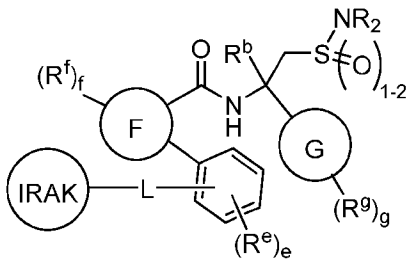

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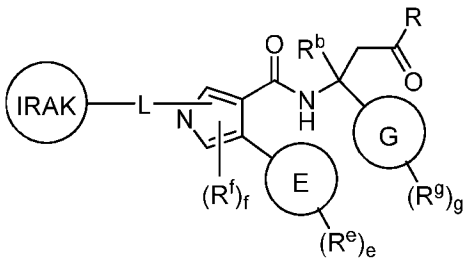

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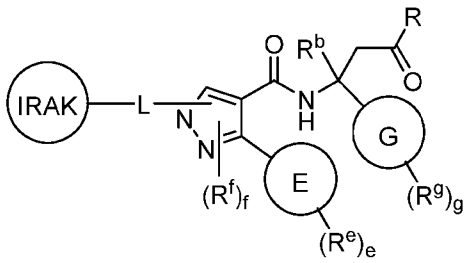

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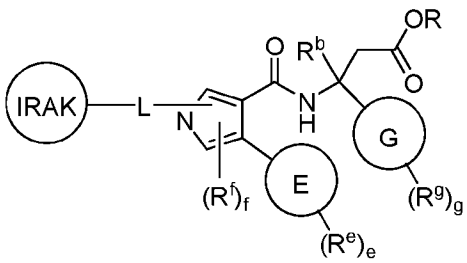

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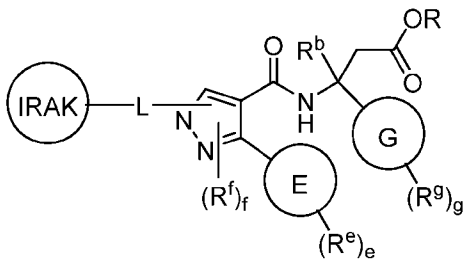

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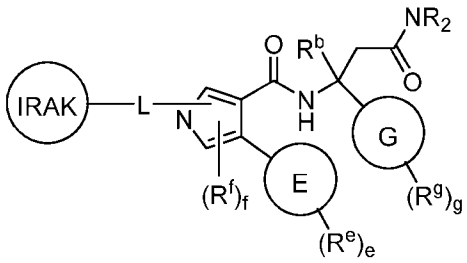

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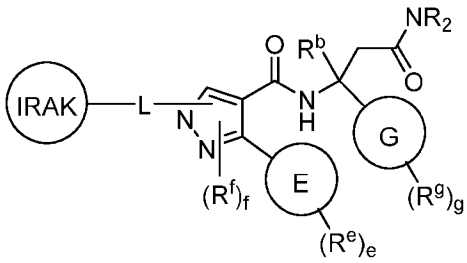

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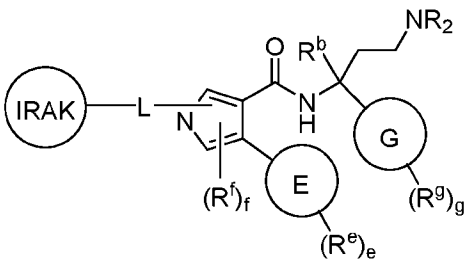

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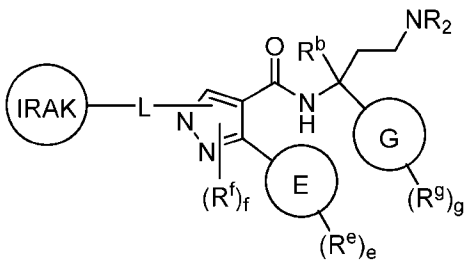

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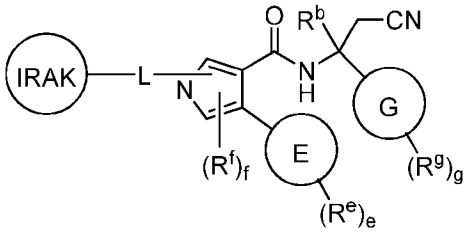

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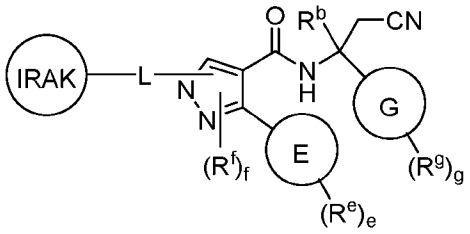

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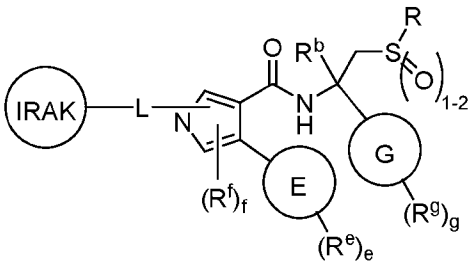

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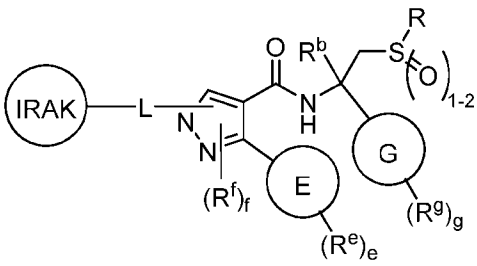

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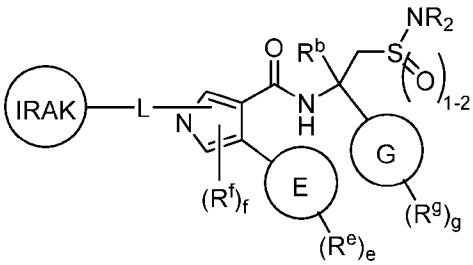

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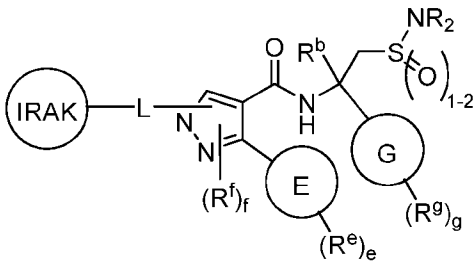

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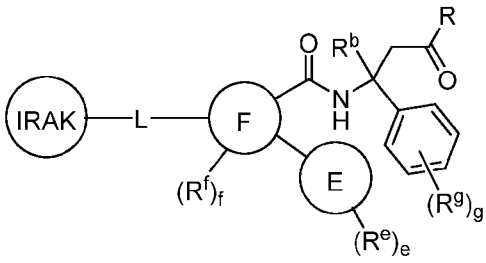

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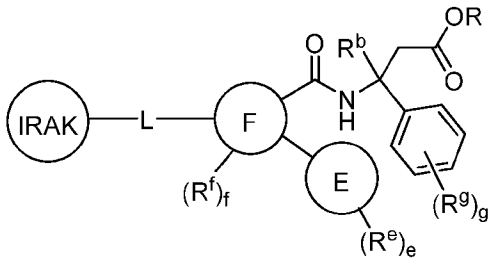

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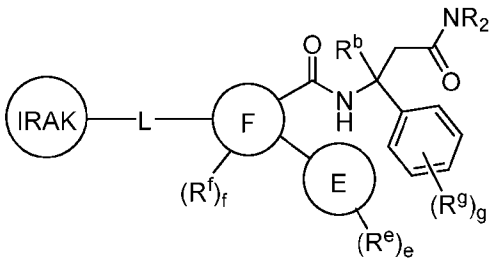

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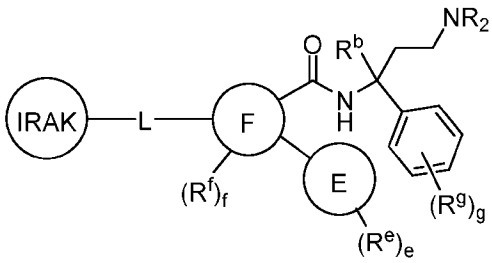

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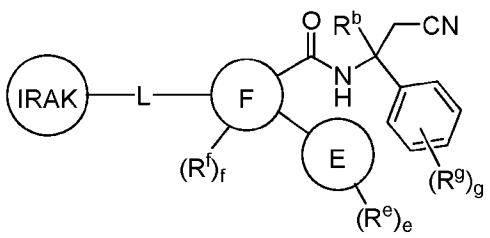

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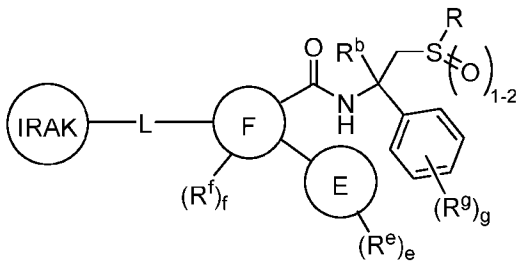

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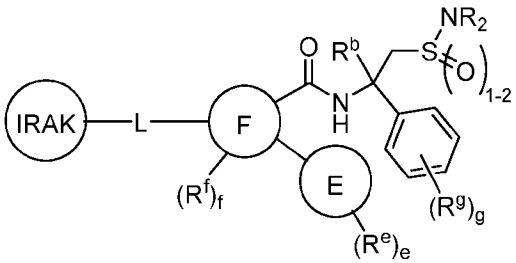

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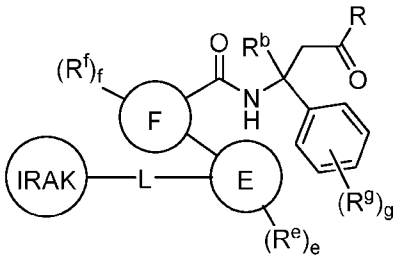

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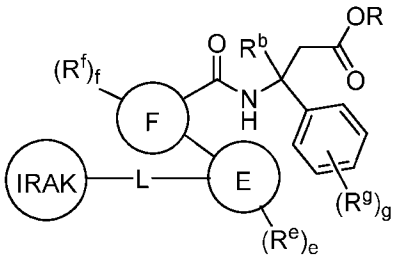

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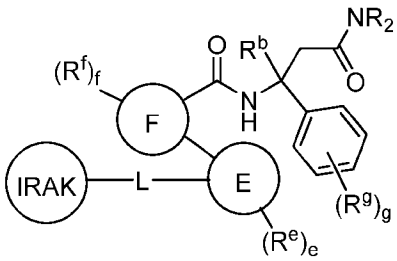

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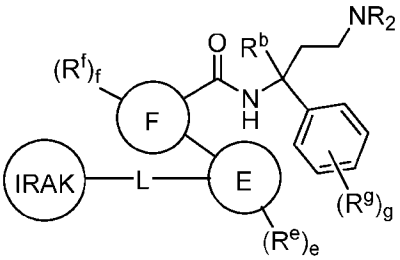
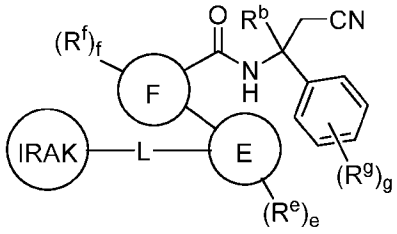
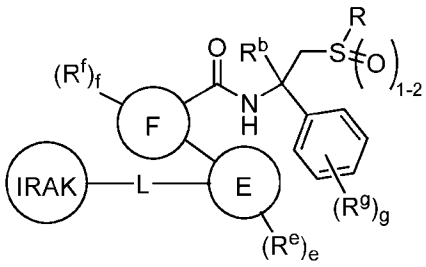


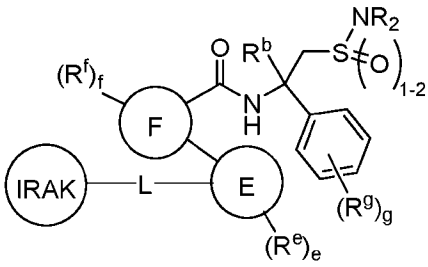
I-a-82



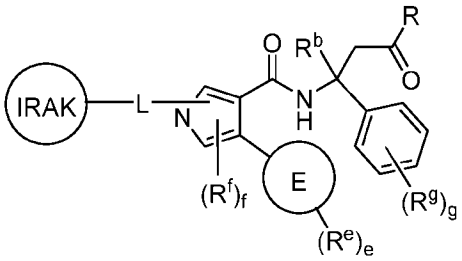
I-a-83



I-a-84



I-a-85



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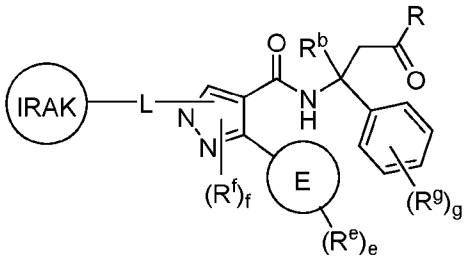

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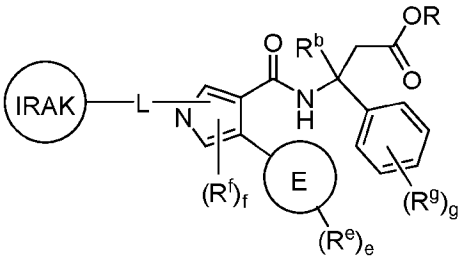

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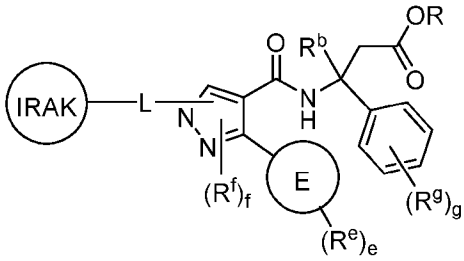

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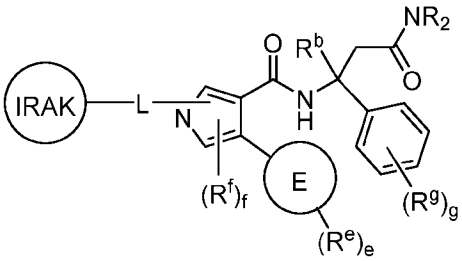

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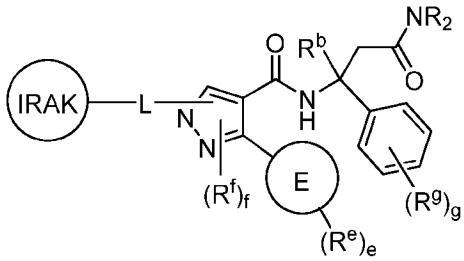

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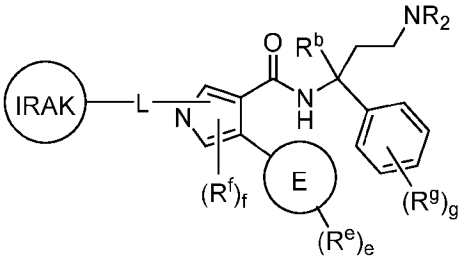

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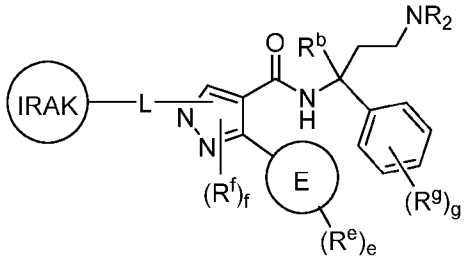

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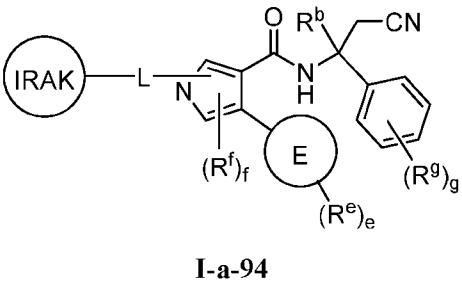

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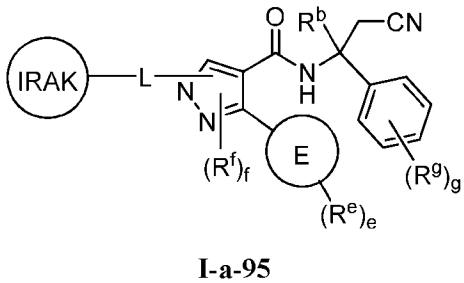

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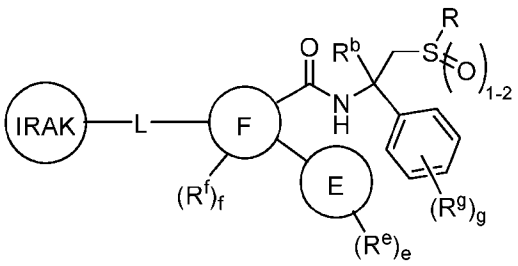

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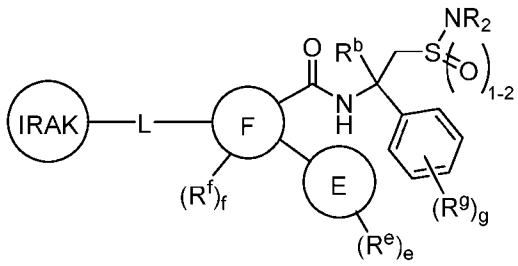

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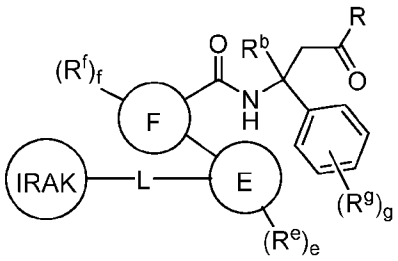

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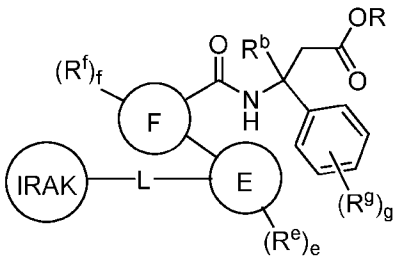

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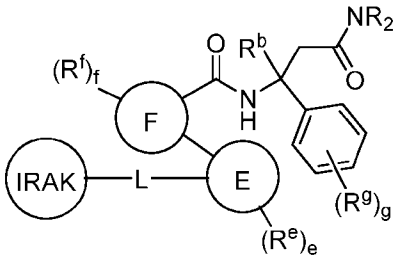

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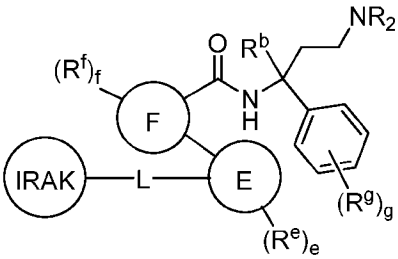

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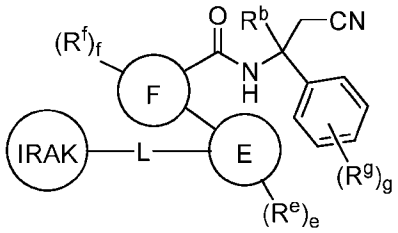

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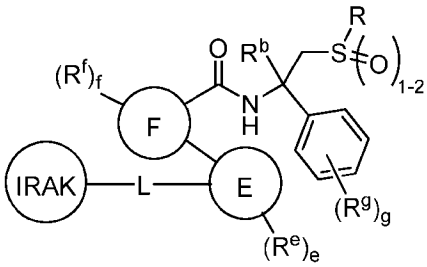

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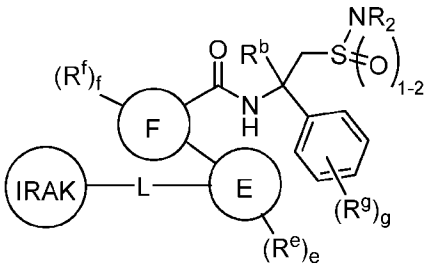

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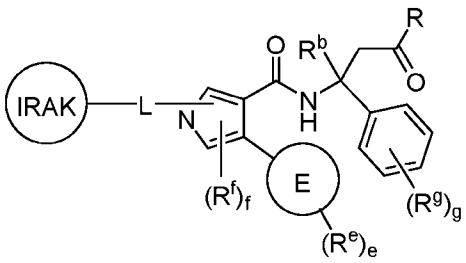

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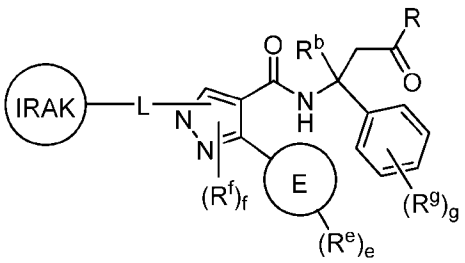

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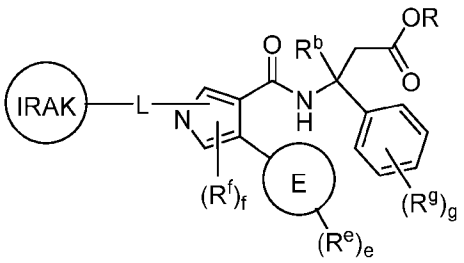

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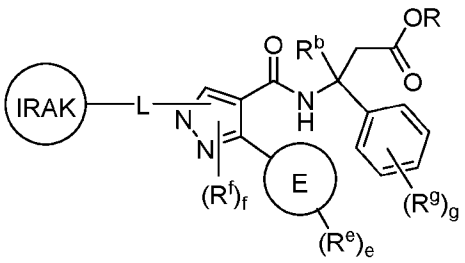

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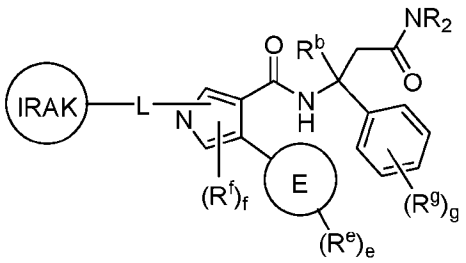

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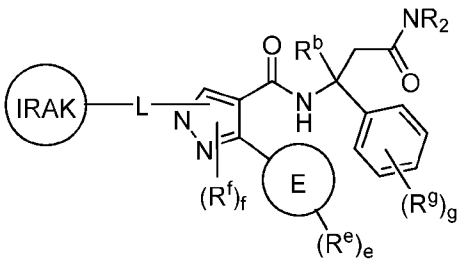

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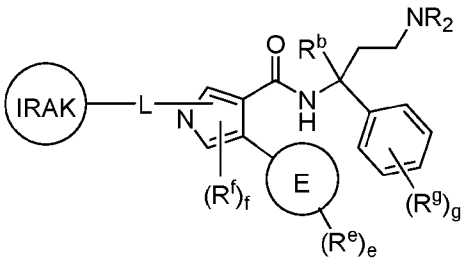

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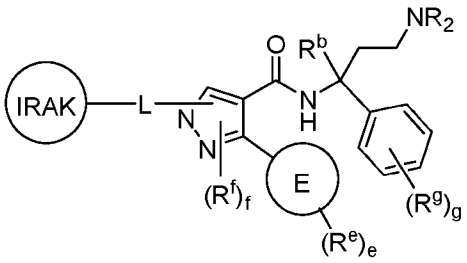

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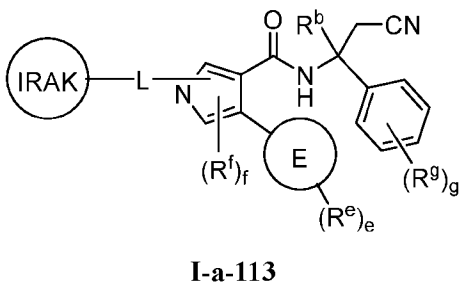

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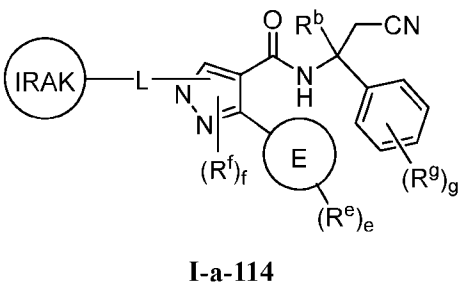

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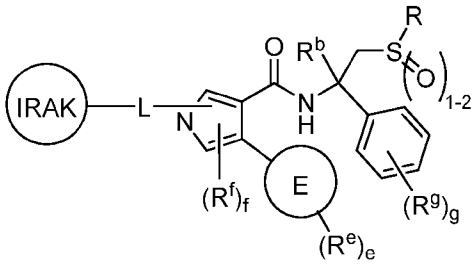

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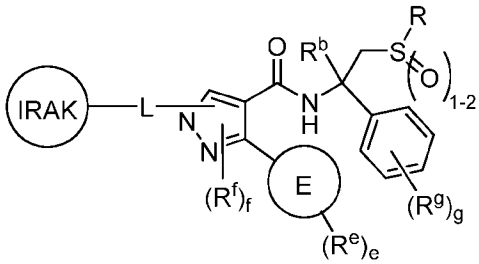

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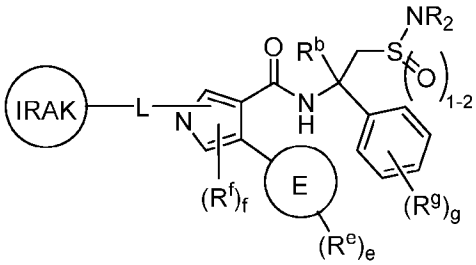

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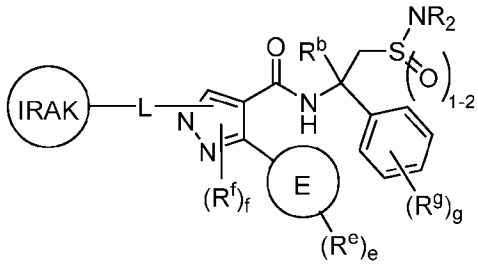

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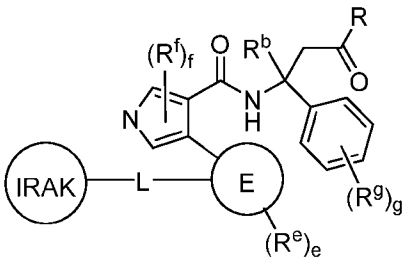

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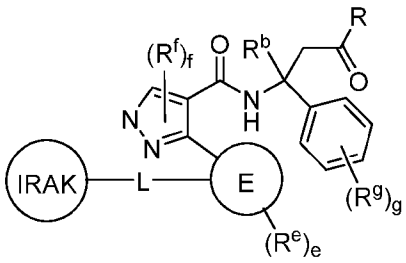

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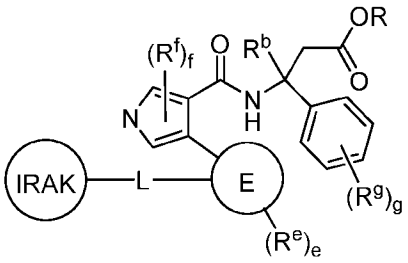

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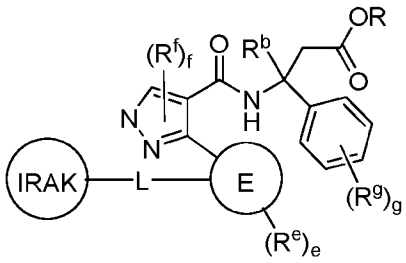

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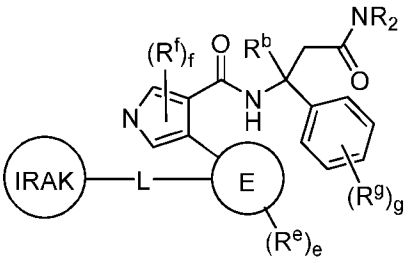

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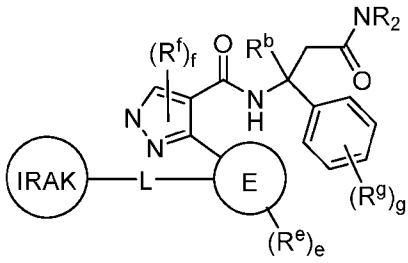

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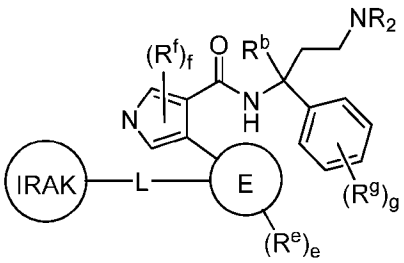

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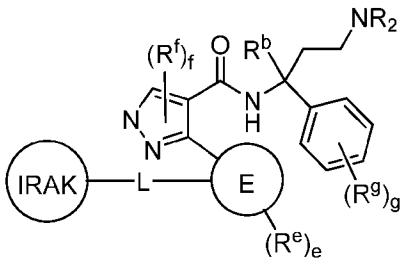

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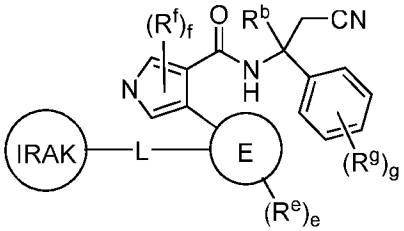

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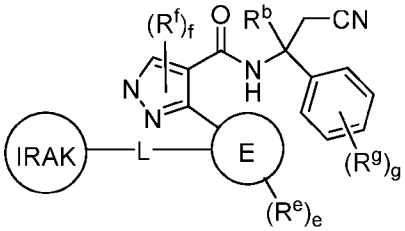

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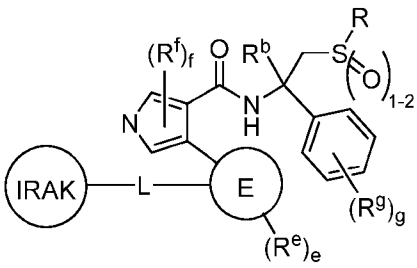

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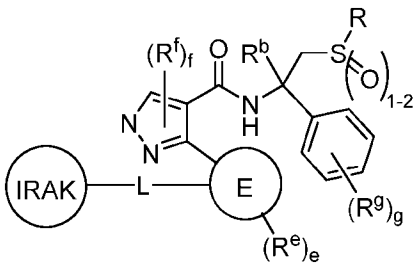

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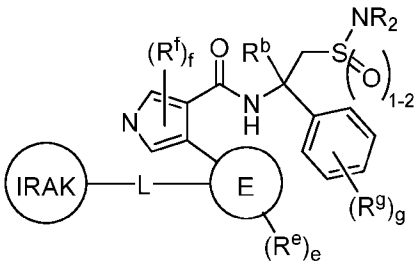

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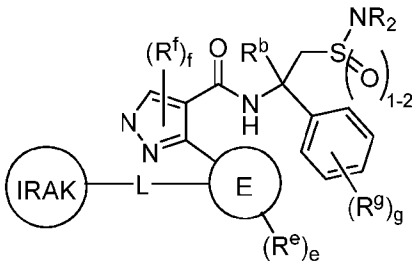

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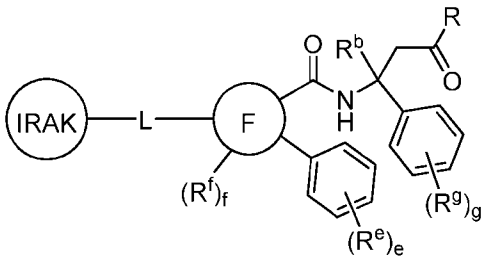

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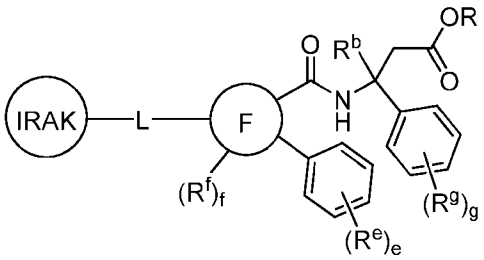

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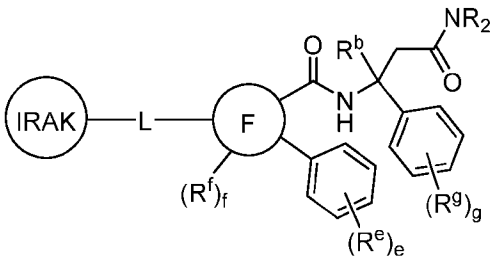

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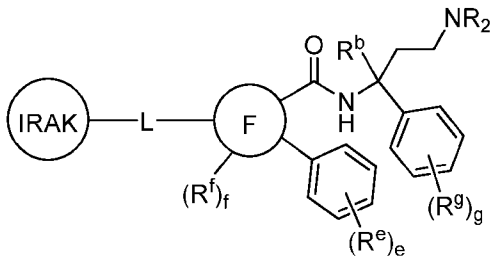

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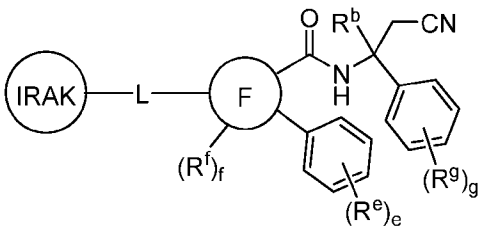

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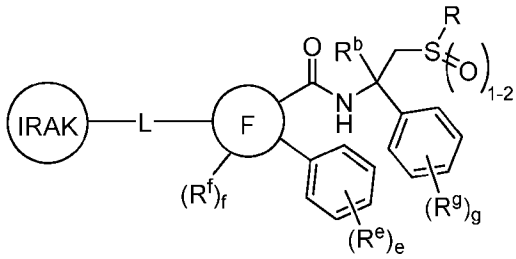

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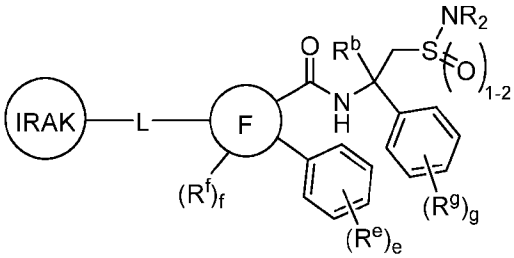

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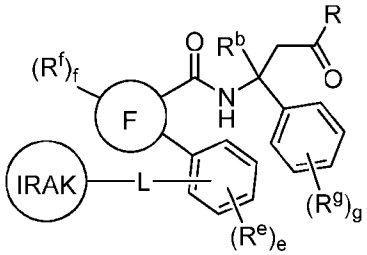
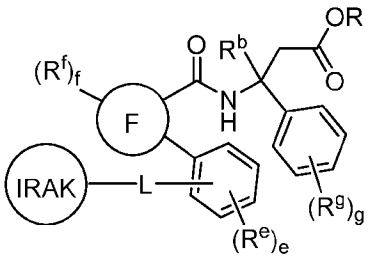
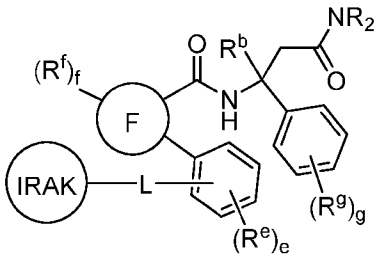


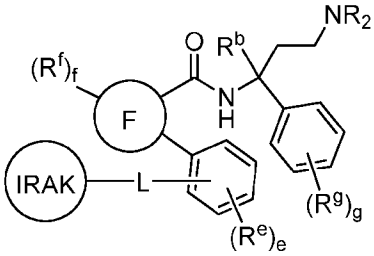
I-a-140



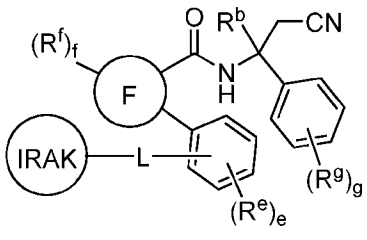
I-a-141



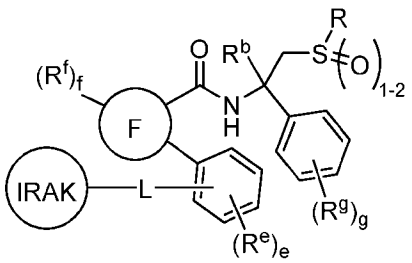
I-a-142



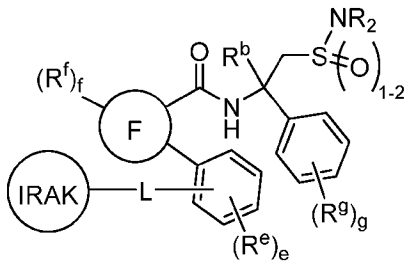
I-a-143



I-a-144



I-a-145



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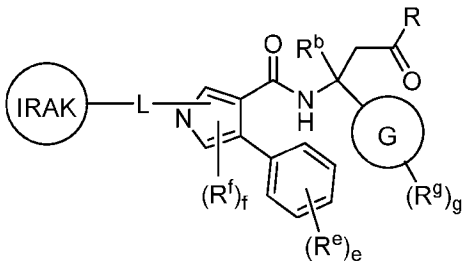
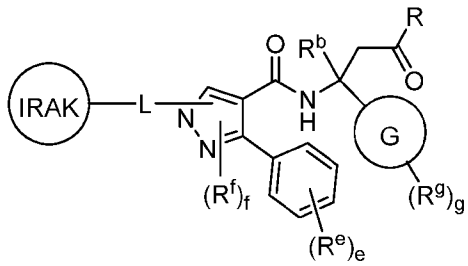
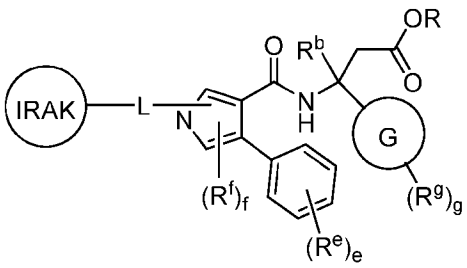


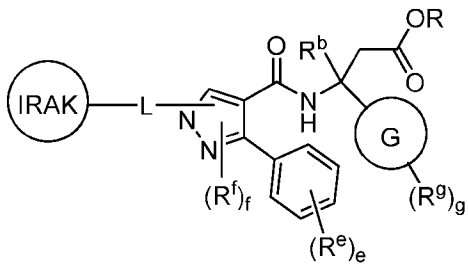
I-a-147



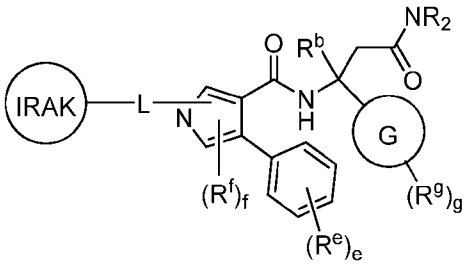
I-a-148



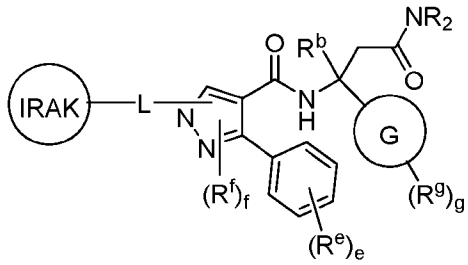
I-a-149



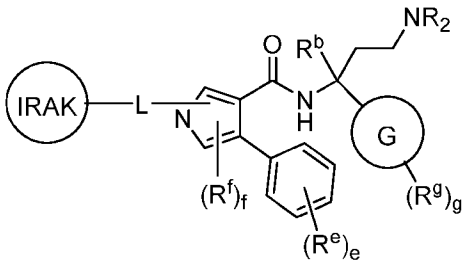
I-a-150



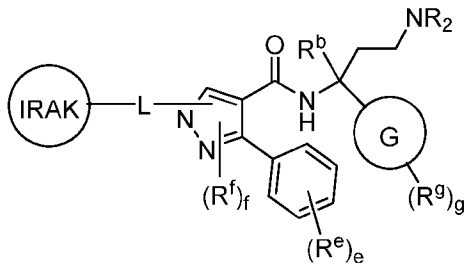
I-a-151



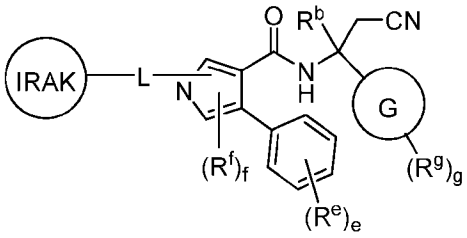
I-a-152



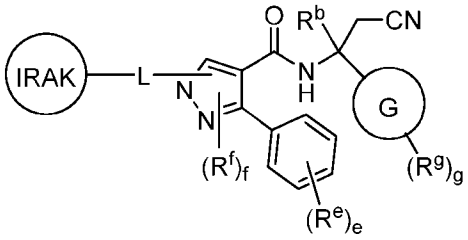
I-a-153



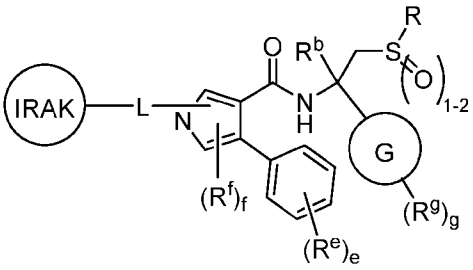
I-a-154



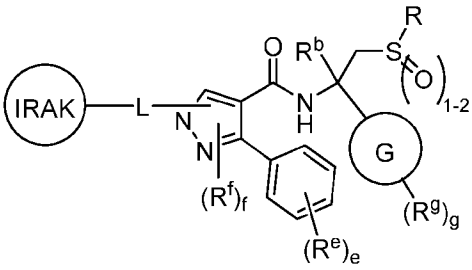
I-a-155



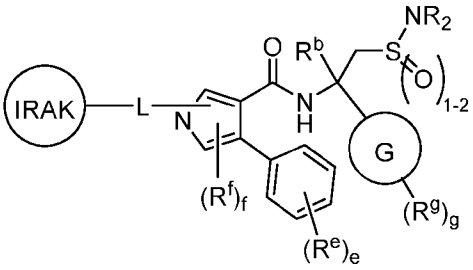
I-a-156



I-a-157



I-a-158



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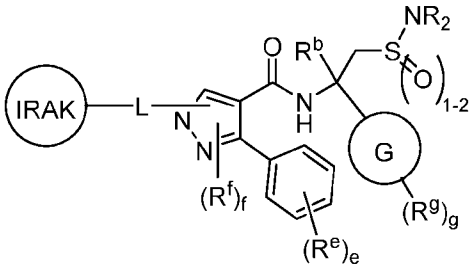

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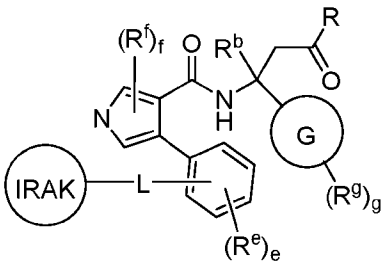
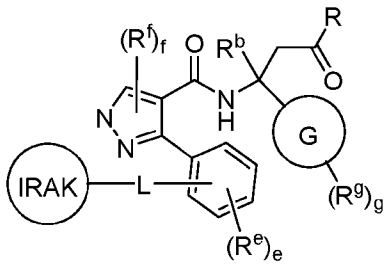
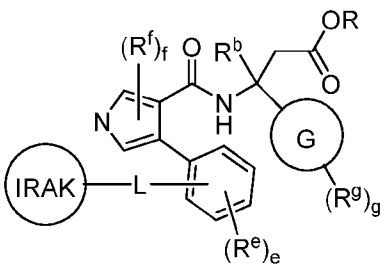


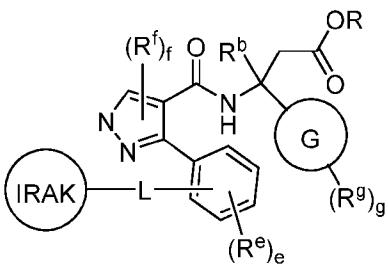
I-a-161



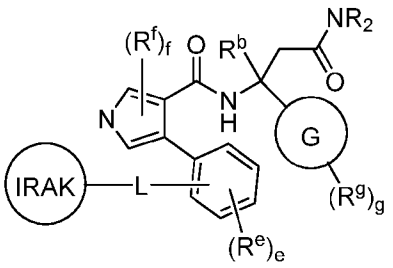
I-a-162



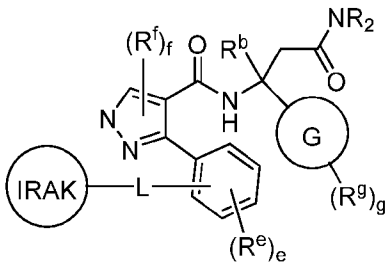
I-a-163



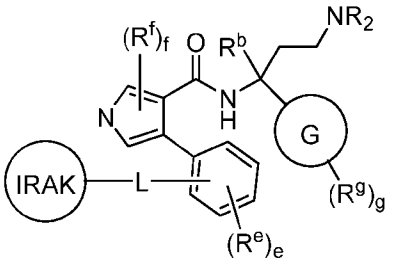
I-a-164



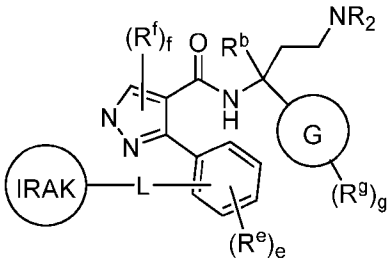
I-a-165



I-a-166



I-a-167



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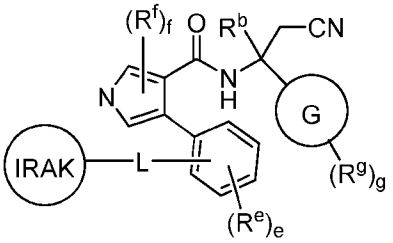

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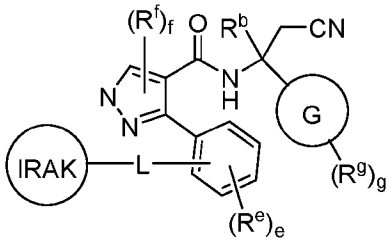
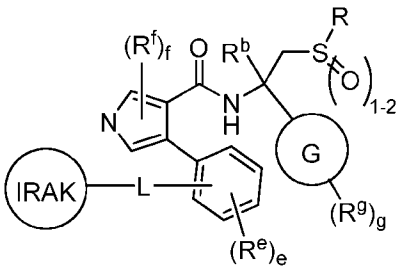


I-a-170



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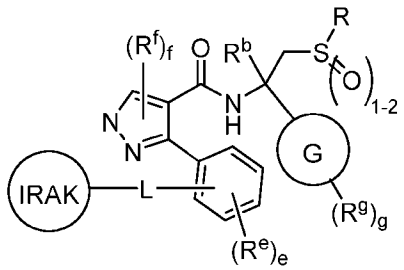
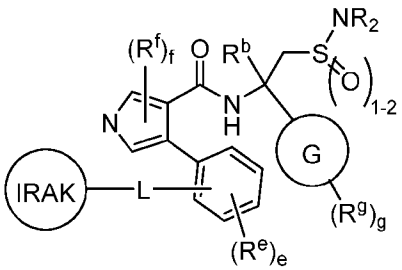
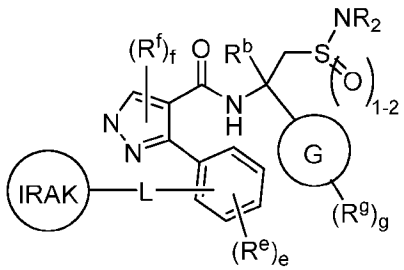


I-a-172



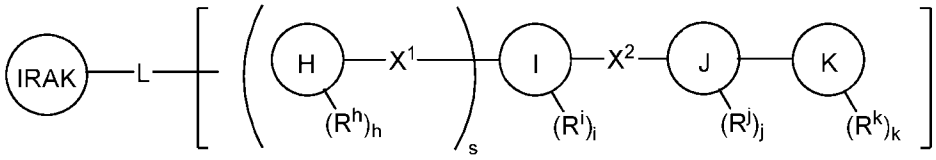
I-a-173



I-a-174

or a pharmaceutically acceptable salt thereof.

73. A compound of formula **I-b'**:



I-b'

or a pharmaceutically acceptable salt thereof, wherein:

Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring I is phenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring J is phenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring K is phenyl, naphthyl, a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-13 membered monocyclic, bicyclic, or tricyclic heteroaryl with 1-5 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^h, R^i, R^j, and R^k are each independently selected from hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, -$P(O)R_2$, -$P(O)(OR)_2$, -$P(O)(OR)NR_2$, and -$P(O)(NR_2)_2$, or:

an R^i group on Ring I and an R^j group or Ring J are optionally taken together with their intervening atoms to form a 5-8 membered saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

an R^j group on Ring J and an R^k group or Ring K are optionally taken together with their intervening

atoms to form a 5-6 membered partially unsaturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

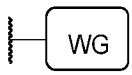
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, naphthyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

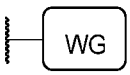
two R groups on the same atom, or on different atoms, are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each of X^1 and X^2 are independently a covalent bond, spiro-fusion between the two rings that X^1 or X^2 connect, or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by $-CR_2-$, -CR(OR)-, -CRF-, $-CF_2-$, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or $-S(O)_2-$;

s is 0 or 1; and

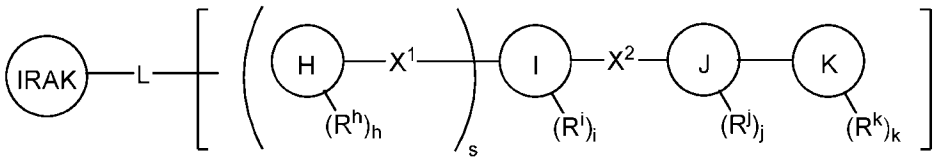
each of w, x, y, and z are independently 0, 1, 2, 3, or 4;

wherein said compound of formula **I-b'** is optionally substituted with 

, and wherein 

is a warhead group.

74. A compound of formula **I-b**:



I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen,

oxygen, and sulfur;

Ring I is phenylenyl, a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered monocyclic or bicyclic heteroarylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring J is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring K is phenyl, naphthyl, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclylenyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-13 membered monocyclic, bicyclic, or tricyclic heteroarylenyl with 1-5 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^h, R^i, R^j, and R^k are each independently selected from hydrogen, oxo, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, $-P(O)R_2$, $-P(O)(OR)_2$, $-P(O)(OR)NR_2$, and $-P(O)(NR_2)_2$, or:

an R^i group on Ring I and an R^j group or Ring J are optionally taken together with their intervening atoms to form a 5-8 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

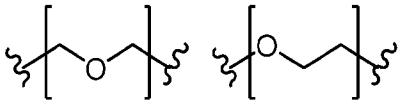
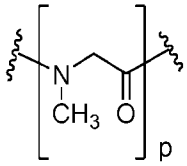
two R groups on the same atom are optionally taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each of X^1 and X^2 is independently a covalent bond, spiro-fusion between the two rings that X^1 or X^2

connect, -CR_2-, -CR(OR)-, -CRF-, -CF_2-, -NR-, -O-, -S-, or -$S(O)_2$-;

s is 0 or 1;

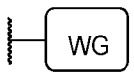
each of w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, -CF_2-, -O-, -N(R)-, -$Si(R)_2$-, -Si(OH)(R)-, -$Si(OH)_2$-, -P(O)(OR)-, -P(O)(R)-, -$P(O)(NR_2)$-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-,  , or  ;

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 3-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

IRAK is an IRAK4 binding moiety;

wherein said compound of formula **I-b** is optionally substituted with  , and wherein is a warhead group.

75. The compound of claim 73 or claim 74, wherein X^1 is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by -CR_2-, -CR(OR)-, -CRF-, -CF_2-, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or -$S(O)_2$-.

76. The compound of any one of claims 73-75, wherein X^1 is a covalent bond, -CR_2-, -CR(OR)-, -CRF-

, -CF_2-, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or -$S(O)_2$-.

77. The compound of any one of claims 73-76, wherein X^1 is a covalent bond.

78. The compound of any one of claims 73-77, wherein X^2 is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-6} hydrocarbon chain, wherein 0-4 methylene units of the hydrocarbon chain are independently replaced by -CR_2-, -CR(OR)-, -CRF-, -CF_2-, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or -$S(O)_2$-.

79. The compound of any one of claims 73-78, wherein X^2 is a covalent bond, -CR_2-, -CR(OR)-, -CRF-, -CF_2-, -C(NR)-, -C(O)-, -O-, -N(R)-, -S-, -S(O)-, or -$S(O)_2$-.

80. The compound of any one of claims 73-79, wherein X^2 is a covalent bond, -CR_2-, or -N(R)-.

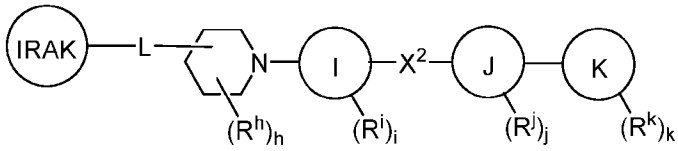
81. The compound of any one of claims 73-80, wherein Ring H is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

82. The compound of any one of claims 73-81, wherein Ring H is a 3-7 membered saturated or partially unsaturated monocyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

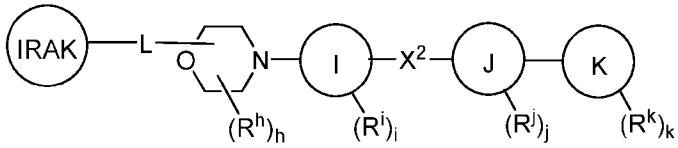
83. The compound of any one of claims 73-82, wherein Ring H is a 6-membered saturated or partially unsaturated monocyclic heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

84. The compound of any one of claims 73-83, wherein Ring H is a 6-membered saturated monocyclic heterocyclyl with 1-2 heteroatoms independently selected from nitrogen and oxygen.

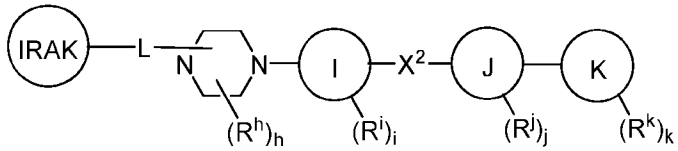
85. The compound of any one of claims 73-84, wherein the compound is any one of the following formulae:



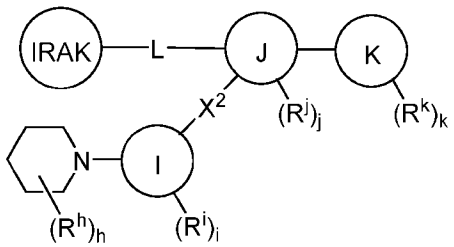
I-b-1'



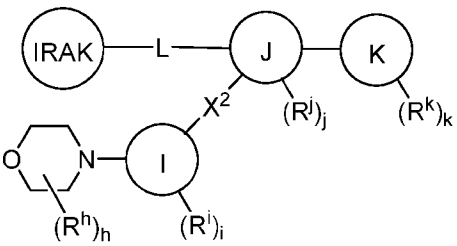
I-b-2'



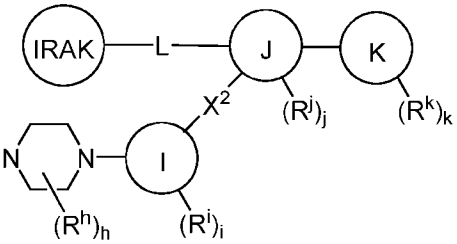
I-b-3'



I-b-4'



I-b-5'



I-b-6'

or a pharmaceutically acceptable salt thereof.

86. The compound of any one of claims 73-85, wherein Ring I is phenyl or a 5-10 membered monocyclic or bicyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

87. The compound of any one of claims 73-86, wherein Ring I is phenyl or a 5-6 membered monocyclic heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur.

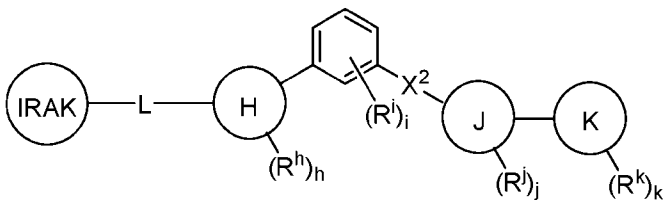
88. The compound of any one of claims 73-87, wherein Ring I is phenyl or a 6-membered monocyclic heteroaryl with 1-2 nitrogen heteroatoms.

89. The compound of any one of claims 73-85, wherein Ring I is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

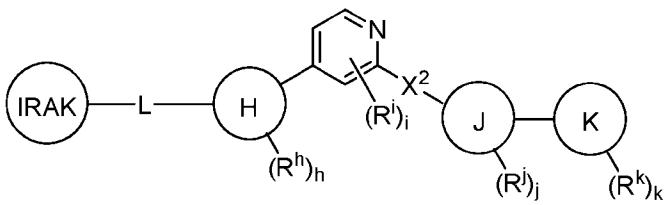
90. The compound of any one of claims 73-85, wherein Ring I is a 3-11 membered saturated or partially unsaturated monocyclic or bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

91. The compound of any one of claims 73-85, wherein Ring I is a 9-membered saturated or partially unsaturated bicyclic heterocyclyl with 1-2 nitrogen heteroatoms.

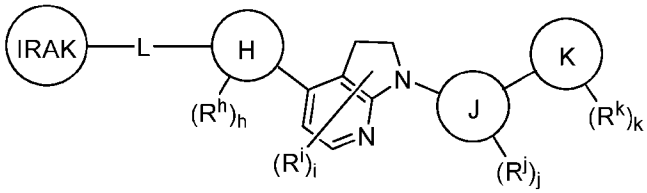
92. The compound of any one of claims 73-91, wherein the compound is any one of the following formulae:



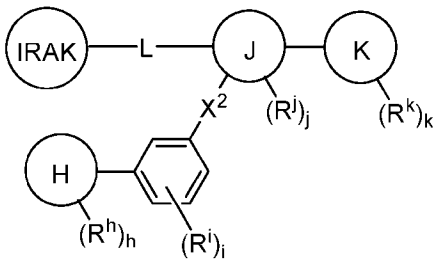
I-b-7'



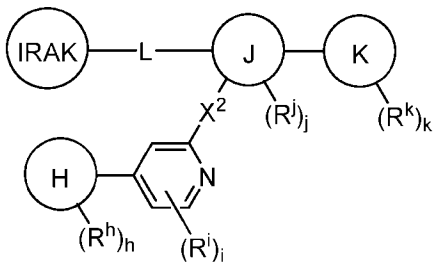
I-b-8'



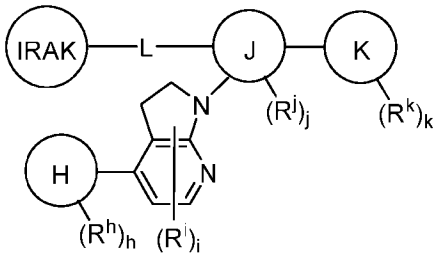
I-b-9'



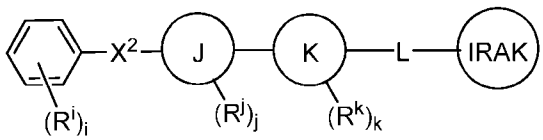
I-b-10'



I-b-11'



I-b-12'



I-b-13'

or a pharmaceutically acceptable salt thereof.

93. The compound of any one of claims 73-92, Ring J is a 3-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3

heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

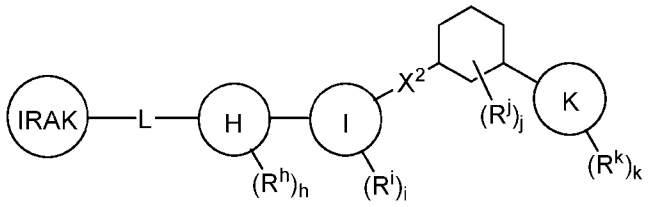
94. The compound of any one of claims 73-93, Ring J is a 6-9 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 9-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

95. The compound of any one of claims 73-94, Ring J is a 6-membered saturated monocyclic carbocyclyl or heterocyclyl with 1 nitrogen heteroatoms.

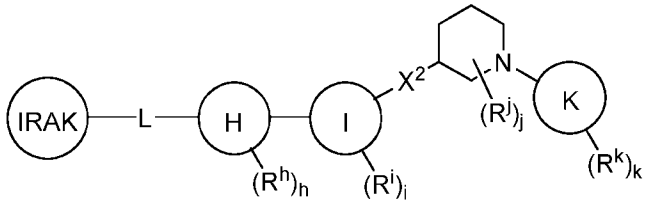
96. The compound of any one of claims 73-94, Ring J is a 9-membered saturated monocyclic heterocyclyl with 1-2 nitrogen heteroatoms.

97. The compound of any one of claims 73-94, Ring J is a 10-membered bicyclic heteroaryl ring having 1-2 nitrogen heteroatoms.

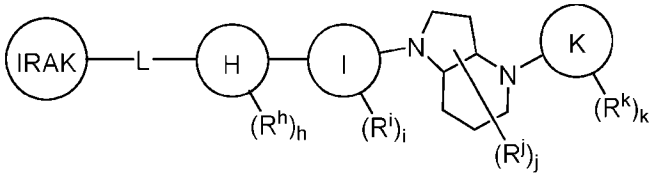
98. The compound of any one of claims 73-97, wherein the compound is any one of the following formulae:



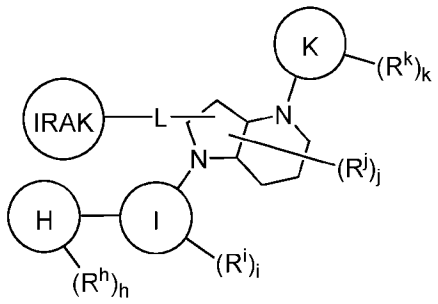
I-b-14'



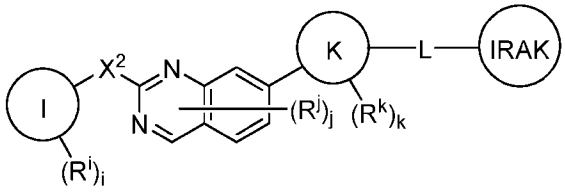
I-b-15'



I-b-16'



I-b-17'



I-b-18'

or a pharmaceutically acceptable salt thereof.

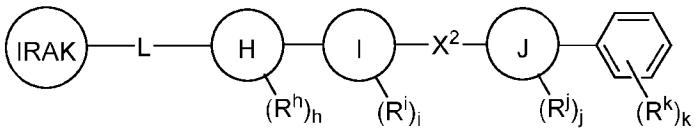
99. The compound of any one of claims 73-98, wherein Ring K is phenyl, a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 9-10 membered saturated or partially unsaturated bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

100. The compound of any one of claims 73-99, wherein Ring K is phenyl or a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

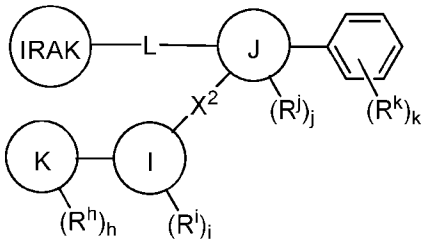
101. The compound of any one of claims 73-100, wherein Ring K is phenyl or a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

102. The compound of any one of claims 73-101, wherein Ring K is phenyl or a 6-membered saturated carbocyclyl or heterocyclyl with 1-2 nitrogen heteroatoms.

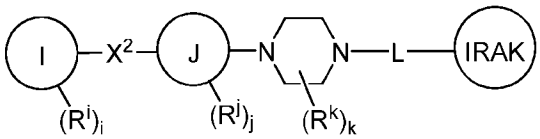
103. The compound of any one of claims 73-102, wherein the compound is any one of the following formulae:



I-b-19'



I-b-20'



I-b-21'

or a pharmaceutically acceptable salt thereof.

104. The compound of any one of claims 73-103, wherein h is 1, 2, or 3.

105. The compound of any one of claims 73-104, wherein h is 1 or 2.

106. The compound of any one of claims 73-105, wherein h is 1.

107. The compound of any one of claims 73-103, wherein h is 0.

108. The compound of any one of claims 73-106, wherein R^h is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

109. The compound of any one of claims 73-106, wherein R^h is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or

-NRS(O)$_2$R.

110. The compound of any one of claims 73-106, wherein R^h is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR$_2$, -C(O)R, -C(O)OR, or -C(O)NR$_2$.

111. The compound of any one of claims 73-110, wherein i is 1, 2, or 3.

112. The compound of any one of claims 73-111, wherein i is 1 or 2.

113. The compound of any one of claims 73-112, wherein i is 1.

114. The compound of any one of claims 73-110, wherein i is 0.

115. The compound of any one of claims 73-113, wherein R^i is R^A, halogen, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

116. The compound of any one of claims 73-113, wherein R^i is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO$_2$, -OR, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -OC(O)NR$_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N(R)$_2$, or -NRS(O)$_2$R.

117. The compound of any one of claims 73-113, wherein R^i is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR$_2$, -C(O)R, -C(O)OR, or -C(O)NR$_2$.

118. The compound of any one of claims 73-117, wherein j is 1, 2, or 3.

119. The compound of any one of claims 73-118, wherein j is 1 or 2.

120. The compound of any one of claims 73-119, wherein j is 1.

121. The compound of any one of claims 73-117, wherein j is 0.

122. The compound of any one of claims 73-120, wherein R^j is R^A, halogen, -CN, -NO$_2$, -OR, -

SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

123. The compound of any one of claims 73-120, wherein R^j is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

124. The compound of any one of claims 73-118, wherein R^j is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

125. The compound of any one of claims 73-124, wherein k is 1, 2, or 3.

126. The compound of any one of claims 73-125, wherein k is 1 or 2.

127. The compound of any one of claims 73-126, wherein k is 1.

128. The compound of any one of claims 73-124, wherein k is 0.

129. The compound of any one of claims 73-127, wherein R^k is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

130. The compound of any one of claims 73-127, wherein R^k is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

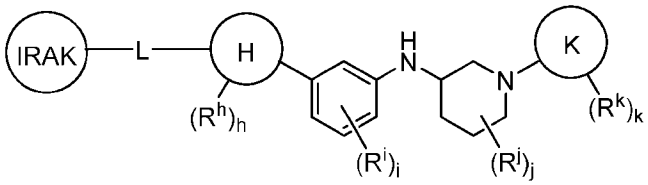
131. The compound of any one of claims 73-127, wherein R^k is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

132. The compound of any one of claims 73-131, wherein Ring H is a 6-membered saturated or partially unsaturated monocyclic heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; Ring I is phenyl or a 5-6 membered monocyclic heteroaryl with 1-4 heteroatoms independently

selected from nitrogen, oxygen and sulfur or a 3-11 membered saturated or partially unsaturated monocyclic or bicyclic heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; Ring J is a 6-9 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 9-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and Ring K is phenyl or a 3-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

133. The compound of any one of claims 73-132, wherein Ring H is a 6-membered saturated monocyclic heterocyclyl with 1-2 heteroatoms independently selected from nitrogen and oxygen; Ring I is phenyl, a 6-membered monocyclic heteroaryl with 1-2 nitrogen heteroatoms, or a 9-membered saturated or partially unsaturated bicyclic heterocyclyl with 1-2 nitrogen heteroatoms; Ring J is a 6-membered saturated monocyclic carbocyclyl or heterocyclyl with 1 nitrogen heteroatoms, a 9-membered saturated monocyclic heterocyclyl with 1-2 nitrogen heteroatoms, a 10-membered bicyclic heteroaryl ring having 1-2 nitrogen heteroatoms; and Ring K is phenyl or a 6-membered saturated carbocyclyl or heterocyclyl with 1-2 nitrogen heteroatoms.

134. The compound of any one of claims 73-133, wherein the compound is any one of the following formulae:



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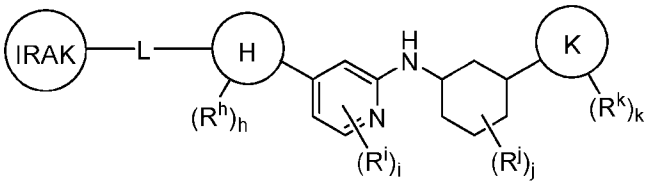

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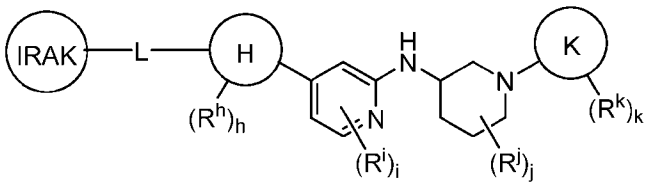
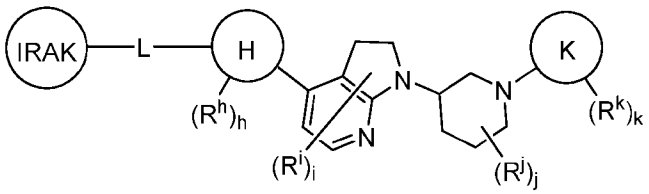


I-b-24



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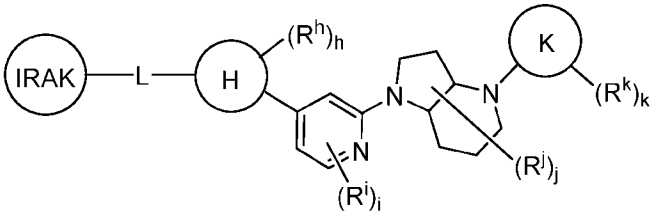
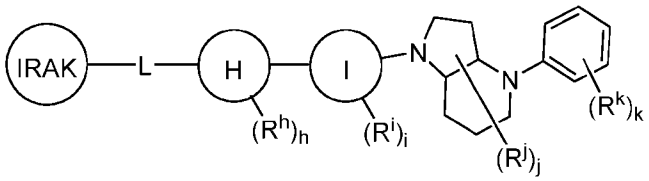


I-b-26



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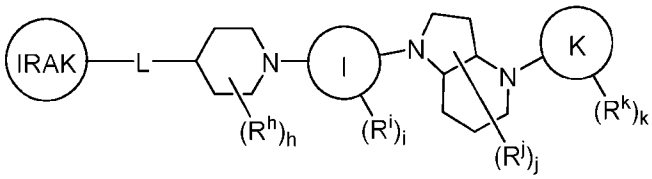
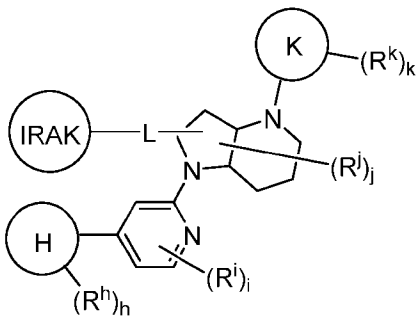
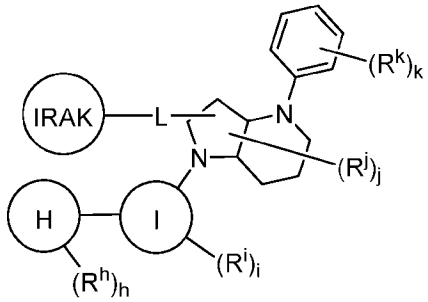


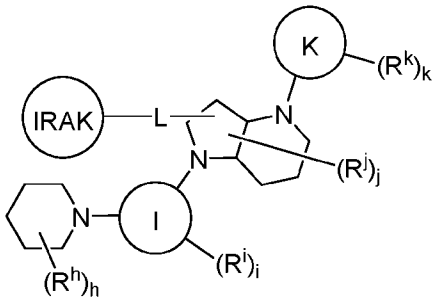
I-b-28



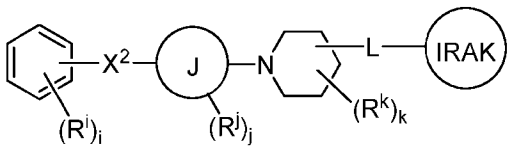
I-b-29



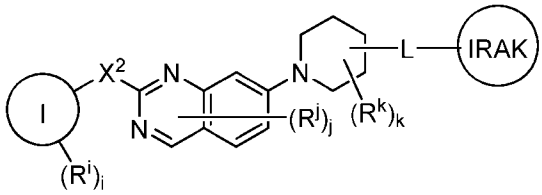
I-b-30



I-b-31



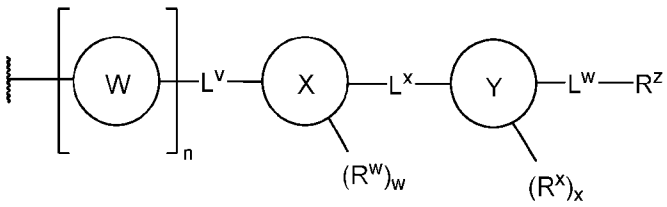
I-b-32



I-b-33

or a pharmaceutically acceptable salt thereof.

135. The compound of any one of claims 1-134, wherein the IRAK4 binding moiety is:



or a pharmaceutically acceptable salt thereof, wherein:

Ring W is phenyl, naphthyl, a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic,

carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring X is phenyl, naphthyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Y is phenyl, naphthyl, a 4-10 membered saturated monocyclic, bicyclic, bridged bicyclic, spirocyclic, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

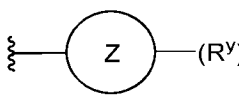
each of L^v, L^w , and L^x is independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-;

each R^w is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, or $-C(O)NR_2$;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom, or different atoms, are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom, or different atoms, to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^x is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^z is selected from 

, hydrogen, or an optionally substituted group selected from C_{1-6}

aliphatic or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Z is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-10} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0 or 1;

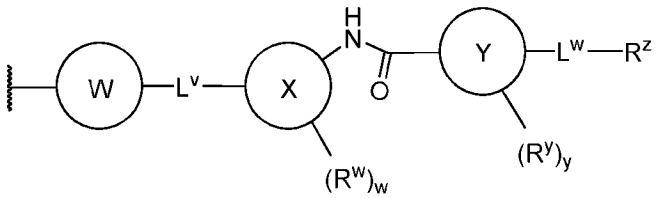
w is 0, 1, or 2;

x is 0, 1, 2, 3 or 4; and

y is 0, 1, 2, 3 or 4.

136. The compound of claim 135, wherein L^x is a covalent bond or -C(O)NH-.

137. The compound of any one of claims 1-136, wherein the IRAK4 binding moiety is:



or a pharmaceutically acceptable salt thereof, wherein:

Ring W is a 4-10 membered saturated mono- or bicyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring X is phenyl, a 4-10 membered saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently

selected from nitrogen, oxygen, and sulfur;

Ring Y is phenyl or a 5-10 membered mono- or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

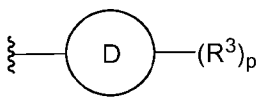
each of L^v and L^w is independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, -CF(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-;

each R^w is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, or $-C(O)NR_2$;

each R is independently hydrogen, deuterium, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spiro, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^x is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^z is selected from 

, hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spiro ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Z is phenyl, a 4-10 membered saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each w is 0, 1, or 2;

each x is 0, 1, 2, 3 or 4; and

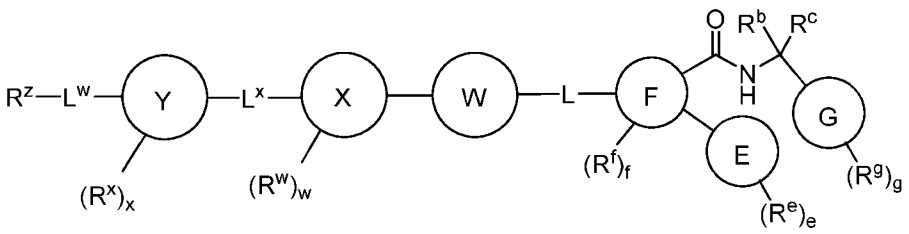
each y is 0, 1, 2, 3 or 4.

138. The compound of any one of claims 135-137, wherein Ring W is a 4-6 membered saturated monocyclic carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

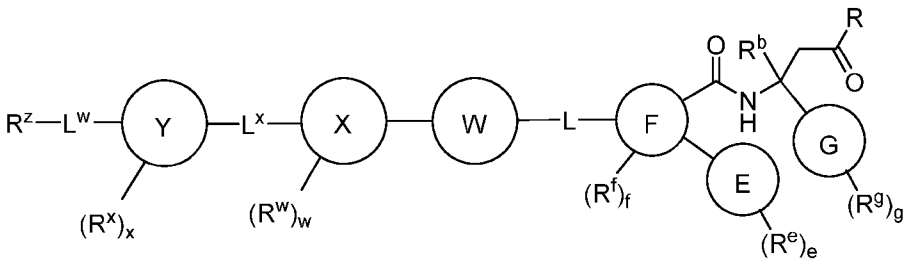
139. The compound of any one of claims 135-138, wherein Ring W is a 6-membered saturated monocyclic carbocyclic or heterocyclic ring having 1 heteroatom.

140. The compound of any one of claims 135-139, wherein L^y is a covalent bond or -C(O)NH-.

141. The compound of any one of claims 135-140, wherein said compound is represented by any one of the following formulae:



I-aa-10



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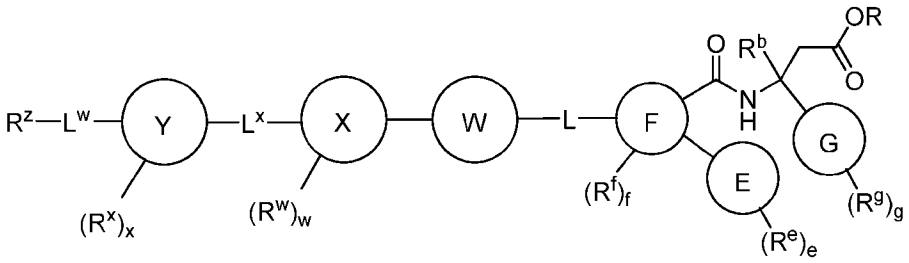
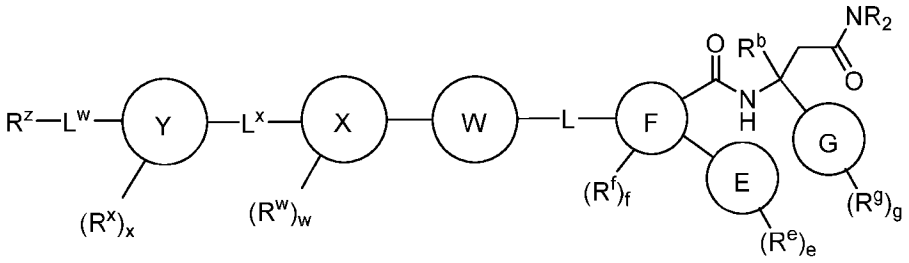


I-aa-12



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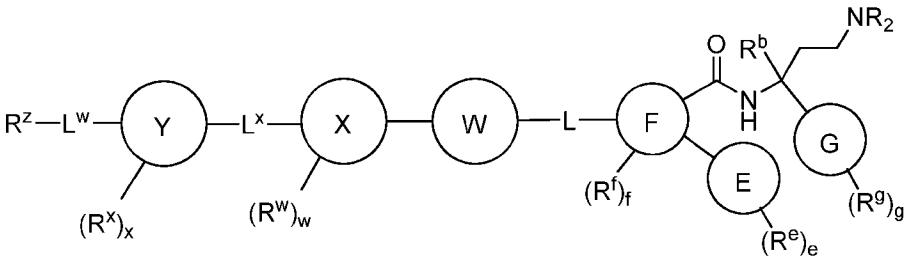

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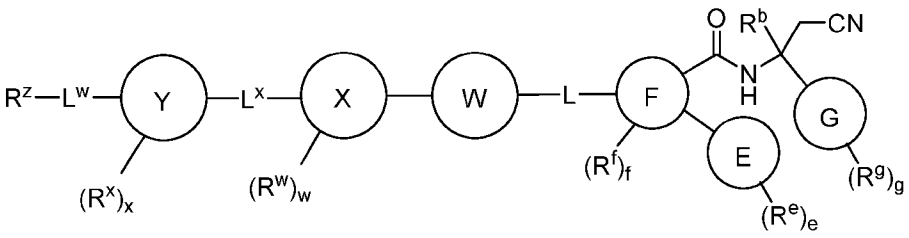
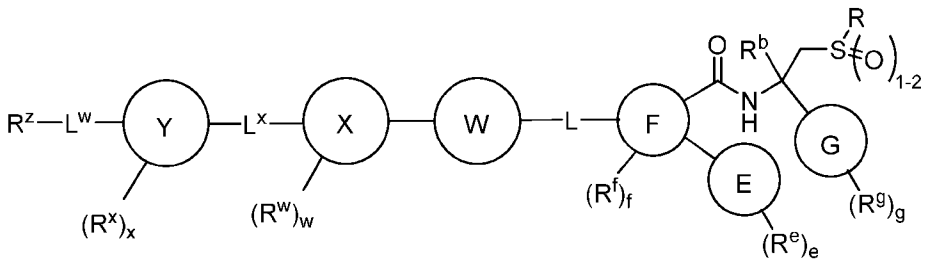


I-aa-15



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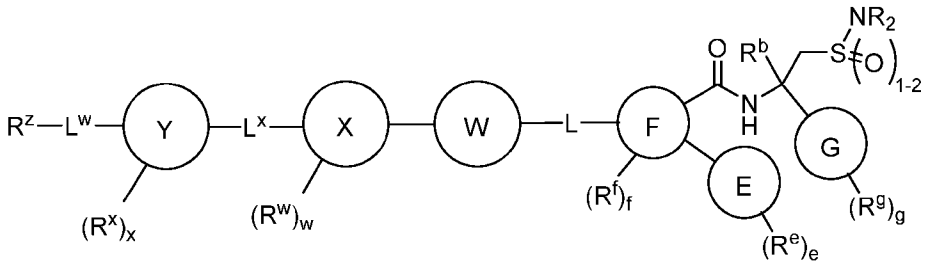

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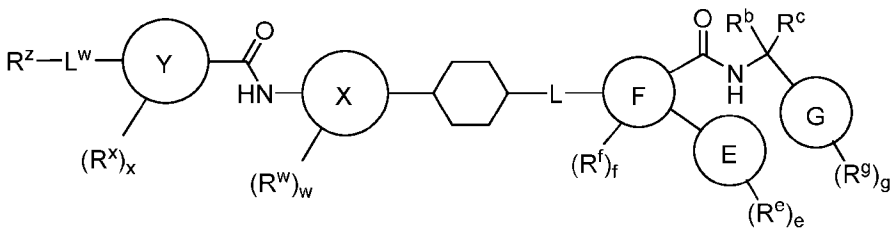

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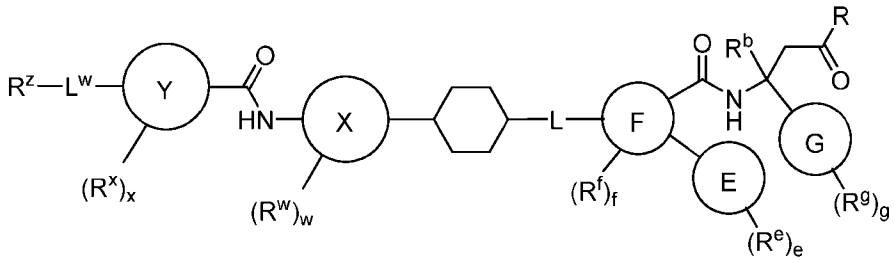

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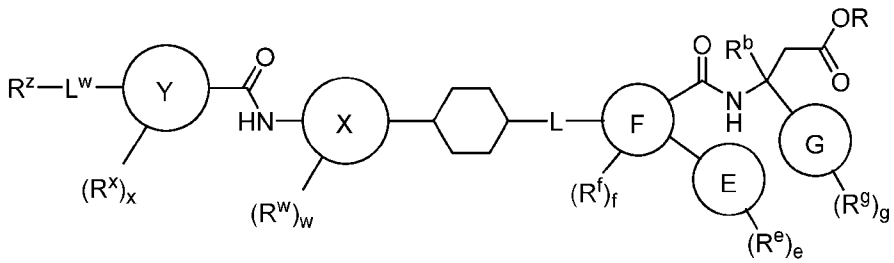
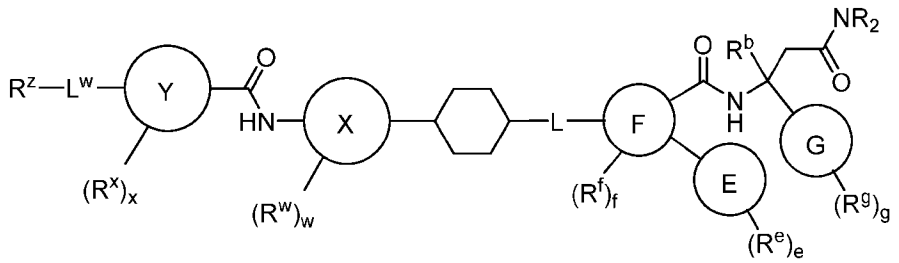


I-aa-20



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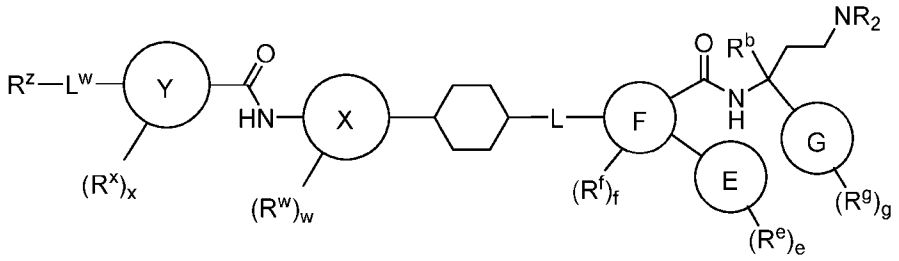

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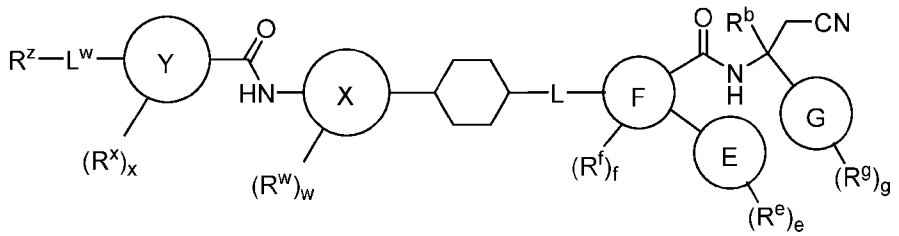

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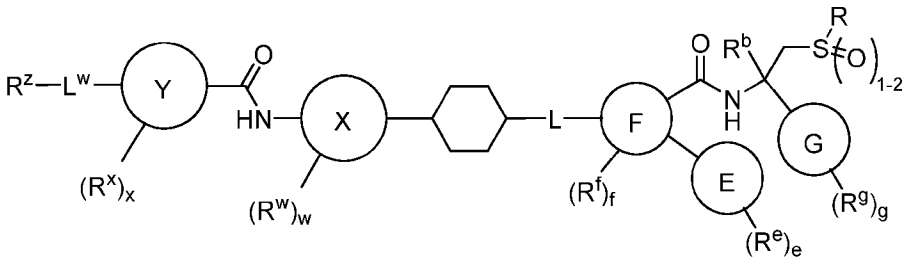
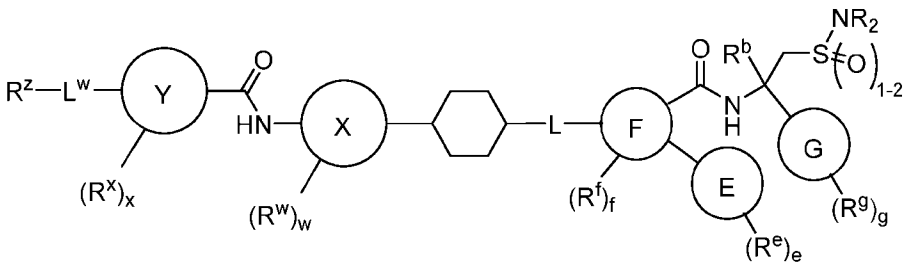
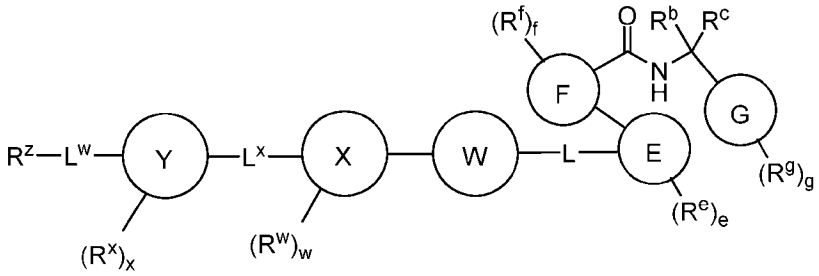


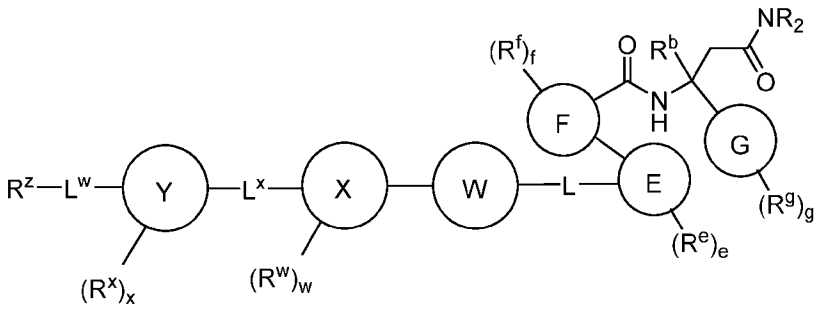
I-aa-24



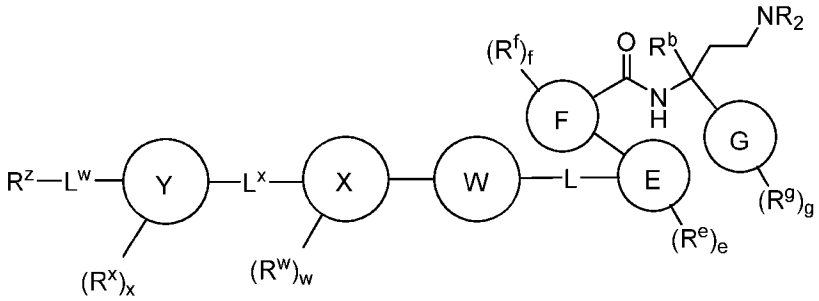
I-aa-25



I-aa-26



I-aa-27



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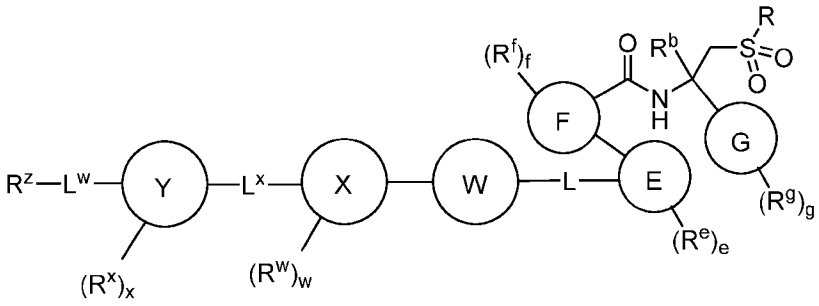

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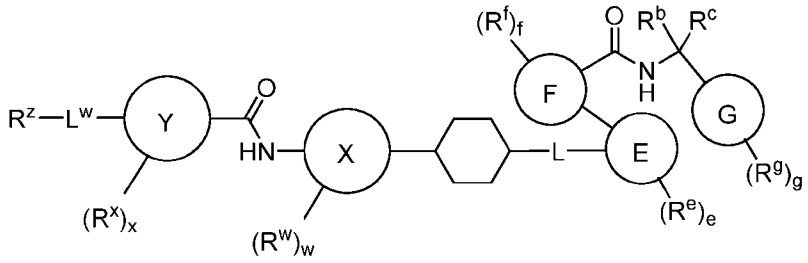

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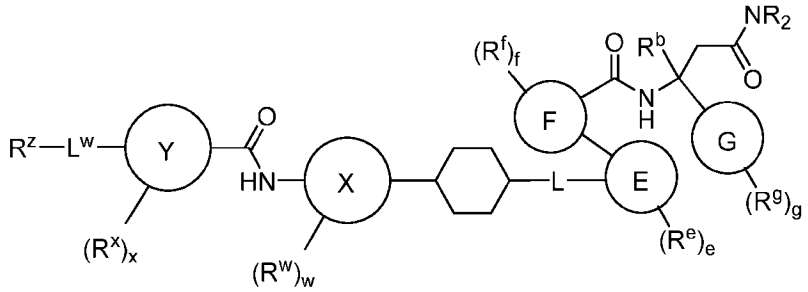

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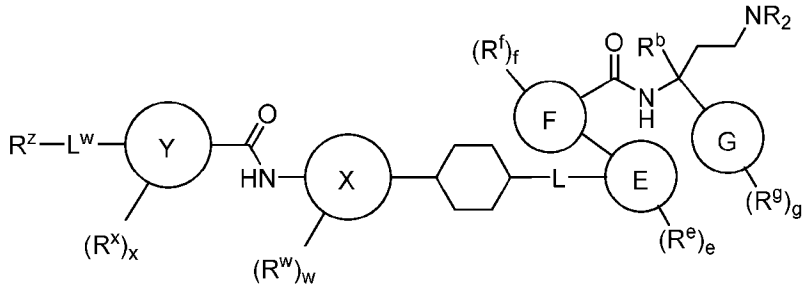

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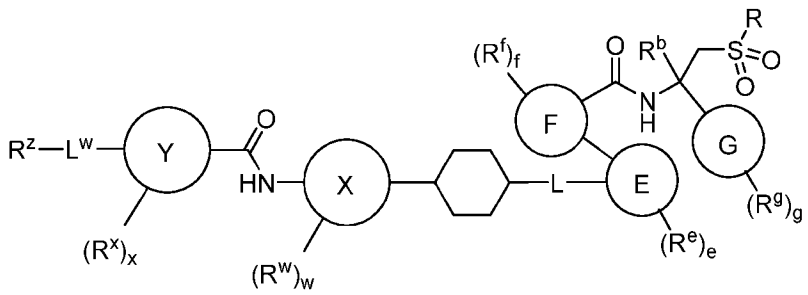
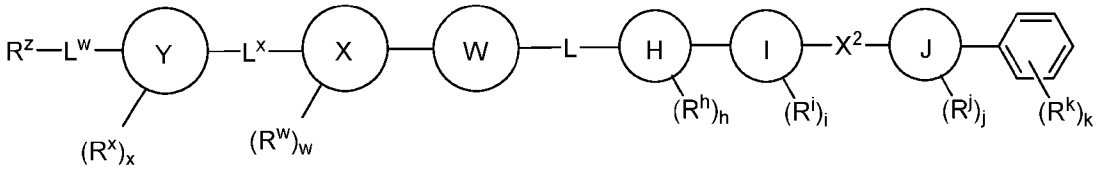


I-aa-33

or a pharmaceutically acceptable salt thereof.

142. The compound of any one of claims 135-140, wherein said compound is represented by any one of the following formulae:



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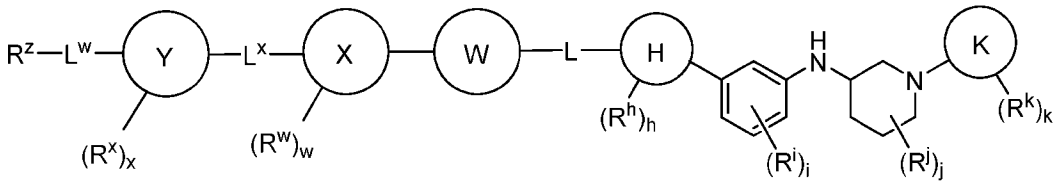

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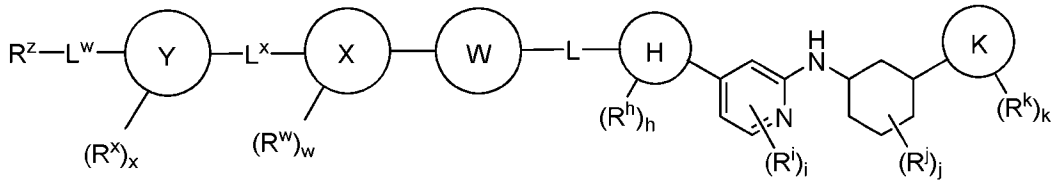

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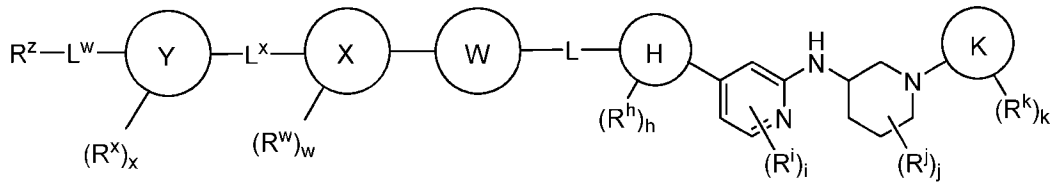

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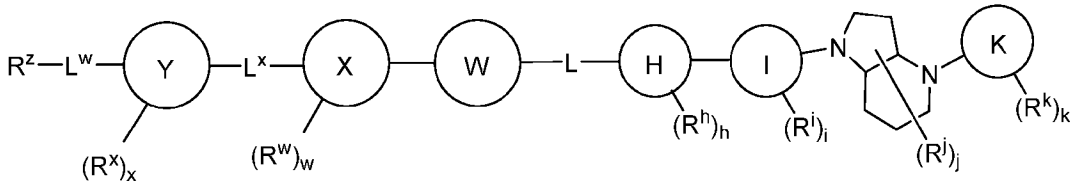

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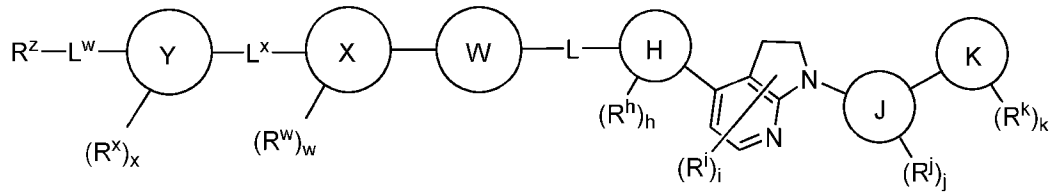

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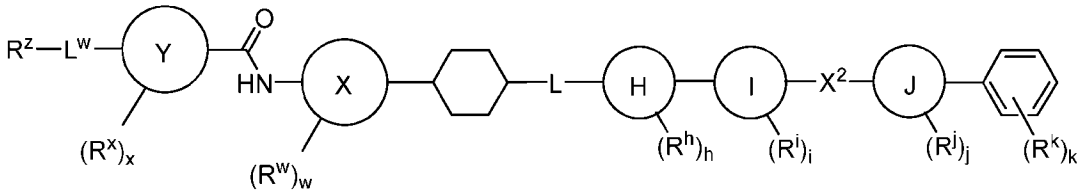

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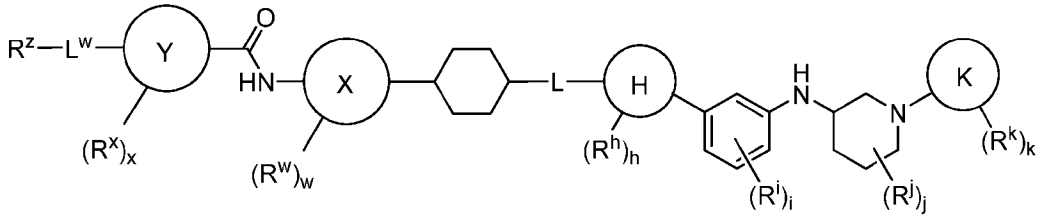

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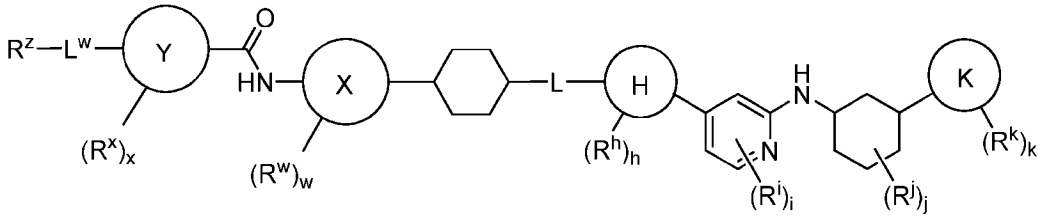

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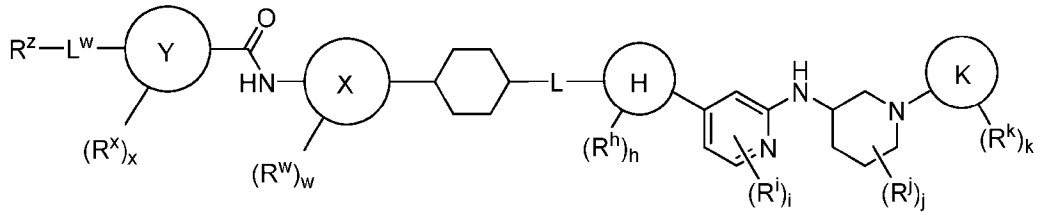

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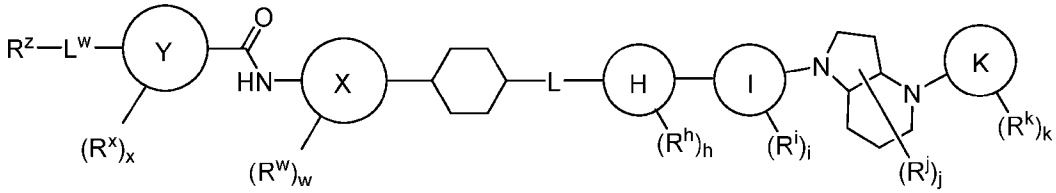

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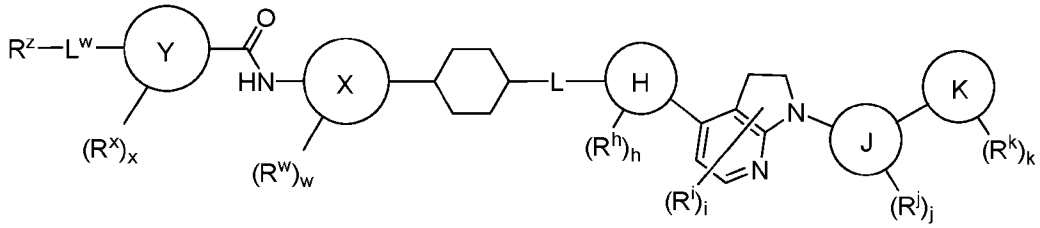

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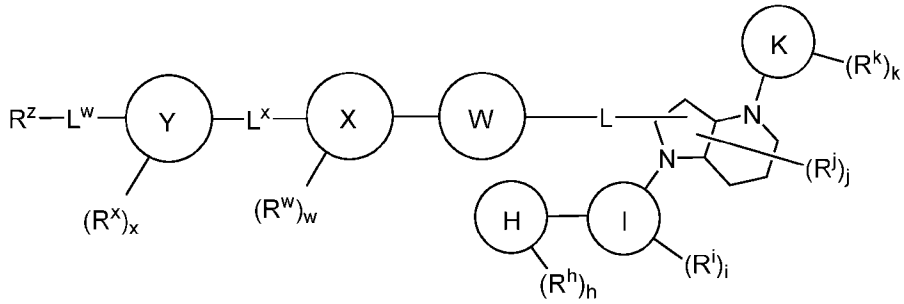

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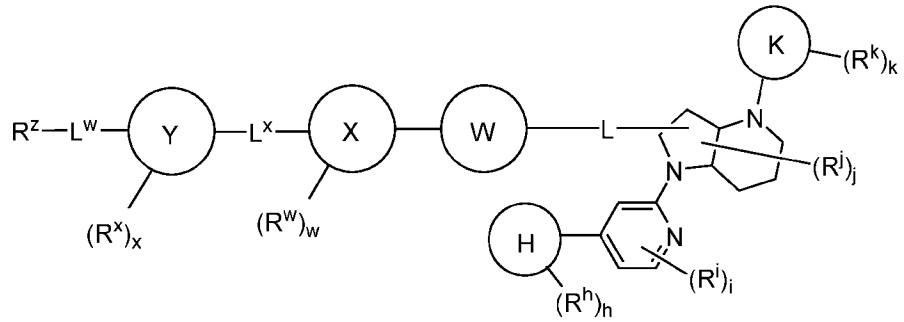

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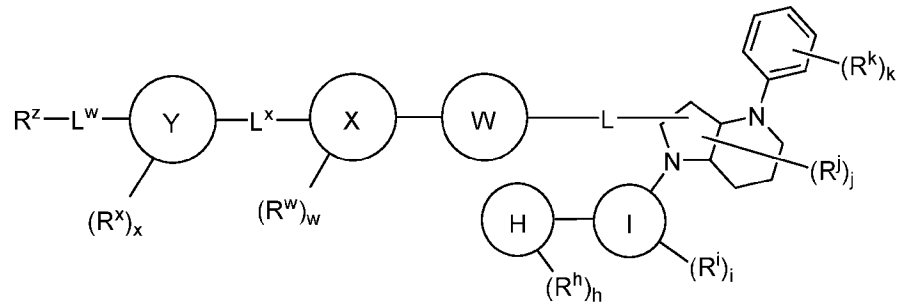

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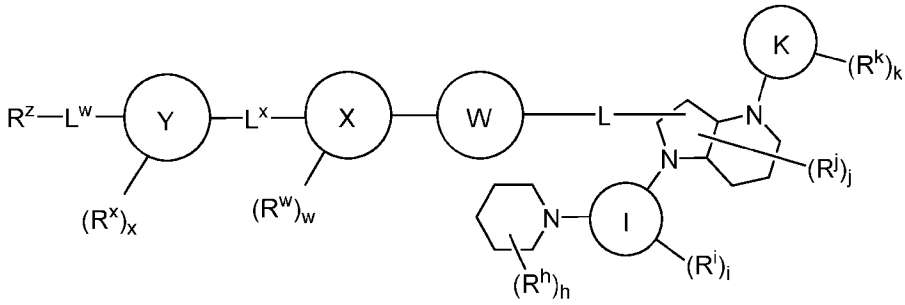

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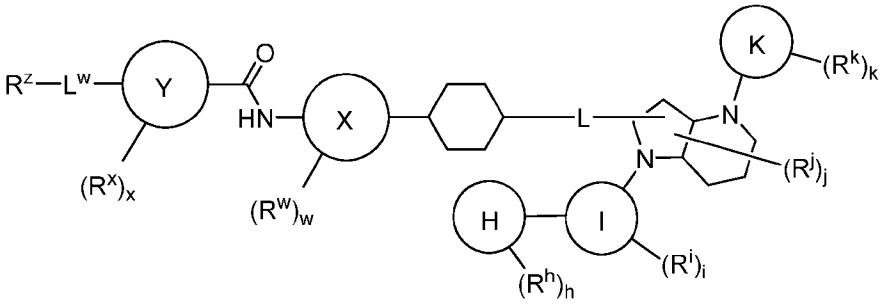

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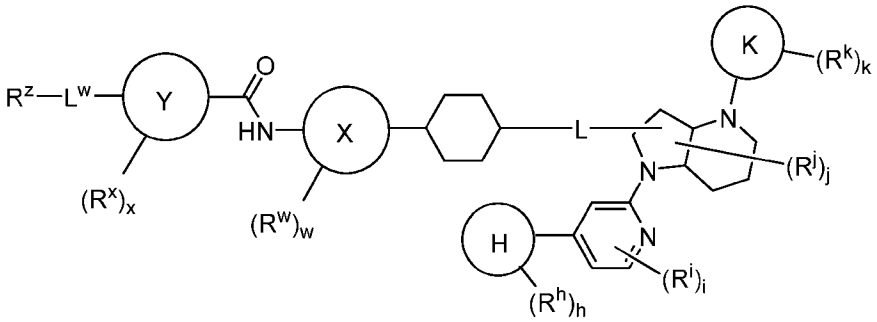

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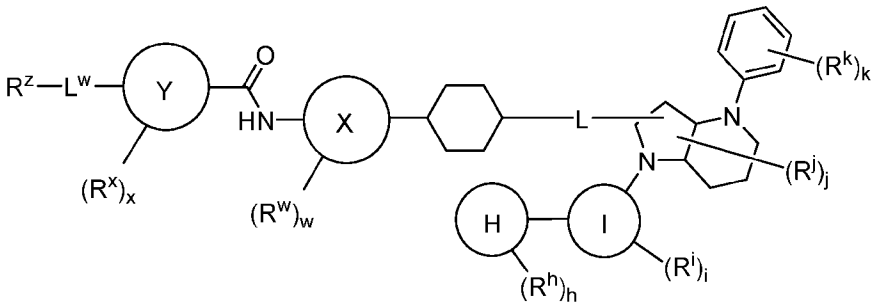

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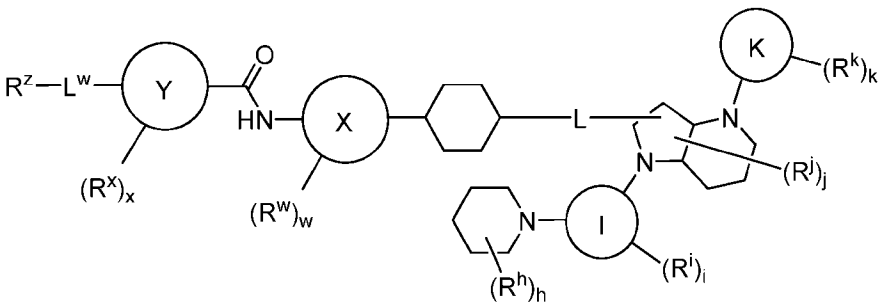


I-bb-29

or a pharmaceutically acceptable salt thereof.

143. The compound of any one of claims 135-142, Ring X is a 5-10 membered monocyclic or bicyclic

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

144. The compound of any one of claims 135-143, Ring X is a 5-membered monocyclic or 9-membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

145. The compound of any one of claims 135-144, wherein Ring Y is phenyl or a 6-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

146. The compound of any one of claims 135-145, wherein Ring Y is phenyl or a 5-membered monocyclic or 9-membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

147. The compound of any one of claims 135-146, wherein w is 1 or 2.

148. The compound of any one of claims 135-147, wherein w is 1.

149. The compound of any one of claims 135-146, wherein w is 0.

150. The compound of any one of claims 135-148, wherein R^w is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

151. The compound of any one of claims 135-148, wherein R^w is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

152. The compound of any one of claims 135-148, wherein R^w is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -$CR_2(OR)$, -OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

153. The compound of any one of claims 135-152, wherein x is 1 or 2.

154. The compound of any one of claims 135-153, wherein x is 1.

155. The compound of any one of claims 135-152, wherein x is 0.

156. The compound of any one of claims 135-154, wherein R^x is R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

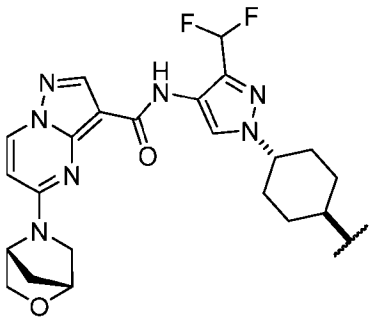
157. The compound of any one of claims 135-154, wherein R^x is optionally substituted C_{1-6} aliphatic, fluoro, chloro, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)NROR, -C(NOR)R, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)N(R)_2$, or -$NRS(O)_2R$.

158. The compound of any one of claims 135-154, wherein R^x is C_{1-6} alkyl, C_{1-6} haloalkyl, fluoro, chloro, -CN, -OR, -NR_2, -C(O)R, -C(O)OR, or -$C(O)NR_2$.

159. The compound of any one of claims 135-158, wherein L^w is a covalent bond.

160. The compound of any one of claims 135-159, wherein R^z is hydrogen or a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

161. The compound of any one of claims 135-160, wherein the IRAK4 binding moiety is



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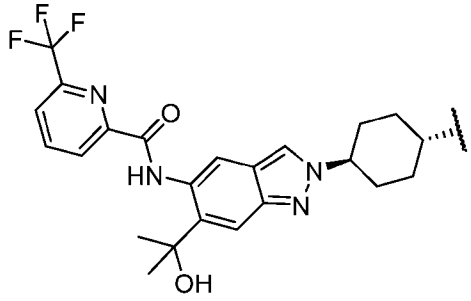

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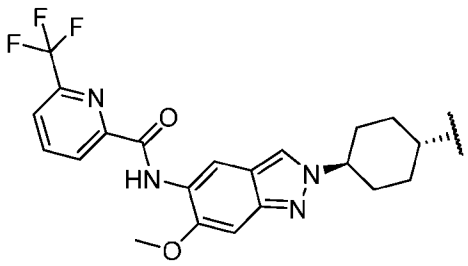
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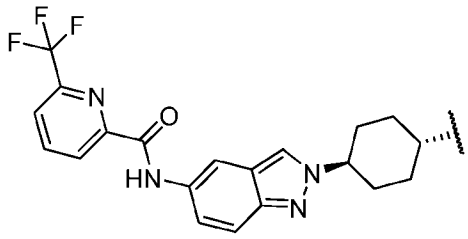
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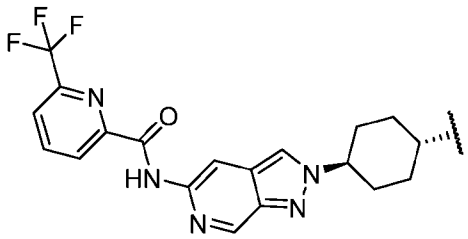
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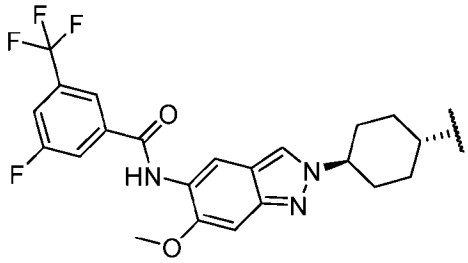
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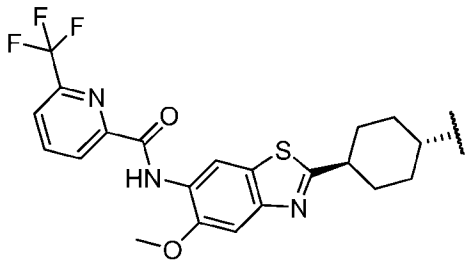
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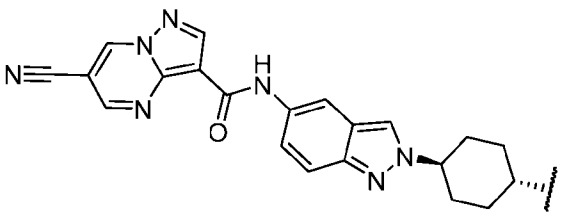
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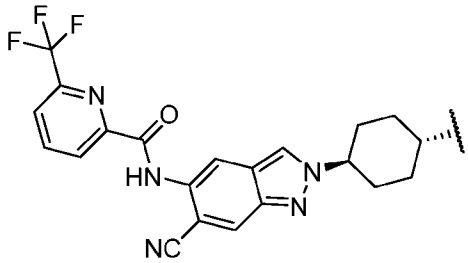
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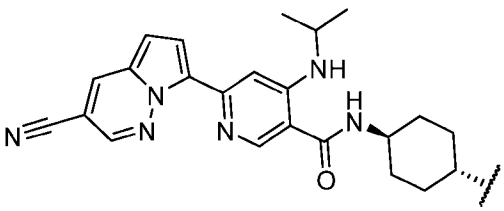
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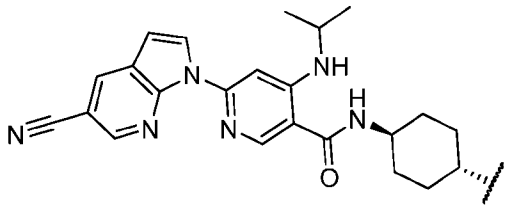
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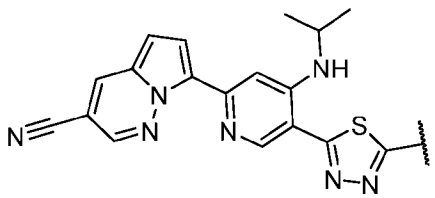
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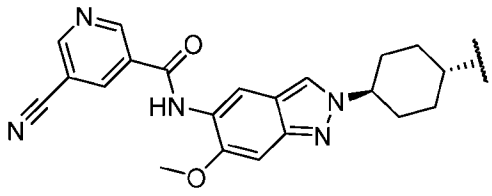
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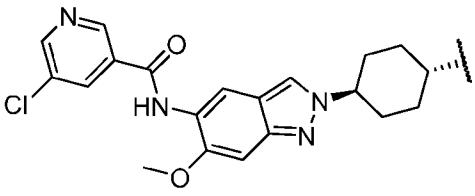
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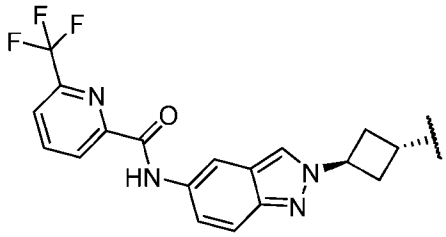

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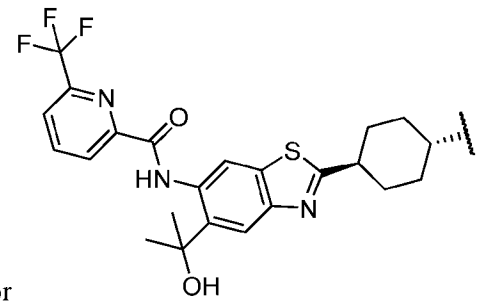

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162. The compound of any one of claims 1-161, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -CRF-, $-CF_2-$, -O-, -N(R)-, -S-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, -N(R)C(O)-, or -N(R)C(O)O-.

163. The compound of any one of claims 1-162, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

164. A pharmaceutical composition comprising a compound of any one of claims 1-163, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

165. A method of degrading IRAK4 protein kinase in a patient or biological sample comprising administering to said patient or contacting said biological sample with a compound of any one of claims 1-163, or a pharmaceutical composition thereof.

166. A method of treating an IRAK4-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound of any one of claims 1-163, or a pharmaceutical composition thereof.

167. The method of claim 166, wherein the IRAK4-mediated disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/077743

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 207/323*** (2023.01); ***C07D 231/12*** (2023.01); *A61K 31/415* (2023.01); *A61P 35/00* (2023.01)

CPC: ***C07D 207/323; C07D 231/12;*** *A61P 35/00; A61K 31/415*

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/119159 A1 (KYMERA THERAPEUTICS INC.) 17 June 2021 (17.06.2021) entire document	1-4, 7
A	US 2022/0056046 A1 (AURIGENE DISCOVERY TECHNOLOGIES LIMITED) 24 February 2022 (24.02.2022) entire document	1-4, 7
A	US 2022/0273668 A1 (KYMERA THERAPEUTICS INC.) 01 September 2022 (01.09.2022) entire document	1-4, 7
A	US 2021/0340124 A1 (SHENZHEN BO LI JIAN MEDICINE CO. LTD.) 04 November 2021 (04.11.2021) entire document	1-4, 7

☐ Further documents are listed in the continuation of Box C. ☐ 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
20 January 2024 (20.01.2024)	**06 March 2024 (06.03.2024)**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US **Commissioner for Patents** **P.O. Box 1450, Alexandria, VA 22313-1450**	**MATOS** **TAINA**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/077743

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

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

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

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

3. ☑ Claims Nos.: **5, 6, 8-72, 76-167**
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:

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

Group I+: claims 1-4, 7, and 73-75 are drawn to compounds of formula I-a', or a pharmaceutically acceptable salt thereof, compounds of formula I-a, or a pharmaceutically acceptable salt thereof, compounds of formula I-b', or a pharmaceutically acceptable salt thereof, compounds of formula I-b, or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound of formula I-a', specifically wherein the compound is formula I-a-8' wherein Ring F is phenyl; Ring G is phenyl; Rb is hydrogen; Rc is halogen; Re, Rf, and Rg are each independently absent; each of e, f, and g are independently 0; L is a covalent bond; and IRAK is an IRAK4 binding moiety, specifically the first shown moiety in instant claim 161, compounds of formula I-b' comprising the same, and compounds of formula I-b comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed element for each of the variables presented in the claims (see claims 1, 16, 161). It is believed that claims 1-4 and 7 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula I-a', specifically wherein the compound is formula I-a-8' wherein Ring F is phenyl; Ring G is phenyl; Rb is hydrogen; Rc is halogen; Re, Rf, and Rg are each independently absent; each of e, f, and g are independently 0; L is a covalent bond; and IRAK is an IRAK4 binding moiety, specifically the second shown moiety in instant claim 161, compounds of formula I-b' comprising the same, and compounds of formula I-b comprising the same. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

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

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

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, IRAK, Ring E, Ring F, Y2, Ra, Rb, Rc, L, s, e, f, Re, Rf, Ring H, Ring I, Ring J, Ring K, X1, X2, Rh, Ri, Rj, Rk, h, i, j, k, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of formula I-a'; a compound having the core structure of formula I-a; a compound having the core structure of formula I-b'; and a compound having the core structure of formula I-b, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2021/119159 A1 to Kymera Therapeutics, Inc. (hereinafter, "Kymera").

Kymera teaches a compound having the core structure of formula I-a' (Para. [0015], the present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein: IRAK is an IRAK binding moiety capable of binding to one or more of IRAK-1, -2, -3, or -4; Para. [0053], the present invention provides a compound of formula where IRAK is a IRAK-4 binding moiety thereby forming a compound of formula 1-a, or a pharmaceutically acceptable salt thereof); a compound having the core structure of formula I-a (Para. [0015], the present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein: IRAK is an IRAK binding moiety capable of binding to one or more of IRAK-1, -2, -3, or -4; Para. [0053], the present invention provides a compound of formula where IRAK is a IRAK-4 binding moiety thereby forming a compound of formula 1-a, or a pharmaceutically acceptable salt thereof); a compound having the core structure of formula I-b' (Para. [0015], the present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein: IRAK is an IRAK binding moiety capable of binding to one or more of IRAK-1, -2, -3, or -4; Para. [0053], the present invention provides a compound of formula where IRAK is a IRAK-4 binding moiety thereby forming a compound of formula 1-a, or a pharmaceutically acceptable salt thereof); and a compound having the core structure of formula I-b (Para. [0015], the present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein: IRAK is an IRAK binding moiety capable of binding to one or more of IRAK-1, -2, -3, or -4; Para. [0053], the present invention provides a compound of formula where IRAK is a IRAK-4 binding moiety thereby forming a compound of formula 1-a, or a pharmaceutically acceptable salt thereof).

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/077743

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

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

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

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

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-4, 7**

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.